Arthritis & Rheumatology

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Cover image: The image on the cover (from Liu et al; pages 1741–1754) shows representative Masson staining of mouse skin tissues with fibrosis. Overexpression of cystathionine γ-lyase effectively mitigates bleomycin-triggered dermal thickening and collagen deposition. These findings suggest that cystathionine γ-lyase-mediated Smad3 S-sulfhydration may represent a potential novel mechanism against fibrosis in systemic sclerosis.

In this Issue

Highlights from this issue of *A&R* | By Lara C. Pullen, PhD

Temporal Trends of Spondyloarthritis and Inflammatory Bowel Disease

Previous research has demonstrated a relationship between spondyloarthritis (SpA) and intestinal inflammation. Likewise, there is considerable overlap between SpA and inflammatory bowel disease (IBD), including shared genetic and nongenetic risk factors, waxing and waning disease course with progressive end-organ injury, disordered immune response with infiltration of target tissue, and complications. p. 1666 **In this issue, Agrawal et al. (p. 1666)** report the results of a two-decade analysis of SpA prevalence in a Danish population-based cohort. They found that SpA is associated with IBD both prior to and after the IBD diagnosis, with the highest prevalence in the few years around diagnosis. They also highlight clinical variables associated with SpA in IBD.

Based on validated definitions of IBD and SpA, 17,108 (16.7%) of the 102,648 individuals in the study had a diagnosis of IBD. Moreover, SpA and IBD diagnoses were associated with each other in the eight-year periods preceding and following an IBD diagnosis. Specifically, the adjusted odds ratios of SpA in the eight years preceding IBD, Crohn disease (CD), and ulcerative colitis (UC) diagnosis compared to matched individuals were 1.95 (95% confidence interval [CI] 1.78-2.14), 2.84 (95% CI 2.43-3.32), and 1.61 (95% CI 1.43-1.81), respectively. The adjusted hazard ratios for SpA in the eight years following IBD, CD, and UC diagnosis, compared with matched individuals, were 2.51 (95% CI, 2.34-2.70), 3.17 (95% CI, 2.81-3.59), and 2.24 (95% CI, 2.05-2.45), respectively. SpA prevalence varied over time, with a sharp increase during the year before and two years after IBD diagnosis.

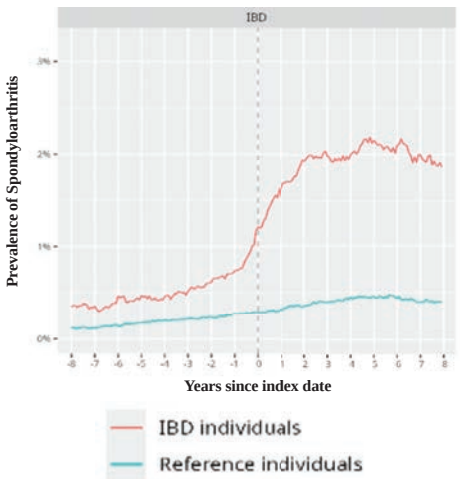

Figure 2. The prevalence of spondyloarthritis (SpA) relative to timing of inflammatory bowel disease (IBD) diagnosis in individuals with IBD compared to matched reference individuals.

Their findings indicate that individuals with SpA, especially axial SpA, are likely to be at increased risk of developing IBD. In addition, women and young adults were more likely than men and older patients to be diagnosed with SpA following IBD diagnosis. SpA was also associated with both CD and UC, with higher estimates for CD. The authors conclude by providing actionable clinical guidance to improve the early diagnosis and treatment of SpA and IBD.

Metabolomic Signatures of Gout Flare Burden With Colchicine

Several metabolites and pathways have been linked with flare burden in patients with gout who are treated with colchicine. **In this issue, Sun et al. (p. 1765)** report that metabolomic profile-defined inflammation status was associated with gout flare outcomes in patients receiving colchicine prophylaxis who initiated urate-lowering therapy (ULT). They conclude that identifying these novel metabolomic predictive signatures before ULT could help optimize clinical decision-making for flare prophylaxis, colchicine dosing, and duration in the first six months after initiation of treat-to-target ULT in gout.

p. 1765

The study included 409 male patients with gout who were predominantly prescribed febuxostat or benzbromarone. Approximately one third (36.9%) of participants experienced at least one flare. However, not all patients who initiated ULT developed gout flares or increased their flare burden from baseline in the first two years of therapy. The investigators identified different metabolomic profiles, including inflammation-modulating metabolites, between patients with no gout flares and those with some flare activity during the first months of ULT while on colchicine prophylaxis. A four-metabolite risk score was able to predict gout flare risk independent of adjusted clinical factors. The researchers also used a machine learning model that incorporated the top-ranked metabolites selected by multivariable methods with unbiased variable selection along with traditional clinical factors, which achieved an area under the receiver operating characteristic curve of 0.77 (95% CI 0.71-0.83) and 0.72 (95% CI 0.61-0.84) for predicting flare risk in the discovery and validation cohorts, respectively.

Predicting Outcomes in Eosinophilic Granulomatosis With Polyangiitis

Rheumatologists have had an evolving definition of relapse in eosinophilic granulomatosis with polyangiitis (EGPA), recently distinguishing between vasculitis-related manifestations and those associated with asthma and ear, nose, and throat (ENT) involvement. p. 1710 **In this issue, Papo et al. (p. 1710)** sought to identify factors specific to vasculitis relapse risk and to separate risk factors for glucocorticoid (GC)-dependent asthma and/or ENT symptom manifestations. The large size of their cohort enabled robust statistical analyses, which enhanced the generalizability of their valuable insights into the long-term evolution of EGPA.

The investigators observed a multicenter European cohort of 809 patients with EGPA for a median of 72 months to develop predictive models for vasculitis relapse and for GC-dependent asthma and/or ENT symptoms. Vasculitis relapse occurred in 228 patients, with a 12-year cumulative incidence of 41.2%. The researchers observed GC-dependent asthma and/or ENT symptoms in 66.4% of patients at two years. Predictors of vasculitis relapse included age, GC-dependent asthma before EGPA diagnosis, arthralgia, myocarditis, peripheral neuropathy, myeloperoxidase–antineutrophil cytoplasmic antibody, and baseline eosinophil count. Predictors of GC-dependent asthma and/or ENT symptoms included older age, GC-dependent asthma at diagnosis, chronic sinusitis, and baseline eosinophil count.

The researchers concluded by identifying risk profiles for vasculitis relapse and GC-dependent asthma and/or ENT symptom manifestations, thereby laying the groundwork for personalized therapeutic approaches for EGPA. They suggested that, following prospective external validation in the current therapeutic era, these predictive models may help guide treatment decisions.

Journal Club

A monthly feature designed to facilitate discussion on research methods in rheumatology.

Efficacy and Safety of Guselkumab in PsA With Inadequate Response to TNFi: A Phase 3, Randomized, Placebo-Controlled Study

Ogdie et al. *Arthritis Rheumatol*. 2026;78:1674–1686.

For many patients with psoriatic arthritis (PsA), a tumor necrosis factor inhibitor (TNFi) is the first type of biologic prescribed. However, many patients either do not respond or eventually lose response to a TNFi. There are currently no clear guidelines on subsequent treatment selection (i.e., cycling to another TNFi or switching to a drug with a different mechanism of action) after an inadequate response to a TNFi (TNFi-IR).

Guselkumab is a fully human monoclonal antibody that selectively inhibits the interleukin (IL)-23p19 subunit. Globally, guselkumab 100 mg at weeks 0, 4, and every 8 weeks (Q8W) is approved for adults with active PsA. Previous phase 3 trials demonstrated the efficacy and favorable safety profile of guselkumab 100 mg Q4W and the Q8W regimen in biologic-naïve (DISCOVER-1/DISCOVER-2) and a limited sample size of TNFi-experienced (DISCOVER-1) participants. The COSMOS study assessed guselkumab in TNFi-IR participants but only evaluated the Q8W dosing regimen. Exploratory post hoc analyses from DISCOVER-1 suggested that TNFi-IR patients may benefit from the more frequent Q4W regimen.

SOLSTICE is a phase 3, randomized, placebo-controlled study evaluating the efficacy and safety of guselkumab Q4W and Q8W in TNFi-IR participants (inadequate efficacy and/or intolerance) with active PsA who had received one prior TNFi. Through week 24 of SOLSTICE, both guselkumab Q4W and Q8W demonstrated efficacy in improving signs and symptoms of PsA across multiple disease domains, with comparable response rates for achieving meaningful improvements in peripheral joint disease, clear or almost clear skin, and minimal disease activity. Safety findings were consistent with the known profile of guselkumab.

Questions

1. **According to international PsA treatment guidelines, what are some factors that should be considered when selecting advanced therapies for patients with active PsA?**
2. **How did the SOLSTICE population differ from those in the DISCOVER-1 and DISCOVER-2 studies?**
3. **How was lack of benefit with a prior TNFi defined for enrollment in SOLSTICE?**
4. **How do these data compare to real-world analyses conducted to determine the effectiveness of guselkumab in treatment-refractory patients with active PsA?**

Clinical Connections

Cystathionine γ-Lyase-Dependent S-Sulfhydration of Smad3: A Novel Target in Systemic Sclerosis

Liu et al. *Arthritis Rheumatol.* 2026;78:1741–1754.

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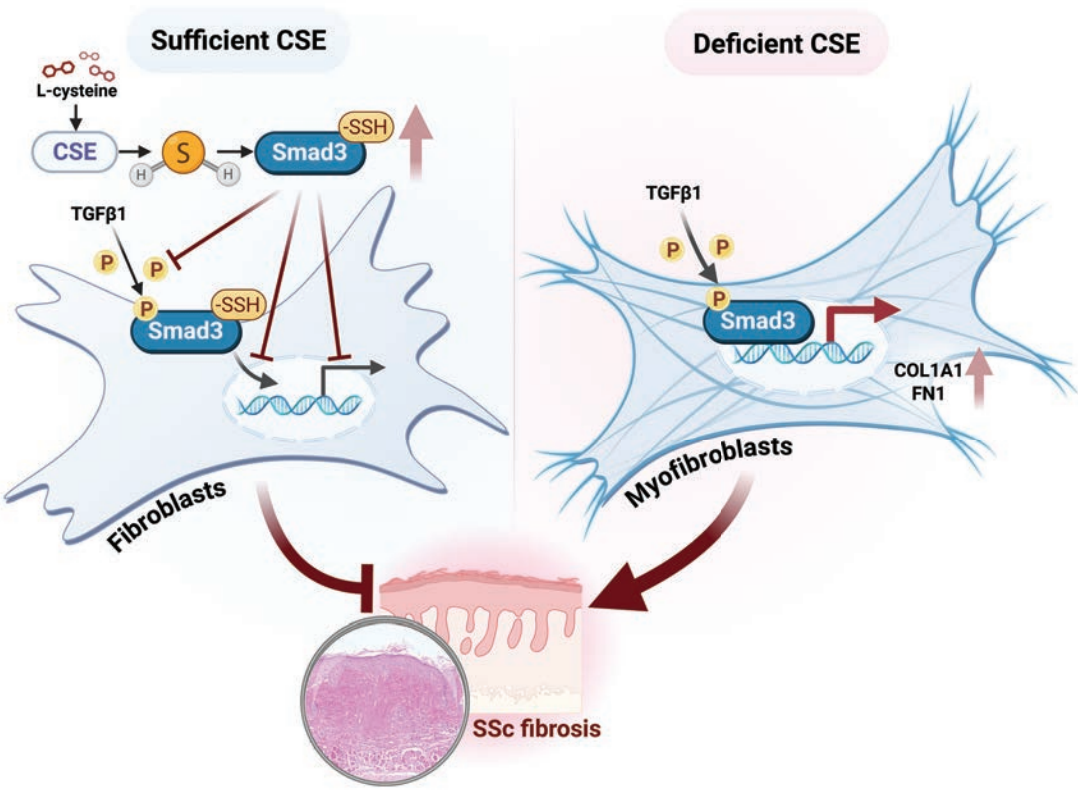

KEY POINTS

- Patients with SSc show reduced CSE/H_2S levels, which correlate with fibrosis severity.
- CSE-mediated S-sulfhydration of Smad3 suppresses TGFβ1/Smad3 profibrotic signaling.
- The Smad3 C121 site is critical for antifibrotic effects of CSE, which was confirmed by mutational analysis.
- CSE overexpression mitigates skin and lung fibrosis in preclinical models, supporting its therapeutic potential.

SUMMARY

Systemic sclerosis (SSc) is a severe autoimmune disease marked by progressive skin and organ fibrosis and that has limited effective treatments. In this study, Liu et al. found that patients with SSc had significantly reduced levels of the enzyme cystathionine γ-lyase (CSE) and its product hydrogen sulfide (H_2S), which also correlated with disease severity.

Mechanistically, CSE promotes a specific protein modification called S-sulfhydration, which was shown to be globally diminished in SSc. The researchers further identified that CSE-mediated S-sulfhydration of Smad3 at cysteine 121 weakens its profibrotic activity by altering protein structure and inhibiting TGFβ1/Smad3 signaling. In preclinical models, overexpression of CSE reduced skin and lung fibrosis. Together, these findings suggest that Smad3 S-sulfhydration may represent a novel antifibrotic mechanism and a promising therapeutic target for SSc.

Proteomics Analysis of Urinary Biomarkers Following Anifrolumab Treatment

Fava et al. *Arthritis Rheumatol.* 2026;78:1692–1699.

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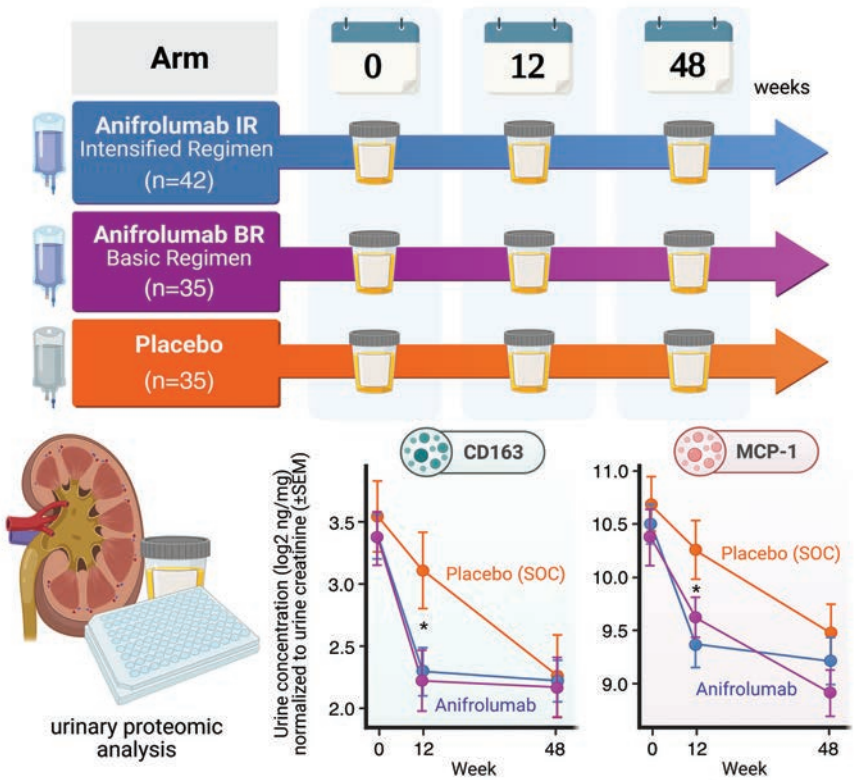

KEY POINTS

- An intensified regimen of anifrolumab reduced key urinary inflammatory biomarkers, including CD163 and MCP-1, by week 12 versus placebo in lupus nephritis.
- Patients receiving placebo showed higher levels of several biomarkers of intrarenal inflammation, suggesting that type I interferon blockade rapidly modulates renal immune activity.
- Urinary biomarkers may reflect intrarenal inflammation better than proteinuria-based endpoints.

SUMMARY

Lupus nephritis (LN) remains one of the most serious complications of systemic lupus erythematosus, with many patients progressing to kidney failure despite treatment. Currently, doctors monitor treatment response by measuring proteinuria, but this measure often does not reflect the resolution of inflammation inside the kidney. In this study, Fava et al. analyzed urine samples from patients with LN enrolled in the phase 2 TULIP-LN trial to determine whether anifrolumab, a medication that blocks type I interferon signaling, could reduce markers of active kidney inflammation.

Patients receiving anifrolumab showed significantly faster reductions in key inflammatory biomarkers—including CD163 (a marker of inflammatory immune cells in the kidney) and MCP-1 (a protein that attracts immune cells)—by just 12 weeks of treatment. Patients receiving standard therapy alone eventually reached similar biomarker levels, but not until week 48. Importantly, even patients who did not achieve a traditional "response" based on proteinuria showed markedly faster reductions in these inflammatory markers when treated with anifrolumab, suggesting the drug suppresses kidney inflammation before it is reflected in conventional clinical measures. These findings indicate that anifrolumab may accelerate the resolution of intrarenal inflammation in LN, which could potentially prevent long-term kidney damage. The results also highlight the value of urinary biomarkers as tools to detect early treatment effects that proteinuria-based measures may miss.

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EDITORIAL

Improvements in Outcomes for Systemic Sclerosis-Associated Interstitial Lung Disease With Expanded Treatment Options

Jeffrey A. Sparks, MD, MMSc[1,2] and Janet E. Pope, MD, MPH, FRCPC[3]

Systemic sclerosis-associated interstitial lung disease (SSc-ILD) is a frequent and deadly complication that affects as many as a third to half of patients with SSc.[1] Although there is still a need for treatment advances, over the last two decades, randomized trials have demonstrated the efficacy of many medications for SSc-ILD that include cyclophosphamide (CYC), mycophenolate mofetil (MMF), rituximab, tocilizumab, nintedanib, and azathioprine (and more recently nerandomilast). These have formed the basis for international guidelines, and many of these findings have been extrapolated to other forms of systemic autoimmune rheumatic disease-associated ILDs.[2,3] However, trends in uptake and associations with outcomes over calendar time for this expanded treatment repertoire have not been thoroughly investigated.

In this issue of *Arthritis & Rheumatology*, Campochiaro et al report that over time, there has been higher use of immune suppression (IS) for patients with SSc-ILD in the European Scleroderma Trials and Research (EUSTAR) study, which comprises many centers with expertise in SSc.[4] They found that from before 2006 to after 2017, IS use markedly increased four-fold (from 13.6% to 57.4%) in 1,409 patients with SSc who met the inclusion criteria of ILD. MMF was most often prescribed in recent times, no doubt because of data from the Scleroderma Lung Study II (SLS II). SLS II found MMF was not superior to CYC but was safer. One year of CYC and no treatment for the following year yielded the same benefit as two years of MMF. However, CYC was associated with more serious adverse events, including infections.[5] Combination therapy with more than one IS increased 1.5-fold from 18% to 27%, whereas the rate of ILD progression was reduced by nearly 50% when comparing 2007 with 2011 and 2011 with after 2017. More therapies were switched in the most recent study interval, likely because of there being more proven treatments available. For instance, although CYC and azathioprine use decreased markedly over time, MMF, rituximab, and tocilizumab increased over time. This could be because of the identification of milder cases as well as screening to detect ILD earlier and increased use of IS and other antifibrotic treatment for ILD in the recent past.[6] Other registries have observed that IS in early SSc has increased over time.[7]

The median age of treatment in the EUSTAR study has increased over time for SSc-ILD, and the proportion of men has also increased. The rates of lung transplantation were very low over time (less than 3%).[4] Many patients with SSc-ILD were not exposed to IS despite data showing IS treatment improve outcomes; thus, in clinical practice, a care gap exists. In the most recent time interval of patients (>2017), nearly 43% of patients with SSc-ILD were not exposed to any IS. The reasons for prescribing (or not prescribing) IS are not easily answered from an observational database unless there are questions as to why treatment was or was not prescribed for each individual at each visit.

The categories of various time intervals may have been arbitrary, but they make sense (studying before many SSc-ILD randomized controlled trials [RCTs] were performed other than CYC in SSc-ILD [SLS I]). Also, over time, the introduction of the use of biologics and antifibrotic treatments for SSc-ILD has also expanded. The sample size of patients in each period was large enough to adjust for confounders (such as age, sex, SSc subtype, and antibody status).

This timely and important article answers some questions with respect to SSc-ILD and the prevention and treatment with IS and antifibrotics. However, there are many unknowns raised by this study that can be further studied in the future. For instance, early identification of SSc-ILD is by screening (including assessing

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patient symptoms, pulmonary function testing, and imaging); other tools may be discovered to be more sensitive for screening patients and determining who will develop ILD or have progressive ILD (biomarkers, more sensitive imaging, etc). The importance of early detection is predicated on early treatment intervention, but the results of early IS in asymptomatic patients with SSc (with or without ILD) is controversial in the prevention of ILD occurrence or worsening. Similarly, not all patients with ILD will progress over a long observational period (such as 5 years), and many who progress will then level or improve and then possibly progress again in the future. Also, some patients develop SSc-ILD even after a negative screen, so it is unclear which patients may need repeated screening. These issues make nonrandomized observational studies difficult to predict who will progress and what factors/treatments are protective.

It seems important to identify and treat ILD in SSc early because of the high progressive mortality rate. A population-based study in Ontario, Canada of incident SSc reported that ILD in these patients had only half the 10-year survival compared with the overall population with SSc (44% survival in SSc overall and 22% survival in SSc-ILD).[8] However, there is controversy as to whether there is benefit in treating early ILD in SSc. In the Canadian Scleroderma Research Group (CSRG) database, early/mild ILD treatment seemed to reduce the progression of ILD, implying a possible window of opportunity for early treatment.[9] The IS treatment could be confounded because the study was uncontrolled and observational. An RCT in mild ILD from SSc concluded that MMF did not improve lung function vs placebo, but the study only had 41 patients so it could have been underpowered and too short to show a difference.[10] However, this study shows that clinicians are overall choosing to treat patients with SSc-ILD with potentially life-saving treatments more often, emphasizing how these clinical trials can change practice and improve outcomes.

Early use of IS was not associated with the prevention of ILD in SSc based on data from both the EUSTAR and Nijmegen Systemic Sclerosis cohort.[11] The incidence of ILD was the same in early IS vs late IS (47% vs 45%). They concluded that early IS did not prevent ILD onset, but this was not a trial, and those with early IS were often those who were anti-topoisomerase positive with diffuse cutaneous SSc (dcSSc).

The current publication showed that far more patients with SSc-ILD are exposed to IS.[4] There is more IS switching and use of combination IS. However, there are still gaps.

Late-onset ILD in SSc is well described in the EUSTAR database and other registries.[12,13] The CSRG identified the usual factors associated with ILD, such as dcSSc, male sex, elevated markers of inflammation, anti-topoisomerase I autoantibodies, and concomitant myositis, whereas patients with SSc with late-onset ILD had more inflammatory arthritis and anti–RNA-polymerase III autoantibodies and were less likely to identify as White.[13]

It is difficult to predict which patients with SSc-ILD will experience progression within the next year. In the EUSTAR database, most patients were slow progressors, with about one-fourth progressing within one year and two-thirds showing progression over five years. Rapid progressors over the follow up were rare (8%).[14] The effects of the slowing of progressive pulmonary fibrosis in SSc-ILD have been demonstrated with nintedanib and more recently with nerandomilast.[3] The benefit of nintedanib in combination with IS has been shown in SSc, but it is being studied with nerandomilast.[15] The added value of combination antifibrotic therapies use routinely with IS in SSc-ILD for slowing the progression of ILD in patients with worsening ILD and/or fibrotic changes on high-resolution computed tomography will be important to study because there can be the potential for polypharmacy and high costs depending on the relevance of combination treatment (eg, 2 IS and 2 antifibrotics) in patients with SSc-ILD who are progressing.

In conclusion, the study by Campochiaro et al[4] has demonstrated improvements in SSc-ILD, but in the future we need to better identify who will develop ILD, who will progress, and when and how continue to apply prevention/treatment strategies, in order to understand optimal treatment for patients with SSc-ILD.

AUTHOR CONTRIBUTIONS

All authors contributed to at least one of the following manuscript preparation roles: conceptualization AND/OR methodology, software, investigation, formal analysis, data curation, visualization, and validation AND drafting or reviewing/editing the final draft. As corresponding author, Dr Pope confirms that all authors have provided the final approval of the version to be published and takes responsibility for the affirmations regarding article submission (eg, not under consideration by another journal), the integrity of the data presented, and the statements regarding compliance with institutional review board/Declaration of Helsinki requirements.

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EDITORIAL

Type I Interferon and Still Disease

Randy Q. Cron, MD, PhD[1] and Karen B. Onel, MD[2]

The treatment for Still disease (SD) in children (systemic juvenile idiopathic arthritis) and adults has been revolutionized by biologics targeting interleukin-1 (IL-1) and IL-6.[1] However, some patients with SD remain difficult to treat, particularly those complicated by macrophage activation syndrome (MAS) and/or lung disease (LD). Controversy surrounding the use of cytokine-targeted biologics and the appearance of SD-LD focuses on drug reactions (eg, drug reaction with eosinophilia and systemic symptoms [DRESS]) versus the cytokine plasticity hypothesis (altered T cell phenotypes) associated with the use of IL-1 and IL-6 inhibitors.[2] In the current issue of *Arthritis and Rheumatology*, Marques and colleagues explore the pathophysiology of SD-LD by examining type I interferon (IFN-I) responses and genetic contributions.[3]

Fifty-seven children and adults with SD referred to the NIH, an admittedly confounded cohort with increased refractory disease, underwent one-time whole blood interferon-stimulated gene (ISG) expression analysis quantified by NanoString array. The resultant ISG-28 scores correlated more strongly with IFN-I (IFNα, IFNβ, IFNω) responsive genes than type II (IFNγ) responses, the latter of which are now being directly targeted by emapalumab in refractory SD-MAS.[4] Patients with SD and parents also underwent HLA typing and trio exome sequencing to explore rare candidate causative gene variants. In addition, clinical history and laboratory data (associated with SD and MAS) were obtained. The authors defined drug-associated immunologic reactions (DAIR), an alternative to the controversial DRESS designation, as anaphylaxis, severe injection site reactions, or generalized pruritic eruption in response to IL-1/IL-6 inhibitors. Correlations were explored among members of the cohort.

Interestingly, 74% of the NIH cohort was female, higher than typically seen for SD, even in those with SD-LD (19% of this cohort).[5,6] Consistent with prior studies, 73% with SD-LD had a history of MAS,[5] and 73% of patients with SD-LD harbored HLA-DRB1*15, previously linked with DRESS.[7] ISG-28 scores were elevated in 16 patients with SD (28%) above the 95% confidence intervals of healthy patients, and the scores did not correlate with disease activity. However, the ISG-28 scores were associated with both SD-LD and with DAIR, with nonsignificant trends toward associations with HLA-DRB1*15 and a history of MAS. Indeed, 100% of those with both HLA-DRB1*15 and high ISG-28 scores had DAIR. Similarly, HLA-DRB1*15 combined with a high ISG-28 score was tightly linked to SD-LD. Patients with SD-LD were also noted to have elevated peripheral blood eosinophil counts. Notwithstanding the associations, there were several patients with these clinical (eg, MAS) or genetic (HLA-DRB1*15) phenotypes/genotypes who had low ISG-28 scores.

Despite high ISG-28 scores associated with DAIR, none of the patients with high ISG-28 scores received anti–IL-6 therapy, previously reported to be a risk factor for DRESS.[7] In addition, the use of IL-1 inhibitors did not differ statistically between the high and low ISG-28 score groups. These findings reinvigorate the challenge of establishing cause and effect versus prior reported associations. Recently, there was found to be no association between IL-1 or IL-6 inhibitors and parenchymal LD among a cohort of 90 patients with SD-LD.[8] A smaller adult SD-LD cohort with pulmonary artery hypertension (PAH; n = 16), however, reported associations of SD-LD and PAH with MAS, eosinophilia, HLA-DRB1*15, and drug reactions to IL-1/IL-6 inhibitors.[9] Thus, the associations among SD-LD with or without PAH, biologic therapeutics, DAIR/DRESS, HLA-DBR1*15, and IFN-I remains unclear.

To further explore the role of IFN-I in SD, Marques and colleagues used trio exome sequencing and overrepresentation analysis. Eighty-nine unique candidate genes relevant to IFN-I were enriched in those with high ISG-28 scores.[3] Genes linked to autophagy, IFN-I production, toll-like receptor (TLR) signaling, and macrophage activation were enriched. Complementary analysis with Enrichr software confirmed the associations with autophagy and TLR signaling. These genetic associations linked to IFN-I production provide rationale for the importance of IFN-I in a subset of patients with SD. Others have previously noted a subset of patients with SD with a high IFN-I signature lending credence to

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this hypothesis.[10] The recognition of high IFN-I expression among patients with SD has implications for therapeutics.

If elevated IFN-I is contributing to SD manifestations, then blocking signaling through the IFN-I receptor with the monoclonal antibody anifrolumab could be considered. Alternatively, several JAK inhibitors (JAKi) disrupt signaling downstream of both IFN-I and IFNγ receptors, as well as several other cytokine receptors. Thus, when JAKi appear to exert benefit in SD, it is difficult to attribute the effect to blockade of a specific cytokine-signaling pathway. There may be some preference for ruxolitinib among JAKi in treating refractory SD in general.[11] JAKi have been explored for specifically treating SD-LD with some success but also are linked with MAS-associated death when stopping IL-1 blockade.[12] Herein lies the conundrum, whether or not to treat SD with IL-1 or IL-6 inhibitors, or perhaps IFN-I inhibition.[2]

We cannot forget the progress made in treating the once devastating disease of SD before the use of cytokine inhibitors (specifically, IL-1 and IL-6 blockade).[1] Curtailing MAS alone has saved countless lives. However, the question remains; is the use of IL-1 and IL-6 inhibitors the cause of frequently fatal SD-LD, whether due to DRESS, DAIR, cytokine plasticity, or something else? Indeed, SD-LD may be inherent in a subset of patients with SD, as some present with eosinophilia before treatment, and many patients with SD develop LD in the absence of IL-1 and IL-6 inhibition.[13] Some individuals with SD-LD have even resolved their disease by addition of aggressive therapies while leaving IL-1 inhibition in place.[6] Returning to prolonged glucocorticoid use and all the associated morbidity will likely not be the answer. The identification of risk factors and screening for them may help guide alternative approaches to treating SD (Table 1).[14,15] Unfortunately, at present, identifiable risk factors incompletely predict LD development among patients with SD and therefore cannot be used to deprive patients of life-saving medications or miss at-risk patients who lack these particular risk factors. Predicting which patients will respond to which therapeutics is the ultimate precision medicine goal. Fortunately, the armamentarium available to treat SD and SD-LD is ever-expanding, including IFN-I and IFNγ inhibitors and, potentially, blockade of IL-18,[16] a prominent cytokine in SD-MAS.

By exploring the role for IFN-I in SD and SD-LD, Marques and colleagues have advanced the science/knowledge for this rare condition.[3] Although many of the correlations were made using a single time point analysis of ISG-28 scores in patients with largely refractory SD, the genetic underpinnings support a role for IFN-I in a subset of individuals with SD. How this study addresses the average patient with SD is unclear, but it does provide insight for some of the sickest patients with SD. The question remains as whether to treat patients with SD with LD risk factors (eg, MAS, HLA-DRB1*15) using IL-1 or IL-6 inhibitors for risk of LD development. Moreover, the report by Marques and colleagues raises the question of whether to target IFN-I with JAKi or monoclonal antibody approaches for SD-LD (Table 1).[3] And although it will take some time to better comprehend the genetic and potentially iatrogenic contributions to the pathophysiology of SD-LD, identifying beneficial therapy is likely a mission possible.

Table 1. Speculated risk factors, screening items, and potential targeted therapeutics for Still disease–associated lung disease*

Risk factors	Screening items	Therapeutic options
Trisomy 21	**History**: digital clubbing	JAKi
<2 y of age	Respiratory symptoms	Anifrolumab (anti-IFNAR)
High disease activity	New atypical rash	Emapalumab (anti-IFNγ)
Macrophage activation syndrome	**Imaging**: high resolution chest computerized tomography	Continued IL-1 or IL-6 inhibition
Congenital heart disease	Chest x-ray	IL-18 inhibition
Drug reaction to biologics	Echocardiogram	Calcineurin inhibition
HLA-DRB1*15	**Laboratory findings**: IFN-I score	
	Bronchoalveolar lavage	
	Eosinophilia	

* IFN, interferon; IFNAR, interferon-alpha/beta receptor; JAKi, JAK inhibitor; IL, interleukin.

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EDITORIAL

Nationwide Trends in Medication Use and Adverse Outcomes in Lupus Pregnancies: Progress and Persistent Gaps

Bella Mehta, MBBS, MS, MD[1,2], and Jane E. Salmon, MD[1,2]

Pregnancy in systematic lupus erythematosus (SLE) has long been a clinical concern for both patients and clinicians. SLE predominantly affects women of childbearing age and disproportionately impacts individuals from historically marginalized racial and ethnic groups and those with lower socioeconomic status. Historically, pregnancy was discouraged for individuals with SLE due to high rates of morbidity and mortality during pregnancy. In the 1960s, fetal loss exceeded 40% and maternal complications were very common.[1] Even today, the maternal–fetal medicine guidelines recommend that pregnancy be generally discouraged in patients with severe maternal risk, including patients with active nephritis; severe pulmonary, cardiac, renal, or neurologic disease; recent stroke; or pulmonary hypertension.[2] Qualitative studies in SLE pregnancies continue to highlight persistent themes of uncertainty surrounding pregnancy in this population.[3] Over the past few decades, however, improvements in disease monitoring, treatment strategies, and risk stratification have dramatically reshaped expectations for SLE pregnancies.[4] Against this backdrop, in this issue of *Arthritis & Rheumatology*, Nguyen et al reports a nationwide Swedish study examining adverse pregnancy outcomes and medication use from the past two decades in patients with SLE offers timely insight.[5]

This descriptive study leveraged comprehensive Swedish national health registers to identify 1,417 SLE pregnancies and 14,133 matched non-SLE pregnancies between 2003 and 2022. The analysis focused on temporal patterns in key adverse pregnancy outcomes—preeclampsia, preterm delivery, and small-for-gestational-age (SGA) births—as well as trends in use of antimalarials, glucocorticoids, and low-dose aspirin. Overall, adverse pregnancy outcomes remained higher in SLE pregnancies compared with matched controls. However, in contrast to the general population, in which rates remained stable, adverse pregnancy outcomes in SLE showed significant declines. Preeclampsia decreased from 14.1% to 9.6%, preterm delivery decreased from 25.9% to 11.2%, and SGA birth decreased from 10.6% to 7.0%. Because they did not distinguish early (severe) preeclampsia from late (mild) preeclampsia, conditions with very different consequences to mothers and offspring, changes in the severity of preeclampsia over time could not be assessed. Improvements in outcomes were driven mainly by nulliparous pregnancies, whereas rates among parous women fluctuated without a clear trend. Among pregnancies complicated by antiphospholipid syndrome (APS), reductions were modest and less consistent. Medication use changed markedly over time. Antimalarial use during pregnancy rose from 23.9% to 76.5% and low-dose aspirin use from 39.8% to 85.6%. Glucocorticoid use declined only slightly, from 43.2% to 40.1%. Notably, the delivery rate in people with SLE increased from 21 to 36 per 1,000 individuals with SLE, consistent with increased pregnancy attempts over time.

The observed declines in adverse pregnancy outcomes align with broader improvements in SLE pregnancy outcomes documented over the past several decades.[4] Prior work has shown that modern management—including disease stabilization before conception, expanded access to rheumatology–maternal–fetal medicine comanagement, increased hydroxychloroquine use, and targeted thromboprophylaxis—has substantially improved fetal and maternal outcomes.[6] APS-specific findings provide an important contrast. Despite improved recognition and standardized diagnostic criteria for APS—leading to more appropriate use of anticoagulation and low-dose aspirin—declines in adverse pregnancy outcomes among women with SLE and APS were less pronounced. This likely reflects the inherently higher baseline risk in this population and the persistent challenge of preventing placental complications. Whereas many large SLE studies using administrative data have historically been unable to reliably

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capture APS,[7] the present study successfully identifies this subgroup. The high rates of adverse outcomes seem to be in line with multicenter Antiphospholipid Syndrome Alliance for Clinical Trials and International Networking Clinical Database and Repository, in which 27% patients had early pregnancy loss and 23% experienced pregnancy-related morbidity, and the Predictors of Pregnancy Outcome: Biomarkers in Antiphospholipid Antibody Syndrome and Systemic Lupus Erythematosus (PROMISSE) study, in which adverse pregnancy outcomes occurred in 23% of patients with SLE with any antiphospholipid antibodies.[8,9]

The finding that improvements were primarily driven by nulliparous pregnancies is also thought-provoking. Historically, many individuals with SLE—especially those with mild disease—avoided pregnancy due to fear of complications. Increasing confidence in modern management may be encouraging more first pregnancies among individuals with lower-risk disease profiles, shifting overall trends. Several studies now support that achieving stable disease for at least six months before conception significantly reduces risk.[10] In general, complications, such as preeclampsia, are more common in first pregnancies, and they are associated with increased risk of similar adverse pregnancy outcomes in subsequent pregnancies.[11]

This study is a well-designed epidemiologic analysis leveraging Sweden's high-quality national registers, which provide near-complete coverage and reliable linkage across health databases. Its ability to examine both clinical outcomes and medication exposures over two decades is particularly valuable given that treatment patterns are rarely captured in long-term population studies of SLE. The inclusion of a non-SLE control group and stratified analyses by APS, nephritis, and parity—clinically relevant factors in pregnancy planning—strengthen the study's validity. Although the number of pregnancies complicated by SLE nephritis was low, adverse outcomes in this subgroup also declined over time, from 50% to 15.1%.

However, several limitations merit emphasis. First, despite nationwide coverage, the sample of 1,417 pregnancies over 20 years is relatively small compared with registry studies in other countries where the population or prevalence of SLE is higher.[12] Second, as with other epidemiologic data, granular clinical data—such as SLE disease activity, serologies, flare characteristics, or damage accrual—were unavailable, limiting interpretation of those on pregnancy outcomes and treatment choices. This is especially relevant when interpreting medication patterns—for example, the persistently high glucocorticoid use (>40%) despite guideline recommendations to minimize steroids. Without knowing whether steroids were used in short bursts or continuously, or whether they reflected clinician or patient preferences, interpretation remains complex. Finally, although country of birth was noted in the methods, the results do not provide detailed stratification, which could illuminate disparities between Swedish-born and immigrant populations.

The cohort is overwhelmingly composed of individuals from a homogeneous, predominantly White, highly educated population with universal health care access. The Swedish context likely reflects high baseline access to care, early disease detection, and adherence to pregnancy and medication guidelines. Whether similar improvements will be observed in more diverse populations is uncertain. As a result, the findings may not generalize to populations disproportionately affected by severe SLE—particularly people of color or those impacted by socioeconomic inequities.

Global disparities in pregnancy outcomes remain stark. A recent meta-analysis from Latin America, aggregating 44 studies and over 2,100 pregnancies, reported substantially higher rates of preeclampsia (11%–52%), preterm delivery (18.6%–70.8%), and fetal loss compared with high-resource countries.[13] Within the United States, the Lupus in Minority Populations: Nature versus Nurture (LUMINA) study demonstrated significant risks of adverse pregnancy outcomes in multiethnic cohorts and those with fewer years of education.[14] Similarly, the multicenter PROMISSE study found an approximately three-fold higher risk among African American and Hispanic women. Adjustment for socioeconomic status attenuated disparities in some of these groups, suggesting social determinants of health—including education, income, and race—play a key role in outcomes in this high-risk population.[15]

This study carries several important implications for both clinical practice and future research. For clinicians, the overarching message is one of reassurance and opportunity: with careful planning, sustained disease control, and guideline-based management, pregnancy outcomes for individuals with SLE continue to improve. The substantial rise in antimalarial and low-dose aspirin use over the study period reflects increasing adherence to evidence-based guidelines and likely contributes meaningfully to the improvements in adverse pregnancy outcomes; yet, the fact that hydroxychloroquine use remains below universal uptake highlights ongoing gaps in counseling, medication reassurance, and coordinated rheumatology–obstetrics care. At the same time, the persistently high use of glucocorticoids—despite well-recognized maternal and fetal risks—suggests that steroid minimization remains an unmet goal, potentially driven by disease activity, clinician practice patterns, or patient preferences for familiar therapies, all underscoring the need for continued education on steroid-sparing strategies. The more modest improvements observed in APS-associated pregnancies reinforce ongoing challenges in this subgroup and point to the need for better risk stratification, optimized anticoagulation approaches, and exploration of adjunctive therapies aimed at inflammation and placental dysfunction. Importantly, because this Swedish cohort reflects a largely homogeneous and high-resource population, questions of global generalizability remain; future studies in more diverse populations with attention to social determinants to health—race and ethnicity, socioeconomic status, and health

care access—are critical. Overall, the improvement in outcomes strengthens the central role of preconception counseling, tight disease control, and coordinated multidisciplinary care, reinforcing the message that well-managed SLE is increasingly compatible with safe and successful pregnancy. The study provides robust evidence for physicians and policymakers to address gaps in care and optimize treatment strategies for women with SLE.

AUTHOR CONTRIBUTIONS

Both authors contributed to at least one of the following manuscript preparation roles: conceptualization AND/OR methodology, software, investigation, formal analysis, data curation, visualization, and validation AND drafting or reviewing/editing the final draft. As corresponding author, Dr Mehta confirms that both authors have provided the final approval of the version to be published, and takes responsibility for the affirmations regarding article submission (eg, not under consideration by another journal), the integrity of the data presented, and the statements regarding compliance with institutional review board/Declaration of Helsinki requirements. Both authors contributed to the investigation, formal analysis of the data, and writing, reviewing, and editing of the manuscript.

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NOTES FROM THE FIELD

Revisiting the Ethics of Urate-Lowering Therapy Clinical Trials for Gout Management

Lisa K. Stamp,[1,2] Dien Ho,[3] and Nicola Dalbeth[4,5]

Introduction

The early 2000s saw a wave of randomized controlled trials (RCTs) of new urate-lowering therapies (ULTs) used in the management of gout. These trials compared the novel medications with placebo or relatively low doses of allopurinol.[1,2] In 2016, Shmerling raised concerns about the design of these trials, advocating for more ethical gout trials that "i) limit enrolment to individuals with gout refractory to appropriately dosed conventional therapies, ii) eliminate placebo arms, iii) routinely provide anti-inflammatory prophylaxis to reduce gout flares, and iv) allow appropriate up-titration of urate-lowering treatments in comparator arms."[3] In this viewpoint, we revisit ethical principles and standards for contemporary phase III and IV ULT clinical trials.

What has been happening recently?

We undertook a rapid literature review[4,5] of RCTs and RCT protocols of ULT for gout published in the last five years. A total of 16 phase III and IV trials were identified (Supplementary Material). Of these, 2 trials (13%) recruited individuals with refractory gout, 12 (75%) had no placebo or placebo-equivalent arm, and 10 (63%) provided routine anti-inflammatory prophylaxis against gout flares. In 10 of 15 trials of oral therapy (67%), ULT was started at a low dose and increased to a set maximum dose rather than to target urate.

Are Shmerling's recommendations fit for purpose in 2026 and beyond?

(i) Should trials of ULT be limited to enrolling individuals with refractory gout? Shmerling recommended enrollment should be limited to people with gout that is "refractory to appropriately dosed conventional therapies."[3] This recommendation raises several issues. First it assumes that existing ULTs are so good when appropriately dosed and that no other ULT could be used first line. However, a new ULT might have benefits over existing therapies, such as more predictable urate-lowering efficacy, fewer gout flares on initiation, less frequent dosing, better tolerability, or fewer adverse events. Second, comparing a novel therapy with a conventional therapy in those who experienced failure of conventional therapies may undermine the external validity of a study that aims to investigate the efficacy of a treatment for the general gout population. Additionally, the reasons for failure of existing ULTs in real-life clinical practice are complex and may not be solved by changing to a different ULT. Thus, the inclusion criteria for participants in any clinical trial of ULT need to be aligned with the primary research aim, the goals of treatment, and the potential benefits and harms of the agent, rather than restricted to those with refractory disease.

(ii) Is a placebo comparator ever ethically justifiable in a phase III or IV ULT trial? Placebos have been used in clinical trials as the comparator against which the efficacy and safety of the medication under investigation is determined. In short-duration, early-phase I and II clinical trials, placebo is justified to determine dosing for efficacy and safety. However, for longer-duration trials and phase III and IV trials, the use of placebo presents greater ethical challenges. The Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Participants[6] states that a placebo or no intervention is only acceptable if no proven intervention exists or if there are "compelling and scientifically sound methodological reasons the use of any intervention other than the best proven one(s), the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention; and the participants who receive any intervention other than the best proven one(s), placebo, or no intervention will not

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be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention." In the case of gout, there are readily available standard of care therapies that are superior to placebo with respect to urate lowering[7]; therefore, the use of placebo is not ethically justifiable in most situations. The exceptions are when a urate-lowering medication is being trialed in a situation in which it is not routinely recommended (eg, those with a single flare or very infrequent flares), when all participants receive some form of ULT and are randomized to either a second ULT (investigational product) or placebo, and/or in truly refractory gout when all other ULTs are contra-indicated or have failed. These principles are not aligned with the 2019 European Medicines Agency Guideline on clinical investigation of medicinal products for the treatment of gout, which states that for confirmatory trials "In general, parallel, randomized, double-blind, placebo-controlled trials should be performed for a minimum of 6 months."[8] This guideline may lead to prolonged exposure to hyperuricemia without appropriate ULT.

(iii) Should anti-inflammatory prophylaxis be provided routinely when starting ULT? Anti-inflammatory prophylaxis is recommended for up to six months when starting ULT to prevent gout flares.[9,10] Colchicine or nonsteroidal anti-inflammatory drugs are the recommended first line agents with low dose glucocorticoids reserved for those with contra-indications or lack of effect with these agents. Of note, in a retrospective cohort study, fewer cardiovascular events occurred during the six-month period of colchicine anti-inflammatory prophylaxis when commencing ULT.[11] These potential benefits need to be weighed against potential harms. All these anti-inflammatory agents can have adverse effects, and there is also an increase in gout flares after discontinuing anti-inflammatory prophylaxis,[12] which, for some individuals, will alter the risk–benefit balance.

We consider that anti-inflammatory prophylaxis should be offered to every participant in trials commencing ULT. Whether anti-inflammatory prophylaxis is used must be a joint decision between the health care provider and the participant, respecting the participant's autonomy and safeguarding the participant's well-being by balancing the potential risks and benefits of the available agents for the individual. From an ethical perspective, unless the trial is specifically designed to investigate the effects of anti-inflammatory prophylaxis, if the individual has made an informed decision that the potential risks outweigh the potential benefits of anti-inflammatory prophylaxis or if there is prior intolerance or contra-indication to anti-inflammatory prophylaxis medications, there is no obvious reason why they should not be eligible to participate in a ULT trial.

(iv) Should appropriate up-titration of ULT be permitted in comparator arms? Shmerling suggested that participants in the "standard of care" arms of some trials were receiving care that the majority of rheumatologists would consider "suboptimal," and the failure to up-titrate allopurinol in these trials resulted in loss of equipoise because there was little doubt that fixed dose allopurinol could reasonably be expected to be less effective than the "novel agent," thereby introducing bias in favor of the "novel agent."[3] This loss of equipoise and positive bias toward the novel agent was illustrated in the phase III febuxostat trials. In the pivotal "Febuxostat compared with allopurinol in patients with hyperuricemia and gout" (FACT) trial, the primary endpoint of serum urate <6.0/dL at the last three monthly measurements was achieved in 53% of participants receiving 80 mg of febuxostat, 62% of those receiving 120 mg of febuxostat, and 21% of those receiving fixed-dose allopurinol ($P < 0.001$ for the comparison of each febuxostat group with the allopurinol group), leading to claims that febuxostat was more effective than allopurinol.[1] However, in the more recent "Comparative effectiveness of allopurinol and febuxostat in gout management" trial, allopurinol and febuxostat were initiated at daily doses of 100 and 40 mg, respectively, with maximum titration to 800 and 120 mg, respectively, according to the serum urate target.[13] In this trial, there was no significant difference in the proportion of participants achieving target serum urate (81.1% allopurinol and 78.4% febuxostat).

Shmerling discussed that the "standard of care" arms in many ULT clinical trials do not reflect best practice. Standard of care in these studies has been based on the treatment that is accepted by medical experts as a proper treatment for a certain type of disease and that is widely used by health care professionals, for example, fixed low dose allopurinol. In comparison, best practice is recognized in major gout management guidelines as starting ULT at low dose with gradual dose titration, when possible, to achieve target serum urate[9,10] in order to decrease the risk of adverse effects and gout flares in the short term and to improve patient-reported outcomes such as flares and tophi over the long term. From an ethical perspective, modern clinical trials should offer best practice for comparator arms. However, we acknowledge the challenges dose titration creates in clinical trial design, especially for blinded trials that are required for regulatory approval.

Other ethical considerations

Need for a predetermined gout flare management plan. Gout flares are episodic, are unpredictable, and have a significant impact on patient quality of life. Early institution of gout flare therapy may shorten the flare duration. Like other chronic diseases, a flare action plan with a readily available supply of therapy is important for people with gout.

Posttrial access to ULT if refractory gout. When exiting any gout ULT clinical trial, participants need a defined management plan for ongoing ULT. This provision should be

Table 1. Recommendations for ethical design of contemporary phase III and IV ULT clinical trials*

	Shmerling[3]	Current review
Inclusion criteria	• Limit enrollment to study participants with gout that is refractory to appropriately dosed conventional therapies	• Align with the primary research aim, the goals of treatment, and the potential benefits and harms of the ULT under investigation, rather than restrict to those with refractory disease
Use of placebo	• Eliminate placebo arms	• Allow placebo for short-duration phase I and II trials • For phase III and IV trials, allow placebo if a urate-lowering medication is being trialed in a situation in which it is not routinely recommended (eg, those with a single flare or very infrequent flares) OR if all participants receive some ULT and are randomized to either a second ULT (investigational product) or placebo OR in truly refractory gout when all other ULTs are contra-indicated or have failed
Anti-inflammatory flare prophylaxis	• Routinely provide anti-inflammatory flare prophylaxis when starting ULT	• Routinely offer anti-inflammatory gout flare prophylaxis when starting ULT with shared decision-making about whether it is commenced • Decision not to take prophylaxis or intolerance/contra-indications to anti-inflammatory flare prophylaxis should not exclude participation in a ULT trial
Dose titration	• Allow appropriate up-titration of urate-lowering treatment in comparator arms	• All comparator ULT arms should adhere to best-practice ULT, including commencing at a low dose with gradual dose escalation to serum urate target unless such an approach is not possible (eg, pegloticase therapy)
Gout flare plan	• No comment	• Provide all study participants with a gout flare action plan and a readily available supply of the chosen flare treatment
Posttrial care	• No comment	• Provide ongoing gout management plan including ULT, including posttrial access to study medication when appropriate
Generalizability	• No comment	• Ensure the trial population is representative of the general gout population with respect to sex, ethnicity, and comorbidities

* ULT, urate-lowering therapy.

included within trial protocols. In those participants with truly refractory gout, when all other funded ULTs are contra-indicated or have failed, posttrial access to the intervention should routinely be offered if the intervention has been shown to be efficacious and reasonably safe, as outlined in the Declaration of Helsinki.[6]

Generalizability. Another key concern is whether participants in gout trials represent the general gout population. This is most evident in the exclusion of individuals with comorbidities associated with gout, especially chronic kidney disease,[14] and the underrepresentation of Indigenous populations.[15] It is imperative in large phase III and IV clinical trials that the trial population is representative of the general gout population.

Lessons from our own investigator-led gout clinical trials. Over the last 15 years, we have considered many of these ethical issues in the design of our own investigator-led clinical trials. The allopurinol dose escalation study[16,17] occurred in the context of standard of care allopurinol prescribing, which restricted allopurinol dose based on renal function. The aim of the allopurinol dose escalation study was to examine the safety and efficacy of nonrenal-based allopurinol dosing. To achieve this, we needed to compare outcomes in a group who received dose-escalated allopurinol (active arm) and a group who remained on allopurinol at a fixed renal-based dose (control arm). However, we considered it unethical to continue fixed allopurinol dose, which rendered individuals above target serum urate for two years, so designed the study so that the control arm began allopurinol dose escalation to achieve target urate at the end of year one. The allopurinol dose escalation trial also highlighted the need to include individuals with comorbidities that are common in gout populations.[16,17] Renal impairment was not an exclusion, and so it provided much-needed evidence about the use of allopurinol in those with renal impairment.

The Easy-Allo clinical trial[18] examines two different strategies for allopurinol dose escalation with no placebo arm. Blinding treatment strategy trials can present logistical challenges and add a degree of complexity that may risk unintentional unblinding. Although this trial is not blinded, the primary outcome of the percentage of participants achieving target urate at month 12 is less likely to be subject to bias because it is a laboratory measurement and is more resistant to investigators' biases. In the colchicine prophylaxis study[19] and the current Easy-Allo clinical trial,[18] all participants have an individualized gout flare management plan, have a best-practice allopurinol dose escalation, and are handed over to their ongoing primary care physician with a gout management plan at the end of the study.

Conclusions

Schmerling challenged gout researchers, pharmaceutical companies, and institutional review boards to conduct ethical

clinical trials that do not cause harm due to suboptimal ULT, particularly for participants randomized to comparator groups. This remains an imperative in contemporary clinical trial design. We acknowledge the tension between drug approval agency recommendations and the ethical principles we have discussed, particularly around the use of placebo. We challenge the drug approval agencies to consider whether their drug approval processes are ethically fit for purpose for ULT in gout management in 2026 and beyond. We also argue that other aspects of gout trial design should also be considered, as summarized in Table 1, to ensure that participants in trials of ULT receive best-practice gout care and that the results from clinical trials can be generalized to all people with gout. All data used in this research are already included in the article or the Supplementary Material.

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All authors contributed to at least one of the following manuscript preparation roles: conceptualization AND/OR methodology, software, investigation, formal analysis, data curation, visualization, and validation AND drafting or reviewing/editing the final draft. As corresponding author, Dr Stamp confirms that all authors have provided the final approval of the version to be published and takes responsibility for the affirmations regarding article submission (eg, not under consideration by another journal), the integrity of the data presented, and the statements regarding compliance with institutional review board/Declaration of Helsinki requirements.

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NOTES FROM THE FIELD

Big Data May Have Big Pitfalls: Ensuring Rigor in Rheumatic Disease Epidemiology

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Introduction

The creation of large databases of patient data has ushered in greater understanding of epidemiology and pathogenesis of rheumatic diseases such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), osteoarthritis, gout, and psoriatic arthritis. Identification of exposures and disease risk factors, characterization of gene–environment interactions, and elucidation of epigenetic, cytokine, metabolomic, and proteomic biomarkers have shed light on how these diseases develop and their outcomes. These insights may also lead to better diagnosis and treatment and potentially to strategies for prevention. Most large databases were not established for the prospective study of incidence or risk factors for chronic rheumatic diseases, but some may provide sufficient data to perform studies with valid results. This commentary examines best practice approaches and three common methodologic pitfalls facing investigators using large databases: correctly defining the disease population, properly characterizing the temporal relationship between exposure and disease onset, and identifying a relevant comparison population for these studies.

Understanding the study population and data: Identifying those with disease

The first challenge is establishing highly accurate disease diagnoses, which is critically important in ensuring the validity of epidemiologic studies examining risk factors such as exposures. Both high sensitivity (ie, accurately capturing as many of those with new-onset disease as possible) and high specificity (ie, not erroneously including those with other diseases) are critical for rigorous epidemiologic studies. There is an inherent trade-off between sensitivity and specificity, and ideally methods using for disease definition will yield a high positive predictive value (PPV) (ie, the proportion of individuals identified who truly have the disease).[1] Although high specificity and a high PPV are generally sought for rare rheumatic diseases for studies of genetics, gene–environmental interactions, and early biomarkers of disease, high sensitivity is prioritized in other types of studies, and the decision is the responsibility of the investigators. High specificity with low sensitivity could bias toward the inclusion of a subset of the sickest patients, who have many visits and are often hospitalized. Not only does this limit generalizability for rheumatic diseases that have heterogeneous severity and inconsistent follow-up visit schedules but it could also lead to spurious associations with exposures (eg, smoking, body mass index, and air pollution) that drive inpatient and outpatient visits for other causes and comorbidities (eg, cancer or cardiovascular disease).

Studies examining potential variation in access to care and health care disparities may need to prioritize sensitivity in case finding, casting a wider net for inclusion. For example, if a study of patients with SLE is aimed at examining variation in patient-level predictors of receiving guideline-driven high-quality care, inclusion of immunosuppressant use or many positive serologic test results in the definition of SLE would lead to inclusion of a population already receiving higher-quality care and with more severe disease, both biasing and limiting generalizability.

Although artificial intelligence methods may be used for case finding in large data sets in the future, the most accurate process today often requires laborious medical record review, such as searching for specific disease classification criteria, for example, the number of swollen joints, which is not always possible. Algorithms for identifying incident or prevalent rheumatic diseases often rely on multiple encounters, for which an appropriate *International Classification of Diseases* (ICD) or Systematized Nomenclature of Medicine (SNOMED) diagnosis code is used for billing, and the use of medications typically prescribed to treat the condition.[2–5] Many research groups have invested time in establishing the validity of methods to identify prevalent and incident

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Table 1. Common biases in observational studies*

Type of bias	Definition	Example
Selection bias	Systematic differences between those included in the study and those who are not	Studying risk factors for RA using only hospital patients may overrepresent severe disease cases.
Ascertainment (detection) bias	Systematic differences in how outcomes or exposures are identified between groups	Patients taking biologics are monitored more frequently, making comorbidities more likely to be detected.
Recall bias	Differential accuracy of recollection about exposures/events between groups	In a case-control study of lupus, patients may better recall sun exposure than controls.
Information (measurement) bias	Errors in how exposure, covariates, or outcomes are measured or classified	Using billing codes to define lupus may misclassify patients.
Immortal time bias	A period during which, by study design, the outcome cannot occur, often misclassified as exposed time	Classifying patients as "treated" before they filled the prescription gives them "immortal time."
Survivor bias	Only those who survive long enough to be included are studied, excluding early events	Studying RA outcomes among specialty clinic patients may exclude those who died earlier.
Disease severity bias	When disease severity influences both treatment choice and outcome	Patients with severe lupus are more likely to get biologics, making drugs look worse.
Healthy user bias	Patients who adhere to treatments often engage in healthier behaviors overall	Statin users may appear to have lower mortality partly due to healthier lifestyle.
Observer bias	Systematic differences in how outcomes are recorded due to observer's knowledge	Health care providers who know patients are taking glucocorticoids are more likely to note weight gain.
Channeling bias	Tendency to give certain treatments to patients with particular prognostic characteristics	Physicians prescribe newer biologics to younger patients, biasing results.
Protopathic bias	Early symptoms of an outcome not yet diagnosed influence exposure	NSAIDs prescribed for early RA symptoms make them appear to cause RA.
Surveillance bias	Exposed groups are observed more closely, leading to higher detection rates	Cancer survivors get more incidental nodules detected than the general population.
Lead-time bias	Earlier detection mistaken for improved survival when prognosis is unchanged	Screening detects lupus earlier, appearing to improve survival.
Length-time bias	Screening detects slower-progressing cases, giving illusion of better prognosis	Screening for ILD in RA identifies indolent cases with longer survival.
Loss to follow-up bias	Differential dropout rates between groups lead to noncomparable groups	Patients with severe lupus drop out more often, underestimating morbidity.

* ILD, interstitial lung disease; NSAID, nonsteroidal anti-inflammatory drug; RA, rheumatoid arthritis.

disease in different databases.[3,6,7] Although including the rheumatologist's diagnosis of a rheumatic disease increases the PPV substantially, medical provider specialty is unfortunately infrequently available.[5] Some databases and cohorts rely on participant self-report to identify prevalent or incident disease. It is important to note that patient self-report alone has not been proven to be valid for identifying rheumatic diseases in many cases. For example, only 7% of the self-reports of new diagnoses of SLE among participants in the Nurses' Health Study could be validated by medical record review.[8]

Understanding the study population and data: Timing of exposure and outcome

Understanding the temporal relationship of the predictor or exposure (eg, smoking, body mass index, serum proteomics) and the outcome (eg, new onset of RA) is a second significant challenge posed in using large patient registries and databases. Rigorous prospective studies examine exposures before the development of disease, but it is challenging to precisely pinpoint the date of disease onset in chronic rheumatic diseases. Conditions such as RA and SLE often develop gradually and do not immediately lead to hospitalization, unlike a myocardial infarction. Misdating the onset of disease may lead to protopathic bias or reverse causation (see Table 1), in which an event in the future may paradoxically be thought to cause an event in the past. For example, the onset of RA may cause a patient to change their lifestyle, such as taking more multivitamins. If the diagnosis date assigned by the investigator is later than the actual date of onset, then multivitamins may be erroneously perceived as a causal exposure. With the exception of genetic factors as predictors, cross-sectional studies limit interpretation of causality because both the exposure and the outcome are identified at the same point in time.

When participants are required by the study design to live for a period of time after exposure but before the outcome can be captured, immortal time (or time-related) bias can be introduced. Spurious associations attributable to this type of bias are common in studies of rheumatic diseases.[9] A classic example is the reported marked decrease in the risk of major coronary heart disease (CHD) among women in the Nurses' Health Study who took estrogen with progestin compared to that in women who

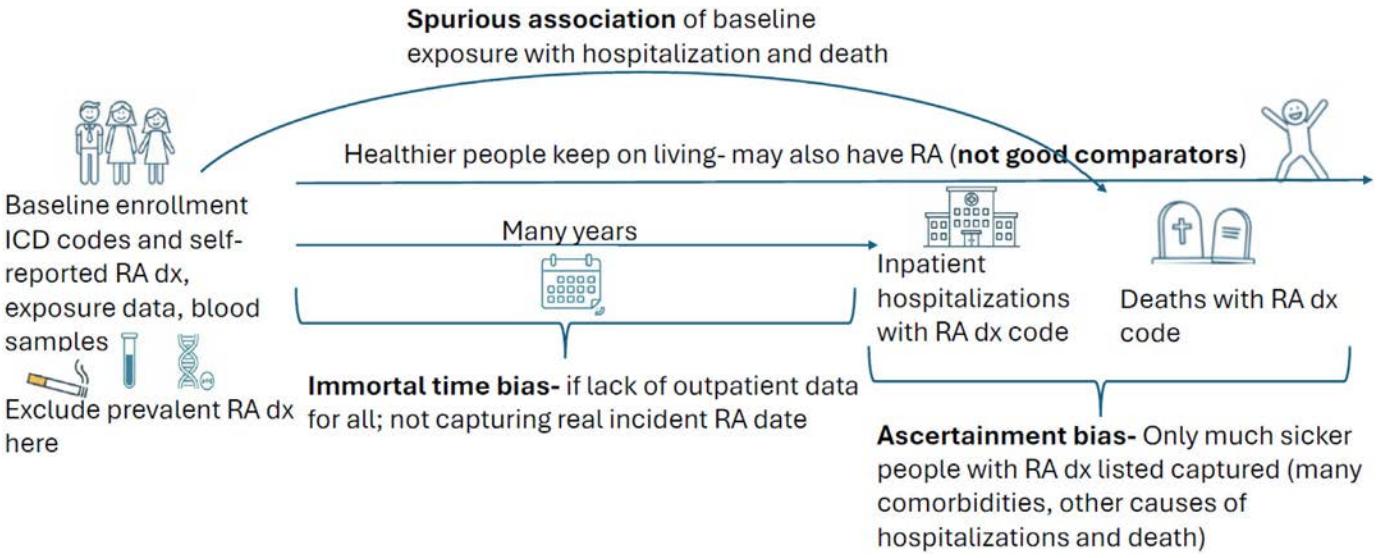

Figure 1. Illustration of how a study in a large data set or biobank not set up as a truly prospective cohort, such as the UK Biobank, if inappropriately used, is flawed by immortal time bias, ascertainment bias, and not using appropriate comparators, leading to spurious associations of baseline exposures with "incident RA," identified in inpatient hospitalizations and death data. dx, diagnosis; ICD, *International Classification of Diseases*; RA, rheumatoid arthritis.

took estrogen alone.[10] A subsequent large randomized trial in the Women's Health Initiative reported increased risk of CHD with this combined therapy.[11] The differences in the results could be largely explained by immortal time in the cohort study design, which required a span of follow-up time during which participants were alive after exposure but the outcome was not assessed.[12]

Temporal relationships between exposure and disease outcome are confused when hospital discharge diagnoses or death data are used to identify the dates of incident rheumatic disease. Many patients with rheumatic diseases are never admitted to a hospital for these diagnoses and typically do not die as a direct result of these diagnoses either. In past studies of disease incidence, the date of hospitalization for a nonrheumatic disease indication that includes the ICD or SNOMED code for a rheumatic disease has been assigned as the "diagnosis date" for that rheumatic disease. Chronic rheumatic diseases such as SLE or RA actually may have been diagnosed years before a hospital visit, but this would not have been identified without outpatient records. This misidentification of the incident disease date due to using mainly hospital diagnoses and death records has been made in studies employing baseline exposure data from the UK Biobank and outcomes of incident autoimmune diseases identified in linked inpatient and death data but lacking complete general practitioner (GP) outpatient data[13–21] (Figure 1).

Understanding the study population and data: Selecting the comparison population

A third major challenge is the choice of the optimal population for comparison, even within the same data set. Epidemiologic studies compare the exposure to a given risk factor among patients who develop the outcome of interest (ie, new rheumatic disease) versus those without this outcome. It can sometimes be difficult to identify a comparison population that has had the same opportunity to be correctly diagnosed at the onset of the disease of interest. Comparing patients who are foreseen in the hospital for a rheumatic disease to a general healthier population with fewer hospital admissions and deaths could induce a strong ascertainment bias. A risk factor that could cause hospitalization for any reason (eg, air pollution, obesity, lack of physical exercise, or smoking) will be found to be strongly related to the rheumatic disease "outcome." Patients in studies in which incident rheumatic disease was identified through hospital records and death data are likely not comparable to patients who were not seen in the hospital and/or did not die with this condition (Figure 1). Thus, carefully considering the possibility of many biases is imperative during study design (Table 1). Investigators should try to ensure that the comparison population is similar to the study population to limit the possibility of incorrect findings due to artifacts in study design.

We are fortunate to have a growing number of publicly available, rich sources of large population data, including the UK Biobank, the All of Us cohort, the US National Health and Nutrition Examination Survey, and the National Hospital Inpatient Survey, as well as administrative data from TriNetX, Komodo, and others. However, we urge caution in the use and interpretation of these data sets to avoid unintentionally misleading conclusions. Unfortunately, these errors have been propagated given misunderstanding and emulation of past published but erroneous studies and by "click-data science."[22]

The UK Biobank in particular has a wealth of well-characterized-risk factor information on participants cross-sectionally at baseline. Linkage to primary care GP records is available for more than half the cohort,[23] with plans to make these outpatient data on all patients in the near future. False associations may be created due to disease misclassification and use of hospital and death data alone for identifying "new-onset disease," which may have been present for many years (despite no earlier self-report) and only associated with a hospitalization at a future date (Figure 1). We applaud the ongoing efforts of UK Biobank leaders to link to GP records for all participants. In the meantime, the subset of participants whose primary care GP records are linked and coded are more suitable for analyses seeking causally associated risk factors for chronic, slow-onset rheumatic diseases diagnosed and treated in the outpatient setting.

Conclusions

In summary, large databases are an important resource for studying the epidemiology of rheumatic diseases, but the use of big data has big potential pitfalls (Table 1). Many large available databases were not designed for the study of incidence or risk factors for rheumatic diseases, limiting the ability to conduct accurate and replicable studies. When considering the use of large available databases, it is imperative to carefully consider potential biases that can be introduced by flaws in study design. Rigorous epidemiologic approaches to identifying date of disease onset, strict application of validated criteria for disease diagnosis, and an understanding of the purpose, data collection, and limitations of the database are necessary to perform high-quality studies in which biases are minimized and the results are valid, reproducible, and generalizable.

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AUTHOR CONTRIBUTIONS

All authors contributed to at least one of the following manuscript preparation roles: conceptualization AND/OR methodology, software, investigation, formal analysis, data curation, visualization, and validation AND drafting or reviewing/editing the final draft. As corresponding author, Dr Costenbader confirms that all authors have provided the final approval of the version to be published and takes responsibility for the affirmations regarding article submission (eg, not under consideration by another journal), the integrity of the data presented, and the statements regarding compliance with institutional review board/Declaration of Helsinki requirements.

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REVIEW

Immune Checkpoint Inhibitor–Associated Inflammatory Arthritis

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Understanding the cellular and molecular mechanisms of T cell activation has enabled the identification of immune checkpoints, such as programmed cell death protein 1 (PD-1) and cytotoxic T-lymphocyte–associated protein 4 (CTLA-4), and the development of immune checkpoint inhibitors (ICIs), which have revolutionized cancer therapy. However, ICI cancer treatment is commonly associated with autoimmune side effects, including inflammatory arthritis (IA). ICI-IA occurs in approximately 6% of ICI-treated patients and often resembles rheumatoid arthritis phenotypically, although it is generally seronegative. Imaging often demonstrates joint inflammation in patients with ICI-associated joint pain, even in the absence of joint swelling. The ICI-IA synovium is characterized by clonal expansion of actively proliferating $CD38^{hi}CD127^{-}CD8^{+}$ T cells and expansion of interleukin-$1\beta^{hi}$ macrophages, communicating along CXCL10-CXCR3 and CCR1-CCL3/5 axes. Activation of naive $CD4^{+}$ T cells and impaired Treg cells play a synergistic and amplifying role, especially in the setting of combination ICI (anti–CTLA-4 plus anti–PD-1). ICI-IA has the potential to teach us about mechanisms underlying the biology and evolution of other forms of IA. In this review, we summarize our current understanding of ICI-IA and propose promising avenues for future research.

INTRODUCTION

Here, we start with an illustrative case of immune checkpoint inhibitor (ICI) associated inflammatory arthritis (ICI-IA), which is followed by a review of our current understanding of this condition.

Clinical case part 1

A 79-year-old man was diagnosed with renal cell carcinoma, accompanied by renal vein thrombosis and tumor extension into the renal pelvis. He underwent radical nephrectomy but 7 months later was found to have bone metastases. The patient was started on combination immune checkpoint inhibitor (ICI) therapy with anti–cytotoxic T-lymphocyte–associated protein 4 (CTLA-4) plus anti–programmed cell death protein 1 (PD-1). However, within 1 month of the first dose, he developed severe pain and swelling in his metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints and knees. His oncologist referred him to Rheumatology for grade 3 (interfering with self-care activities) arthritis and prescribed prednisone 15 mg daily. On presentation to Rheumatology 1 week later, the patient was found to have swelling of multiple MCP and PIP joints, knees, and ankles, and he had pain with range of motion of his shoulders. His Clinical Disease Activity Index score was 30, and his Health Assessment Questionnaire score was 1.4. Laboratory test results revealed an erythrocyte sedimentation rate of 83 mm/h, C-reactive protein level of 8.3 mg/dL (reference 0–1.0 mg/dL), rheumatoid factor (RF) of 25.3 IU/mL (reference <20 IU/mL), and negative anticyclic citrullinated peptide (anti-CCP) antibodies. The patient was diagnosed with ICI-associated inflammatory arthritis (ICI-IA).

Although this patient's arthritis was triggered by combination immunotherapy, his presentation, with symmetrical polyarthritis involving the large and small joints, elevated markers of inflammation, and a low-level RF is very reminiscent of rheumatoid arthritis (RA). What is ICI-IA? What is its relationship to RA and other forms of de novo IA? What can ICI-IA teach us about the transition from preclinical to clinical manifestations of these de novo diseases? These questions have preoccupied investigators over the last 5 to 10 years, and what follows is an overview of our current understanding of this new rheumatic autoimmune condition. This review draws from the published scientific literature; no primary data were used.

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Overview of immune checkpoint inhibitors

Understanding the cellular and molecular mechanisms of T cell activation has enabled us to identify immune checkpoints and develop ICIs, which have revolutionized cancer therapy.[1] Naive T cells require two signals for full activation: (1) binding of the antigen presented by the major histocompatibility complex on antigen-presenting cells (APCs) to the cognitive T cell receptor (TCR) on T cells and (2) costimulation by engagement of CD28 on T cells with CD80/86 on APCs. Once activated, T cells undergo robust proliferation and clonal expansion. Soon after activation, T cells express inhibitory receptors, termed immune checkpoints, on their surface to fine-tune the TCR signal and prevent unnecessary tissue injury.[2] Numerous checkpoints have been identified,[3] among which we will focus on CTLA-4 and PD-1 in this review as most reported immune-related adverse events (irAEs), including ICI-IA, arise from blockade of CTLA-4 and PD-1.[1]

CTLA-4. CTLA-4 inhibits the engagement of CD28 with CD80/86 because of its greater affinity for CD80/86, thereby inhibiting the second signal and terminating T cell activation. Treg cells, a specialized $CD4^+$ T cell subset that regulates immunity, constitutively express CTLA-4, which is one of their suppressive mechanisms.[4]

CTLA-4 knockout (KO) mice die within 4 to 6 weeks because of severe lymphoproliferative disorders involving the heart, lungs, and intestine.[5] Unopposed CD28 signaling mediated by lymphocyte-specific protein tyrosine kinase in the CD28 cytosolic tail[6] plays a key role in this lethal lymphoproliferation. Besides T cells, selective depletion of CTLA-4 on B cells results in expanded germinal centers and follicular helper T cells in secondary lymphoid organs as well as the emergence of various serum autoantibodies, suggesting that CTLA-4 is involved in humoral immunity as well.[7] Cases of patients with heterozygous germline mutations in CTLA-4 have been reported.[8,9] Consistent with findings in $CTLA\text{-}4^{KO}$ mice, these patients exhibit lymphocytic infiltration (predominantly $CD4^+$ T cells) into multiple tissues including the intestine, kidney, central nervous system, lungs, and bone marrow. They also develop hypogammaglobulinemia and recurrent infections. Cellular analyses revealed reduced CTLA-4 expression in Treg cells, impaired Treg suppressive function, and decreased CTLA-4–mediated transendocytosis. In addition, total B cells and class-switched memory B cells (IgM^- $CD27^+$) are also reduced in these patients.[8] Polymorphisms in the CTLA-4 gene have been reported in multiple autoimmune diseases including RA, systemic lupus erythematosus (SLE), multiple sclerosis, type 1 diabetes (T1D), and myasthenia gravis.[9] These observations suggest that CTLA-4 plays a pivotal role in autoimmune disease pathogenesis. Indeed, abatacept, a soluble fusion protein consisting of the extracellular domain of human CTLA-4 linked to a modified Fc portions of human IgG1, is being widely used in the treatment of RA, psoriatic arthritis, and juvenile idiopathic arthritis.[10]

PD-1. Within 24 hours of activation, T cells express PD-1 on their surface. The PD-1 signal down-modulates TCR signaling by abrogating phosphatidylinositol 3-kinase activity, one of the key components in the TCR signal.[11] Subsequently, the PD-1 signal attenuates the functions and survival of Teff cells. It is noteworthy that although the CTLA-4 signal is critical during T cell priming in secondary lymphoid organs, the PD-1 signal is important for effector cell functions and survival in peripheral tissues.[12] PD-1 has two ligands: programmed death-ligand 1 (PD-L1) and programmed death-ligand 2 (PD-L2). Constitutively, low-level expression of PD-L1 is found on major immune cell subsets including dendritic cells, macrophages, neutrophils, T cells, and B cells.[11] Corneal, syncytiotrophoblast, and Langerhans islet cells also constitutively express PD-L1.[13,14] Of note, PD-L1 is broadly inducible across tissues in response to inflammatory cytokines, including interferons (IFNs), tumor necrosis factor (TNF), and vascular endothelial growth factor (VEGF).[15] Thus, the induction of PD-L1 in tissues within an inflammatory milieu may be a protective mechanism to down-regulate Teff cell activity and prevent tissue injury.[16] In contrast to PD-L1, expression of PD-L2 is largely restricted to dendritic cells and macrophages.[14] In the tumor microenvironment, where T cells continuously encounter antigens, T cells progressively become less proliferative and produce fewer cytokines in response to the antigens, a state termed "exhaustion," in which PD-1 signaling plays a significant role.[17] In ICI-treated patients, PD-1 inhibitors activate $TCF\text{-}1^+$ progenitor exhausted T cells, promoting their differentiation into cytotoxic effector progeny that mediate antitumor immunity.[18–20]

Aged $PD\text{-}1^{KO}$ mice on a C57BL/6 background develop lupus-like phenotypes, including arthritis and glomerulonephritis, with predominant IgG3 deposition.[21] $PD\text{-}1^{KO}$ mice in a different mouse strain (BALB/c) develop spontaneous dilated myocarditis with IgG deposition.[22] In humans, genome-wide association studies reveal that PD-1 gene polymorphisms are associated with various autoimmune diseases, including RA, SLE, ankylosing spondylitis, multiple sclerosis, and T1D.[23] Soluble PD-1 binds PD-L1 and PD-L2 in the extracellular space, thereby preventing their engagement with membrane-bound PD-1 on T cells, promoting T cell activation. Serum levels of soluble PD-1 are increased in patients with RA, SLE, and primary Sjögren disease and correlate with disease activity.[24]

Guo et al[25] analyzed synovial tissues from healthy individuals and patients with osteoarthritis (OA), undifferentiated arthritis, early RA, and late RA. Compared with synovial tissues from healthy individuals and those with OA, a gene expression pattern similar to that seen after treatment with nivolumab, a PD-1 inhibitor, was highly enriched in synovial tissues from patients with early RA. This suggests there is an important role for down-regulated PD-1 signaling in RA pathogenesis, especially at the early stage.[25]

Indeed, peresolimab, a humanized IgG1 agonistic antibody to PD-1, has shown clinical promise in RA.[26]

CTLA-4 and PD-1. In summary, upon activation, T cells express immune checkpoints, which are receptors that provide inhibitory signals on the activated T cells to prevent excessive tissue damage. Animal and translational studies show that down-regulation of CTLA-4 and PD-1, two of the most commonly therapeutically targeted immune checkpoints, contributes to the development of autoimmune diseases. The soluble fusion protein CTLA-4-Ig and agonistic PD-1 antibodies are either used (CTLA-4-Ig) or under intensive investigation (PD-1) in rheumatology. Conversely, inhibiting PD-1 and CTLA-4 boosts the effector functions of antitumor T cells to eradicate cancer. ICIs, especially combination ICIs, are often associated with irAEs, including ICI-IA.

Immune related adverse events (irAEs)

ICI treatment commonly results in autoimmune side effects, termed irAEs. A large metanalysis of clinical trials demonstrated that irAEs occur in 74% (95% confidence interval [CI] 69%–79%) of patients treated with anti–PD-1or anti–PD-L1 and that they are high grade (grade 3–5) in 14% (95% CI 12%–16%).[27] The frequency of high-grade irAEs is much higher after combination ICI (anti–CTLA-4/PD-1; 41%, 95% CI 35%–47%), and these high-grade irAEs often occur early after ICI initiation.[27,28] High-grade irAEs may necessitate early ICI discontinuation and this, along with immunosuppressive treatments, may negatively impact cancer survival.

Immune checkpoint inhibitor associated inflamatory arthritis (ICI-IA)

ICI-IA occurs in approximately 6% of ICI-treated patients[29] a median of 4 (interquartile range 1–6) months after ICI initiation.[30] Unlike most other irAEs, ICI-IA tends to persist even after ICI discontinuation.[31] Risk factors for ICI-IA persistence include ICI-IA severity and treatment with combination ICI.[31] Clinically, ICI-IA-resembles RA in approximately 60% of cases, but it can also resemble polymyalgia rheumatica (15%) or be oligoarticular and more akin to a spondyloarthropathy.[30] Enthesitis and tenosynovitis can also be seen.[32] There is no female predominance in ICI-IA as there is in RA, and patients with ICI-IA are older on average than patients with RA.[33] Treatment of ICI-IA often borrows from that of primary rheumatic diseases and can include glucocorticoids, methotrexate, and/or biologic disease-modifying antirheumatic drugs (DMARDs).[34]

Imaging

Ultrasound (US) imaging can detect joint and tendon inflammation in ICI-IA, even in those without objective synovitis on physical examination. In one study of 34 patients with ICI-associated musculoskeletal complaints, US imaging demonstrated synovial proliferation in 80%, hyperemia (color power Doppler signal) in 70%, and tenosynovitis in 60%.[35] Ten of the 14 patients without objective synovitis on physical examination had US evidence of inflammation, including three who had synovial fluid cell counts <2,000 cells/μL. The sensitivity of US imaging was also demonstrated in a multicenter study of 101 patients with ICI arthritis (n = 48) or ICI arthralgia (n = 53), in which 94% overall had US evidence of synovitis.[36] The most commonly affected joints were the wrists (38%) and knees (33%). Of those with ICI arthralgia, 47% had subclinical synovitis, 19% tenosynovitis, 2% digital extensor peritendinitis, and 25% enthesitis. Bone erosions (in the hands or wrists) were seen in 25% of patients with ICI arthritis and 7.5% with ICI arthralgia.

The insensitive nature of physical examination for the identification of joint inflammation in patients with ICI-IA has also been shown using magnetic resonance imaging (MRI). For example, in a recent study by Harnden et al,[32] gadolinium-enhanced whole-body MRI was performed on 60 patients with ICI arthralgia and 25 with ICI arthritis. Total joint synovitis, joint erosion, enthesitis, and tenosynovitis scores were similar between the ICI arthralgia and ICI arthritis groups. In both groups, the most commonly affected joints were the glenohumeral (75%), wrist (73%), and MCP (59%) joints. Evidence of myofasciitis was found in four patients involving the shoulders, knees, and pelvis and was generalized in one patient. Daoussis et al[37] also reported evidence of myofasciitis on MRI in 3 of 10 imaged patients with ICI-associated musculoskeletal complaints.

Fluorodeoxyglucose positron emission tomography/computed tomography imaging can sometimes incidentally identify evidence of polymyalgia rheumatica[38] or joint inflammation[39] when patients undergo imaging for cancer surveillance. Of note, the radiologist's final impression may omit these non–cancer-related findings, which may be buried in the body of the report.

In summary, imaging studies demonstrate joint erosions in a substantial minority of patients with ICI-IA, and a small subset has evidence of tenosynovitis, enthesis, and/or myofasciitis. In patients with ICI arthralgia, US and MRI often demonstrate synovitis and even erosions, suggesting that similar treatment approaches should be used in these patients as in those with ICI-IA.

Autoantibodies and HLA

Before the initiation of ICI, autoantibodies levels are lower in patients who subsequently develop severe irAEs but then rise significantly after ICI initiation.[40] With regard to RA-specific autoantibodies, seropositivity for anti-CCP and/or RF is seen in approximately 11% of patients with ICI-IA,[41] less than in RA (~70%)[42] but much more than in healthy individuals, who generally lack these antibodies.[43] However, anti-CCP titers are lower in patients with ICI-IA than RA and tend to target fewer citrullinated

peptides.[44] In one longitudinal study of 33 seronegative patients with ICI-IA, only 1 of them seroconverted to CCP positive over time.[45] One small study of three patients with CCP-positive ICI-IA who had pre-ICI treatment serum available demonstrated pretreatment CCP positivity in all three patients.[46] This suggests that seropositive ICI-IA may reflect a distinct ICI-IA subtype.

Cappelli et al[47] identified antibodies to heterogeneous nuclear RNP A2/B1 ("anti-RA33") in 11.4% of patients with ICI-IA (two of nine were also CCP positive), 7.7% of patients with RA, and 2% of healthy controls, whereas these antibodies were absent in ICI-treated patients without IA. Eleven percent of the anti–RA33-positive patients received combination immunotherapy, compared with 29% of the anti–RA33-negative patients (P = not significant). In RA, anti-RA33 antibodies are associated with early disease and low erosion scores,[48] so their presence in ICI-IA provides indirect evidence that the development of this disease may recapitulate processes that lead to the development of RA, at least in a subset of patients. Gatto et al[49] measured autoantibodies to 74 native or citrullinated "joint-related proteins" in six patients with ICI-IA and 15 ICI-treated patients without irAEs and demonstrated a higher proportion of patients with ICI-IA with antibodies to citrullinated epitope 19 in joint protein 5 (43% vs 0%; P = 0.023) and citrullinated type II collagen epitope C1 (28% vs 0%, P = 0.09). Whether these antibodies are pathogenic or an epiphenomenon resulting from the release of antigens from inflamed synovium is unknown.

RA is strongly associated with the HLA DRB1 shared epitope (SE) allele, at least in seropositive individuals.[50,51] Studies have provided conflicting results as to whether there is an association between the development of ICI-IA and the SE allele. Cappelli et al[52] studied 26 patients of European descent with ICI-IA and demonstrated at least one SE allele in 61.5% of them, similar to RA controls (65.9%) but significantly higher than healthy blood donors (41.2%; odds ratio 2.3, P = 0.04). Only 7.7% of the patients with ICI-IA were homozygous for the SE, compared with 23.6% of RA controls. In contrast, Ghosh et al[44] found no difference in the prevalence of the SE in patients with ICI-IA compared with ICI-treated patients without IA. However, neither of these studies had sufficient CCP-positive patients with ICI-IA (7.7% and 11%, respectively) to determine whether the SE is enriched in that subpopulation as might be expected.

In summary, seropositivity in ICI-IA is less frequent than in RA but more frequent than in the general population. It is still unknown whether seropositive patients with ICI-IA are at greater risk for persistent and/or erosive disease or whether their disease differs pathologically from seronegative disease. Future studies of CCP-positive patients with ICI-IA will help to determine whether the SE allele is enriched in that subpopulation. Given that <1% of ICI-treated patients develop CCP-positive ICI-IA, it will be challenging to identify and study these patients prospectively (starting at ICI initiation) to shed light on early RA pathogenesis, but it remains a research goal.

Histology

There are a limited number of studies describing histologic findings in ICI-IA synovium. The findings are overall heterogeneous, possibly because of the differing effects of anti–CTLA-4, anti–PD-1, and the combination (Table 1). In one report of anti–CTLA-4 (ipilimumab)-induced ICI-IA, synovial tissue from a PIP joint demonstrated proliferative chronic lymphoplasmacytic synovitis with fibrosis with infiltrates of $CD4^+$ and $CD8^+$ T cells as well as $CD20^+$ B cells.[53] The B cells were clustered in lymphoid follicles, whereas the T cells were spread throughout the tissue. Macrophages were also present, albeit in smaller numbers. Scattered $CD163^+$ histiocytes and $CD138^+$ plasma cells were also present. There were vascular proliferation, perivascular inflammatory infiltrates, and perivascular fibrosis. This one case demonstrates the full range of immune cells infiltrating the synovium in anti–CTLA-4–associated ICI-IA, with lymphoplasmacytic infiltrates similar to those seen in RA, except for the widespread distribution of T cells throughout the synovium. Although anti–CTLA-4 is no longer used as monotherapy, it is commonly used in the context of combination anti–CTLA-4/anti–PD-1 treatment.

In 2020, Murray-Brown et al[54] published findings of an arthroscopic synovial biopsy in a patient with severe ICI-IA after anti–PD-1 therapy (nivolumab) paired with three control patients with RA. Arthroscopic images show extensive hypervascularization and synovial hyperplasia in both ICI-IA and RA, and hematoxylin and eosin staining revealed lymphoid follicles in both conditions. Immunohistochemistry demonstrated diffuse $CD68^+$ macrophage infiltration in ICI-IA, whereas in RA the macrophages were localized to the subsynovial lining layer. B cells were absent in the ICI-IA tissue, whereas they were present in two of the three RA tissue samples. (The absence of B cells in this case was reminiscent of histologic findings that have been demonstrated in ICI sicca where, in contrast to Sjögren-related sicca, B cells are absent.[55]) In the ICI synovial tissue samples from both the patients with ICI-IA and RA, there were abundant memory T cells and strong TNFα staining, but little interleukin (IL)-6 staining. PD-L1 was present in both ICI-IA and RA tissues, but only the RA tissues stained positive for PD-1. However, the absence of PD-1 staining in the ICI-IA was attributed to sustained occupancy of the receptor by anti–PD-1 therapeutic antibody, despite the biopsy being performed 200 days after the last dose of nivolumab. This prolonged receptor occupancy in the synovium could partly explain the tendency of ICI-IA to persist even after ICI discontinuation.[31]

There is evidence that ICI-IA histology can be heterogeneous, even within the same individual. For example, in one patient with ICI-IA who underwent sequential bilateral total knee replacements 6 months apart, both knees demonstrated features of acute and chronic inflammation with mononuclear cell and extensive $CD3^+$ T cell infiltration. However, in the first knee the infiltrate was diffuse and there were prominent neutrophil infiltrates and fibrin exudate, whereas in the second knee there were

Table 1. ICI-associated inflammatory arthritis joint histology*

Author, year	Total, n	ICI	T cells	B cells	Macrophages	Pathology
Medina et al, 2021[53]	1	Anti–CTLA-4	$CD4^+$ and $CD8^+$	Present	10% of cells	Proliferative chronic lymphoplasmacytic synovitis with fibrosis
Murray-Brown et al, 2020[54]	1	Anti–PD-1	Abundant memory T cells	Absent	Diffuse infiltration	Hypervascularization, synovial hyperplasia, and lymphoid follicles. Strong TNF labeling and little IL-6 labeling
Wang et al, 2023[56]	1 patient, two knees; 5 additional synovial fluid samples	Anti–PD-1	$CD4^+$ and $CD8^+$ T cells	Small population	–	First knee: diffuse infiltrate with prominent neutrophils and fibrin exudate. Second knee: extensive and organized lymphocyte aggregates, plasma cells, and Russel bodies
de Bellefon et al, 2025[57]	13	11 anti–PD-1 or anti–PD-L1; 2 anti–CTLA-4/PD-1	Present	Present	Present	Sublining hyperplasia, inflammatory infiltrates, fibrinoid necrosis, and hypervascularization
Chan et al, 2026[58]	5	4 anti–PD-1; 1 anti–CTLA-4/PD-1	–	–	–	Chronic proliferative and exudative synovitis with lymphoplasmacytic inflammation
Taguchi et al, 2025[59]	1	Anti–PD-1	Predominantly $CD4^+$ T cells	–	–	Proliferative synovium and inflammatory cell infiltration

* CTLA-4, cytotoxic T-lymphocyte–associated protein 4; ICI, immune checkpoint inhibitor; IL-6, interleukin-6; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; TNF, tumor necrosis factor.

extensive and organized lymphocyte aggregates, plasma cells, and Russel bodies, indistinguishable from RA.[56] Single-cell RNA sequencing of lymphocyte clusters in this patient's synovial tissue, plus synovial fluid from five additional patients with ICI-IA, demonstrated the presence of $CD4^+$ and $CD8^+$ T cells, natural killer cells, and a small population of B cells. This case suggests that ICI-IA histology may evolve over time, from one dominated by innate immune cells to one dominated by cells of the adaptive immune system. However, another interpretation is that ICI-IA is histologically heterogeneous both between people and between joints in the same individual.

Recently, Meric de Bellefon et al[57] published a series of synovial biopsies performed in 13 patients with ICI-IA (1 with prior RA and 2 with prior psoriasis), 11 of whom were treated with anti–PD-1 or anti–PD-L1 therapy and 2 with combination anti–CTLA-4/anti–PD-1. The biopsies were compared with biopsies from 22 age- and sex-matched controls with early RA. With a few exceptions, the histologic findings in ICI-IA and RA were similar, including sublining hyperplasia, inflammatory infiltrates, fibrinoid necrosis, and hypervascularization. The immune infiltrates in both conditions were composed of $CD3^+$ T cells, $CD20^+$ B cells, $CD138^+$ plasma cells, and $CD68^+$ macrophages. The degree of synovial inflammation did not correlate with disease activity measures such as the Disease Activity Score in 28 joints or swollen or tender joint counts.

Another recent case series that included five patients with ICI-IA who underwent hip or knee arthroplasty reported chronic proliferative and exudative synovitis with lymphoplasmacytic inflammation, suggestive of RA, in the joint explants.[58] Similar histologic findings were reported in a case of ICI-IA by Taguchi et al, but the infiltrating cells were noted to be predominantly $CD4^+$ T lymphocytes.[59]

Thus, the histology of ICI-IA can bear a close resemblance to that seen in RA, with lymphoplasmacytic infiltrates. However, in a minority of cases there are diffuse macrophage and/or neutrophilic infiltrates and/or absent B cells. Whether these exceptions are a manifestation of disease heterogeneity or whether the condition evolves over time remains to be seen.

Immune cell subsets

T cells. In RA, the inflamed synovium is characterized by an expansion of $CD4^+$ T peripheral helper cells, and these cells are thought to drive local production of autoantibodies.[60] These cells are not expanded in ICI-IA synovium, where instead there is expansion of $CD8^+$ T cell populations.[56] For example, Kim S. et al,[61] in a study of blood and synovial fluid from patients with ICI-IA, found clonal expansion of $CX3CR1^{hi}$ $CD8^+$ T cells in the blood and $CXCR3^{hi}$ $CD8^+$ T cells in the synovial fluid. These two T cell populations had shared TCR repertoires, suggesting that $CX3CR1^{hi}$ $CD8^+$ T cells migrate from the blood to the joint, where they transition to $CXCR3^{hi}$ $CD8^+$ T cells. The data also suggested that $CX3CR1^{hi}$ $CD8^+$ T cell entry into the joint is mediated by CXCL9/10/11/16 expressed by myeloid cells.

The characteristics of expanded $CD8^+$ T cell populations in ICI-IA was also investigated by Wang et al,[56] who demonstrated clonal expansion of actively proliferating $CD38^{hi}CD127^-CD8^+$ T cells in ICI-IA. These expanded clones were found not only in the synovial fluid and synovial tissue but also in the blood, and, in one case, shared clones from the same patient were isolated from two different knee joints aspirated 6 months apart, suggesting the cells travel between the blood and the joint. $CD38^{hi}CD127^-$ $CD8^+$ T cells express a strong IFN signature, and in vitro treatment of synovial $CD8^+$ T cells from patients with RA or psoriatic arthritis with type IFN-1β (but not IFNγ) was sufficient to induce the $CD38^{hi}CD127^-$ phenotype, suggesting a role for this cytokine in ICI-IA. $CD38^{hi}CD127^-$ $CD8^+$ T cell clones were bound by therapeutic anti–PD-1 antibodies in patients with ICI-IA, suggesting these cells are directly targeted by ICI.[56] Although $CD38^{hi}CD127^-$ $CD8^+$ T cells represent an attractive ICI-IA treatment target, it is possible that they are instrumental in antitumor immunity.

Comparing ICI-IA with RA, Zhou et al[62] found a higher proportion of exhausted $CD8^+$ T cells, $CD8^+$ effector memory T cells, and Treg cells in ICI-IA synovial fluid compared with RA and a lower proportion of $CD4^+$ T effector memory and exhausted $CD4^+$ T cells.

Although cytotoxic $CD8^+$ T cells are the prime mediators of ICI's anticancer effects and they are identified in the synovium of patients with ICI-IA, it is the pretreatment abundance of naive $CD4^+$ T cells (even more so than that of naive $CD8^+$ T cells) that is associated with the development of severe irAEs, at least in patients who receive combination ICI.[63] Severe irAEs are also associated with the pretreatment abundance of activated $CD4^+$ memory T cells and their TCR diversity.[64] Similarly, Kovacsovics-Bankowski et al[65] found that patients with melanoma who later developed severe irAEs had a higher frequency of naive $CD4^+$ T cells and lower frequencies of Treg cells before ICI initiation. These findings suggest that $CD4^+$ T cells also contribute to irAEs; however, compared with $CD8^+$ T cells, the role of $CD4^+$ T cells in the pathogenesis of irAEs, including ICI-IA, is underexplored.

Th1 and Th17 cells. The immune system has tailored its effector functions in response to different types of antigens. Accumulating studies suggest that there are three types of immune responses: type 1, type 2, and type 3, and that $CD4^+$ T cells govern each immune response.[66] Type 1 immunity consists of T-bet^+ $IFN\gamma^+$ Th1 cells, $CD8^+$ cytotoxic T cells, natural killer cells, and group 1 innate lymphoid cells (ILCs). These cells activate monocytes/macrophages and play a crucial role in defending hosts from intracellular antigens, including viruses and cancers. Type 2 immunity consists of $GATA3^+$ $IL\text{-}4^+$ Th2 cells and group 2 ILCs, which activate mast cells, basophils, and eosinophils, as well as IgE, to cope with parasites. Type 3 immunity consists of retinoic acid–related orphan receptor γt^+ $IL\text{-}17^+$ Th17 cells and group 3 ILCs, which activate macrophages and neutrophils to fight against extracellular antigens such as bacteria and fungi. Notably, type 1 and/or type 3 immunity contribute to the pathogenesis of autoimmune diseases.[66,67]

Given the critical role of type 1 responses to anticancer immunity,[68] as well as the recognized expansion of $CD8^+$ T cells in patients with irAEs, it is hypothesized that Th1 cells are critical to irAE development. Indeed, Reschke et al[69] analyzed skin and colon samples from patients with ICI dermatitis and ICI colitis, respectively, using multiparameter immunofluorescence, spatial transcriptomics, and RNA in-situ hybridization (RISH). Immunofluorescence analysis revealed that tissue-resident memory T (Trm) cells were preferentially expanded in the skin and colon of patients with ICI dermatitis/colitis compared with healthy controls. Notably, spatial transcriptomics and RISH analyses revealed that these Trm cells express Th1-associated genes. Likewise, Kim S. et al[61] observed an expansion of IFNγ-expressing Th1 cells in the synovial fluid of patients with ICI-IA.

Type 3 immunity, governed by Th17 cells, is essential to the pathogenesis of multiple autoimmune diseases. IL-1β, IL-6, IL-17A, and IL-23 are critical cytokines for Th17 cell differentiation (IL-1β and IL-6), survival (IL-23), and function (IL-6, IL-17A, and IL-17F). Blockade of these cytokines is widely used in the management of Th17 cell–mediated autoimmune disorders.[67,70,71] Notably, Kao et al[72] observed that increases in serum IL-6 and IL-17F showed the strongest association with grade ≥2 irAEs both early in treatment (1–2 months after ICI initiation) and at the time of an irAE. Studies by Kim K. et al and Wu et al revealed that higher levels of circulating Th17 cells pre-ICI are associated with the development of irAEs.[73,74] Gray-Gaillard et al[75] analyzed serum cytokines from patients with ICI-IA and demonstrated a correlation between IL-6 levels and ICI arthritis disease activity. Consistent with this, Kim S. et al[76] reported a case series demonstrating the efficacy of an IL-6 inhibitor for the treatment of ICI-IA. The same group also demonstrated enhanced Th17 cell signatures in synovial fluid from patients with ICI-IA, especially in patients treated with combination ICI.[61] Together, these translational and clinical studies suggest that Th17 cells contribute to ICI-IA disease pathogenesis, especially ICI-IA induced by combination ICI therapy.

B cells. Although ICIs are typically thought of as targeting T cells, some B cells populations express PD-1 after activation, including naive B cells, peripheral IgM memory B cells, and B cells that exert regulatory function via Toll-like receptor (TLR) 4 activation.[77] However, PD-1 is not expressed on germinal center B cells, and PD-L1 and PD-L2 are expressed on B cells only after activation of TLR9.[77] As shown in Table 1, B cells are represented in the synovium of many (although not all) patients with ICI-IA.

In a study by Das et al,[78] patients receiving combination ICIs who went on to develop severe irAEs had a decline in the overall number of circulating B cells after ICI initiation and an increase in $CD21^{lo}$ B cells and plasmablasts. $CD21^{lo}$ memory B cells are expanded in peripheral blood during chronic inflammation and, although they are in a semiexhausted state, they have the potential to differentiate into plasmablasts.[79] Plasmablasts are rapidly produced, cycling but short-lived effector cells of the early antibody response that differentiate into long-lived, postmitotic plasma cells.[80] In the study by Das et al,[78] $CD21^{lo}$ B cells had greater clonality and higher PD-1 expression than other B cell subsets. Interestingly, these B cell changes, which occurred early and preceded the onset of an irAE, were likely driven by anti–CTLA-4 because they were also seen in patients treated with anti–CTLA-4 monotherapy but not in patients treated with anti–PD-1 alone. Combination ICIs were associated with higher levels of CXCL13 than in either monotherapy cohort, suggesting germinal center activation.[78]

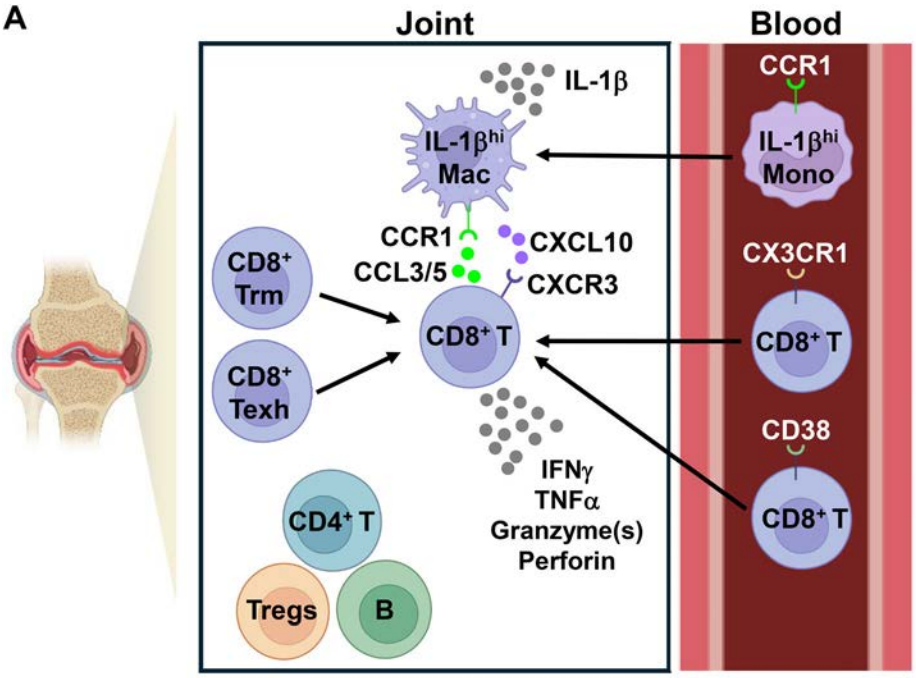
In a study comparing seven patients with ICI-IA (four treated with anti–PD-1 and three with combination ICI) with 15 ICI-treated patients without irAEs (all treated with anti–PD-1), Gatto et al[49] demonstrated expansion of a subset of circulating transitional B cells in the patients with ICI-IA after ICI initiation, characterized as $CD10^{+}CD24^{hi}$ $CD38^{hi}$. These cells represented a median of 8.1% of $CD19^{+}$ B cells in patients with ICI-IA as compared with 3.6% in non-irAE controls ($P < 0.007$). The cells expanded in the blood >1 month before ICI-IA onset, and their proportion declined as ICI-IA disease activity lessened. Transitional B cells are released from the bone marrow and represent an intermediate stage of maturation before progression to mature splenic or follicular B cells.[49] Still to be determined is whether the $CD10^{+}CD24^{hi}$ $CD38^{hi}$ transitional B cells are present in the synovium or synovial fluid of patients with ICI-IA, and whether they are also expanded in patients with other irAEs and/or in patients with RA and other forms of IA.

Macrophages. Zhou et al[62] demonstrated an expansion of IL-$1\beta^{hi}$ macrophages in the synovial fluid of patients with anti–PD1–induced ICI-IA. In contrast, they found that RA synovial fluid was enriched for monocyte-like macrophages (early inflammatory) and $SPP1^{+}$ macrophages (associated with chronic inflammation, tissue remodeling, and fibrosis).[81] Trajectory analysis suggested that the IL-$1\beta^{hi}$ macrophages differentiated from IL-$1\beta^{hi}$ $CD14^{+}$ monocytes in the peripheral blood. TNF signaling through NF-κB was significantly up-regulated in the IL-$1\beta^{hi}$ macrophages. Notably, cell-cell interaction analyses revealed that IL-$1\beta^{hi}$ macrophages communicate with $CD8^{+}$ T cells via the CXCL10-CXCR3 and CCR1-CCL3/5 axes. Together, these data indicate that activated $CD8^{+}$ T cells and IL-$1\beta^{hi}$ macrophages are central to the pathogenesis of anti–PD-1–induced arthritis.

In summary, studies of cell subsets in patients with ICI-IA suggest a scenario whereby CXCR3-expressing $CD8^{+}$ positive T cells, unleashed from their exhausted state by anti–PD-1, are activated and recruit IL-1β–producing monocytes into the joint. These $CXCR3^{hi}$ $CD8^{+}$ T cells and IL-$1b^{+}$ macrophages play a central role in PD-1 inhibitor–induced arthritis (Figure 1). Activation of naive $CD4^{+}$ T cells and impaired Treg cells appears to play a synergistic and amplifying role, especially in the setting of combination ICIs. Finally, several lines of research point to a role for B cells in irAEs, including the expansion of plasmablasts and increased production of autoantibodies after combination ICIs, as well as the presence of well-formed germinal centers in the synovium of some patients with ICI-IA. The role of B cells in ICI-IA development is likely through the help they provide to T cells, whereas the importance of antibody production is less clear.

Return of tolerance

Compared with other irAEs, ICI-IA tends to persist for as long as 1 to 2 years after ICI discontinuation.[31,82] Braaten et al[31] conducted a prospective observational study of 60 patients with ICI-IA and observed that less than half of the participants (46.7%) experienced resolution of ICI-IA at a median follow-up of 9 months after ICI cessation. Patients with a shorter duration of ICI therapy, those receiving anti–PD-1 monotherapy, and those without prior irAEs were more likely to see improvement in their ICI-IA after stopping ICIs. Although nivolumab (anti–PD-1) has a serum half-life of 12 to 20 days, and drug-bound $CD8^{+}$ circulating T cells disappear within 28 weeks after the cessation of ICIs,[83] Murray-Brown et al[54] demonstrated sustained occupancy of the PD-1 receptor by nivolumab in a synovial biopsy performed 200 days after the last nivolumab dose. Wang et al[56] demonstrated that the clonally expanded $CD38^{hi}CD127^{-}$ $CD8^{+}$ T cell population in the blood and synovium of patients with ICI is bound by therapeutic anti–PD-1 antibodies. This suggests that ICI-IA persistence may be because of ongoing ICI binding in synovial tissues. However, persistent symptoms could also be because of ongoing T cell responses that take time to fade or to come under the control of tolerance mechanisms. In a subset of patients, symptoms of ICI-IA do in fact persist long term. Detailed cellular, epigenetic, and molecular mechanisms are needed to better understand the mechanisms underlying the restoration of peripheral tolerance.



B

	RA	ICI-IA
Sex differences	Female predominant	None
Pattern of arthritis	Small symmetric polyarthritis	Varies
Shared epitopes	Yes	No
RF/CCP	Positive in general	Negative in general
Histology	Expansion of Tph and B cells; Macrophages localized to sub-synovial lining layer	Varies (see Table 1)

Figure 1. Proposed model of mechanisms of ICI-IA. (A) Activated CXCR3^{hi} CD8$^+$ T cells mediated by programmed cell death protein 1 inhibition, likely heterogeneous populations of exhausted T cells, tissue-resident memory T cells, and recruited CX3CR1- and/or CD38-expressing T cells produce CCL3 and CCL5. These chemokines recruit IL-1β–producing monocytes via CCR1. Once recruited to the joint, IL-1β–producing monocytes differentiate into IL-1β–expressing macrophages. In turn, these macrophages produce CXCL10, which helps the activated CD8$^+$ T cells reside in joints. The CD8$^+$ T cells also produce effector molecules, including IFNγ, TNFα, granzymes, and perforin. The role of CD4$^+$ T cells, Treg cells, and B cells in ICI-IA is under active investigation, especially in combination ICI-induced IA given the role of CTLA-4 in the biology of CD4$^+$ T cells and B cells. (B) Main differences between RA and ICI-IA. CCP, cyclic citrullinated peptide; ICI-IA, immune checkpoint inhibitor–associated inflammatory arthritis; IFNγ, interferon γ; IL-1β, interleukin-1β; Mac, macrophage; Mono, monocyte; RA, rheumatoid arthritis; RF, rheumatoid factor; Texh, exhausted T cell; TNFα, tumor necrosis factor α; Tph, T peripheral helper cell; Trm, tissue-resident memory T cell.

Future directions

ICI-IA represents a form of IA in which both the trigger and its timing are known. Thus, this condition has the potential to teach us about the mechanisms underlying the evolution of other forms of IA. The challenge is to identify patients at risk for this condition in advance, so that longitudinal studies, starting at the time of ICI initiation, can be done. Studies done so far demonstrate that ICI-IA is a heterogeneous condition, differing biologically, depending on whether it follows anti–PD-1/PD-L1 monotherapy or combination ICIs, and clinically, possibly because of host factors. Understanding these factors will likely provide clues to the pathogenesis of IA outside the ICI realm. From an immunologic

perspective, the study of paired synovial and tumor tissue from patients with ICI-IA may help to identify treatment targets that can suppress joint inflammation without abrogating ICI's therapeutic effects in the tumor microenvironment. Finally, the development of murine ICI-IA models that recapitulate the immunologic and clinical features of human ICI-IA is critical. Such models would enable mechanistic in vivo studies that complement analyses of patient samples, facilitating integrated translational and reverse-translational approaches. These strategies will allow investigation into the cellular and molecular mechanisms underlying ICI-IA, identification of predictive and disease-associated biomarkers, and rational development of targeted therapeutic strategies.

Clinical case part 2

The patient required treatment with 20 mg of prednisone twice per day for his ICI-IA, which partially controlled his symptoms. A computed tomography scan performed 1 week after his first Rheumatology visit showed further progression of his renal cell carcinoma, and he was started on cabozantinib (a tyrosine kinase inhibitor) as an alternative to pembrolizumab (anti–PD-1) ICI. Because of the severity of his arthritis and his need for high-dose prednisone, the decision was made to add a fast-acting biologic DMARD. Because there is some evidence that IL-6R inhibition is safer than TNF inhibition regarding cancer survival,[84] tocilizumab (anti–IL-6R) 4 mg/kg monthly was added for arthritis control, and the dose was later increased to 8 mg/kg monthly. The patient continued to take tapering doses of prednisone for 15 months, and required intravenous tocilizumab for a total of 17 months. Seven months after discontinuing tocilizumab, the patient experienced progression of his cancer while taking cabozantinib.

CONCLUSION

ICI-IA is a new form of arthritis that presents phenotypically like more prototypical forms of inflammatory arthritis like RA and PMR and yet differs at the biological level. The synovium in ICI IA contains an expanded population of cytotoxic CD8+ T cells (CD38+CD127-PD1+) and IL1beta^{hi} macrophages, and these cells express a strong interferon signature. Although ICI-IA can persist for 1–2 years, it does generally resolve and thus the condition has the potential to teach us about factors associated with the onset and resolution of other inflammatory arthritides.

AUTHOR CONTRIBUTIONS

All authors contributed to at least one of the following manuscript preparation roles: conceptualization AND/OR methodology, software, investigation, formal analysis, data curation, visualization, and validation AND drafting or reviewing/editing the final draft. As corresponding author, Dr Bass confirms that all authors have provided the final approval of the version to be published and takes responsibility for the affirmations regarding article submission (eg, not under consideration by another journal), the integrity of the data presented, and the statements regarding compliance with institutional review board/Declaration of Helsinki requirements.

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Multimodal Integration of Protein Interactomes With Genomic and Molecular Data Discovers Distinct Rheumatoid Arthritis Endotypes

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Objective. Rheumatoid arthritis (RA) is a heterogeneous autoimmune disease characterized by clinical and molecular heterogeneity, notably in the presence of anti–cyclic citrullinated peptide (CCP) antibodies. Patients with CCP+ RA exhibit more severe disease progression and distinct treatment responses compared to patients with CCP – RA. Although previous studies have investigated cellular and molecular differences between these subtypes, their genetic differences are understudied.

Methods. We leveraged the Rheumatoid Arthritis Comparative Effectiveness Research cohort, comprising 555 patients with CCP+/rheumatoid factor (RF)+ RA and 384 patients with CCP–/RF+ RA. Using a novel framework, we integrated a network-based genome-wide association study (GWAS) with multiomic data to uncover corresponding genetic and molecular differences.

Results. We uncovered a significant heritability difference between these disease groups. Network-based GWAS uncovered 14 putative gene modules, including many genes outside the HLA loci, that explained genetic differences between CCP+/RF+ and CCP–/RF+ RA. Heritability partitioning and multivariate expression analyses validated four modules, highlighting novel genetic loci underlying phenotypic differences. Module functional significance was established using multiple orthogonal cohorts, underscoring their biologic relevance.

Conclusion. Our findings demonstrate the use of network-based approaches in revealing differential genetic risk factors underlying CCP+/RF+ and CCP–/RF+ RA. Disease-associated gene modules detected in synovial tissue were also observed in peripheral blood, indicating joint-specific molecular programs are reflected systemically. This cross-tissue concordance highlights the potential for blood-based assays to capture pathogenic mechanisms active in the joints, enabling practical patient stratification. Our findings highlight why patients with CCP+/RF+ and CCP–/RF+ RA exhibit distinct clinical courses and therapeutic responses, supporting precision-guided treatment strategy development in RA.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, progressive autoimmune disease characterized by inflammation of synovial joints and systemic immune dysregulation. According to the Global Burden of Diseases, Injuries, and Risk Factors Study 2021, approximately 17.6 million people worldwide are affected by RA.[1] Beyond its clinical manifestations, RA exhibits considerable molecular and cellular heterogeneity, which contributes to variations in disease onset, progression, and treatment response.

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[Correction added on 23 April 2026, after first online publication: Affiliation 3 was initially assigned incorrectly to Dr. Fan Zhang and has now been correctly reassigned to Affiliation 6 in this version.]

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A key source of this heterogeneity lies in the anti–cyclic citrullinated peptide (CCP) antibodies and rheumatoid factor (RF) in the serum. Although these autoantibodies form part of the diagnostic criteria for RA, many patients are seronegative for one or both.[2]

The serological profile of these autoantibodies defines two major subgroups: CCP+/RF+ (doubly seropositive) and CCP–/RF+ (singly seropositive) RA. Although CCP seropositivity has been associated with a more aggressive disease course and a higher risk of joint destruction,[3] some studies suggest that patients with CCP+ RA may respond more favorably to certain disease-modifying antirheumatic drugs.[4] Despite these clinical differences, both subgroups are treated with the same therapeutic interventions, reflecting the assumption that they share similar pathogenic mechanisms. However, emerging molecular evidence suggests that these subgroups may represent distinct biologic endotypes rather than variations of a single disease.[1]

Previous studies have reported immunologic and transcriptomic differences between CCP+/RF+ and CCP–/RF+ RA,[5–7] yet their genetic basis remains poorly understood. Comparisons of findings from case-control studies for CCP+/RF+ and CCP –/RF+ RA have shown that both disease endotypes have shared and distinct genetic loci underlying their pathogenic architectures.[8–10] However, there have been limited efforts directly comparing them.[11] Variants that distinguish RA cases from healthy controls are concentrated within the HLA region and reflect general autoimmune susceptibility; further, most studies have considered either disease subtype but not both or have grouped them together.[12–16] However, whether genetic differences separating CCP+/RF+ and CCP–/RF+ RA arise from the same broad pathways that drive RA versus control differences or distinct processes has not been systematically explored. Addressing this gap is essential for defining the specificity of endotype-associated mechanisms and for identifying genetic programs that shape disease heterogeneity beyond overall autoimmunity.

Genome-wide association studies (GWASs) involve testing differences in allele frequency to find associations between genetic variants and phenotypes.[17] Although GWASs remain a cornerstone of genetic research, they have several limitations.[18] Importantly, the statistical power for detecting associations depends on the sample size of the cohort. This is especially limiting when studying disease subsets with small cohort sizes. Given that increasing sample size to facilitate discovery of novel genetic loci is not always feasible, other methods are needed to improve discovery. One such method is network-based GWAS. It involves leveraging biologic networks, such as protein–protein interaction (PPI) networks, because interacting proteins usually are involved in the same molecular pathways and are often implicated in the pathogenesis of the same trait.[19] By propagating the signal from a GWAS over the PPI network, it is possible to augment signal by borrowing strength from functionally similar genes, which were not significantly associated with the trait due to low power, and thus identify additional disease-associated loci.[20] Although network-based analyses have provided mechanistic insights in other autoimmune conditions, such as multiple sclerosis[21] and Crohn disease,[22] they have rarely been applied to distinguish within-disease heterogeneity. Applying such a framework to characterize patients with RA defined by differences in CCP and RF serology provides a unique opportunity to reveal whether their genetic architectures represent extensions of the same disease spectrum or reflect fundamentally distinct pathophysiology.

This study employs a multitiered analytical framework integrating genomic and transcriptomic data to uncover molecular architecture distinguishing CCP+/RF+ and CCP–/RF+ endotypes. Although conventional GWASs assume independence among genetic loci and identify individual loci associated with phenotype, they often fail to reveal how these variants converge into functional biologic processes, leaving a gap between genetic associations and clinical manifestation. To bridge this gap, we first used genetic data to assess differences in heritability, providing an indication of difference in genetic architectures between the two endotypes. Partitioning heritability across gene modules demonstrated the prioritized modules capture a substantial proportion of endotype-specific genetic variance. Integration of transcriptomic data and multiomics analysis further refined these modules by adding a layer of cell-type and tissue specificity, linking heritable variation to gene expression programs and cellular phenotypes. Together, this integration provides mechanistic insight into how genetic risk manifests in tissue-specific and cell-type–specific contexts.

METHODS

Cohort description. In this study, we used data from the University of Pittsburgh Rheumatoid Arthritis Comparative Effectiveness Research (RACER) registry, which consisted of prospectively enrolled patients with RA recruited through the University of Pittsburgh Medical Center. The cohort included 555 and 384 patients with CCP+/RF+ and CCP–/RF+ RA, respectively. Genotype data was collected for all 939 patients using the MegaChip array. We filtered subjects based on the quality of raw genotypes as well as relatedness to exclude highly related subjects (kinship value >0.12 = same family) because they are likely to introduce biases. A total of 7,173,418 single nucleotide polymorphisms (SNPs) were imputed using the Sanger imputation server.[23] This study was approved by the University of Pittsburgh Institutional Review Board (protocol 19090282) and adhered to the principles outlined in the Declaration of Helsinki.

Genome-wide association analyses adjusting for appropriate covariates. Phenotypes were encoded in a vector Y of length 939, with values of 1 for CCP+/RF+ and 0 for CCP–/RF+ RA. Genotype data comprised 7,173,418 SNPs per

individual and were organized into a 939 × 7,173,418 matrix (X, with rows representing individuals and columns representing SNPs. To adjust for confounding, we included biologic sex, age, and the first five genetic principal components as covariates. Genotype quality control was performed using PLINK,[24] applying filters for SNP and sample missingness (≤1%) and minor allele frequency (≥5%). Conditional analyses were conducted using the COJO tool in Genome-Wide Complex Trait Analysis (GCTA).[25] Primary SNPs were first identified via stepwise selection (–cojo-slct), followed by conditional GWAS (–cojo-cond) across the significant HLA region.

Heritability estimation using LDAK. We used the LDAK[26] model to estimate heritability of the phenotypic trait. To determine the difference in heritability, we began by computing the genetic relatedness matrix (GRM) using the ldak5.2 linux executable obtained from the LDAK website. After obtaining the GRM, we applied the –reml option to calculate heritability differences.[27] Details of the heritability estimation are provided in the Supplementary Notes.

Network propagation using random walk with restart using gene-centric scores. In this study, we applied the HotNet2 algorithm to conduct network propagation analyses on the reference human PPI network.[28] Additional details are explained in the Supplementary Notes.

Heat diffusion and module detection in network propagation to uncover functionally coherent subnetworks. Gene-level relevance was quantified by assigning each gene a heat score defined as the –log(P value) from restricted maximum likelihood (REML) LDAK heritability estimates for SNPs within 50 kb, encoding endotype status (doubly seropositive = 1; singly seropositive = 0), propagating these scores across a PPI network using a random walk with restart algorithm,[29] and identifying statistically significant subnetworks via 500 degree-preserving network permutations, yielding 14 validated modules comprising 4 to 54 genes.

Heritability partitioning using LDAK: module-specific kinship matrix calculation and REML analysis. Heritability was partitioned across 14 gene modules using the LDAK tool by constructing module-specific kinship matrices (–calc-kins-direct,–power –0.25) and estimating module-level heritability via REML while adjusting for sex and principal components (Supplementary Notes).

Imputation of gene expression using PrediXcan for tissue-specific analysis of discriminatory gene networks. We used PrediXcan[30] to impute tissue-specific gene expression from genotypes using linear allele–expression models. Expression was imputed for whole blood and subcutaneous adipose tissue, relevant to RA. Linear regression tested associations with CCP+ versus CCP– RA, and –log10(P value) quantified tissue-specific network module discrimination across RA endotypes and network modules analysis (Supplementary Notes).

Evaluation of gene module discriminatory performance using bulk RNA-sequencing data. Bulk RNA-sequencing (RNA-seq) data from sorted synovial T cells, B cells, monocytes, and fibroblasts in 29 Accelerating Medicines Partnership RA phase 1 patients[31] with available CCP/RF serostatus were obtained from ImmPort (SDY998), filtered for low-variability genes, and analyzed using least absolute shrinkage and selection operator (LASSO)–regularized logistic regression in R to evaluate the discriminatory power of network-derived gene modules, with model training and performance assessed by leave-one-out cross-validation and area under the receiver operating characteristic (ROC) curve (AUC)–based tuning. Additional details are in the Supplementary Notes.

Replication GWAS using All of Us cohort. As a replication cohort, we analyzed 248 RF+ participants of European ancestry from the All of Us Research Program,[32] stratified into CCP+/RF+ (n = 93) and CCP–/RF+ (n = 155), with phenotype encoded as a binary vector and genotype data comprising 6,879,629 SNPs, which were quality controlled using PLINK with genotype missingness (10%) and minor allele frequency (5%) filters. Additional details are in the Supplementary Notes.

Evaluation of gene module performance in cell-type abundance phenotype and treatment response classification using single-cell RNA-seq data. Using single-cell RNA-seq (scRNA-seq) data from 70 patients with RA from the Accelerating Medicines Partnership RA phase 2 cohort,[33] we generated pseudobulk profiles across immune and stromal cell types and applied LASSO-regularized logistic regression in a one-versus-rest framework to evaluate the predictive performance of network-derived gene modules for cell-type abundance phenotype (CTAP) and treatment response classification, with model training, cross-validation, and ROC-AUC–based performance assessment conducted in R using glmnet, caret, pROC, and dplyr. Additional details are in the Supplementary Notes.

Code and data availability. All data and code associated with the manuscript are available at https://github.com/jishnu-lab/RAEndo.

RESULTS

We leveraged the RACER cohort,[34] which comprised 555 and 384 patients with CCP+/RF+ and CCP–/RF+ RA, respectively (Figure 1A), predominantly of White ancestry.

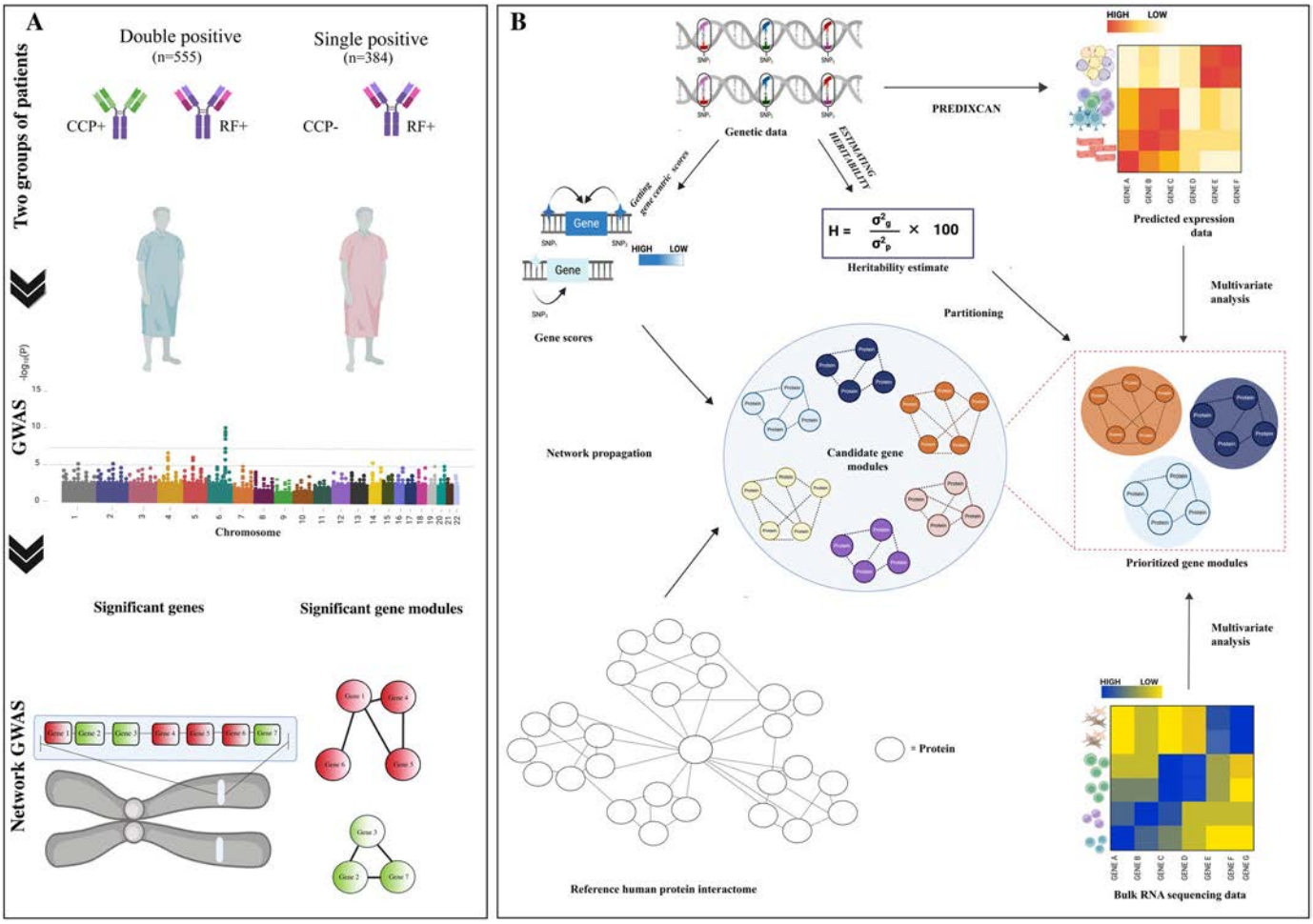

Figure 1. Multiscale network-informed genetic analyses to identify heritability and phenotypic differences across CCP+/RF+ and CCP–/RF+ rheumatoid arthritis. (A) Conceptual overview of our study. (B) Schematic representation of analytical pipeline used to identify and validate genetic loci underlying phenotypic differences between CCP+/RF+ and CCP–/RF+ rheumatoid arthritis. CCP, anti–cyclic citrullinated peptide; GWAS, genome-wide association study; RF, rheumatoid factor; SNP, single nucleotide polymorphism.

We looked to elucidate genetic and molecular differences between these subtypes of RA. Because a conventional GWAS would not be sufficiently powered at these sample sizes to elucidate differences between these disease subtypes, we employed a network-based GWAS approach. By considering the interactions and relationships among genes, a network-based GWAS can identify genetic associations that may be missed by traditional single-variant analysis (Figure 1B). Using this method, we could prioritize clusters of genes or gene modules that can shed light on functionally relevant pathways. These modules underwent further orthogonal analyses to establish biologic significance.

Heritability analysis highlights distinct genetic underpinnings of CCP+/RF+ and CCP−/RF+ RA, but conventional GWAS implicates only HLA loci. To quantify genetic differences between CCP+/RF+ and CCP−/RF+ RA, we estimated subgroup-specific heritability using genotypes from 939 RACER participants. After excluding variants with minor allele frequency <0.05, approximately 7.2 million SNPs were analyzed, and heritability differences were estimated using the LDAK REML approach.[10] Given the female predominance (women:men 3.5:1) and the known role of age in RA risk, we evaluated two fixed-effect models: (1) adjusting for one principal component and sex (Figure 2A) and (2) adjusting for five principal components, sex, and age. Ages were similar between patients with CCP+/RF+ (60 years) and CCP–/RF+ RA (Supplementary Figure 1A). Both models yielded a heritability difference of 0.30 (P = 0.03; Figure 2A), indicating that approximately 30% of phenotypic differences are genetically driven and supporting distinct endotypes. These results align with a Swedish familial aggregation study reporting heritability of approximately 50% for CCP+/RF+ RA and approximately 20% for CCP–/RF+ RA[35] but contrast with findings from a prior twin study.[36]

To identify which genetic loci underlie these differences, we conducted a GWAS using two covariate models: (1) adjusting for one principal component and sex (Figure 2B) and (2) adjusting

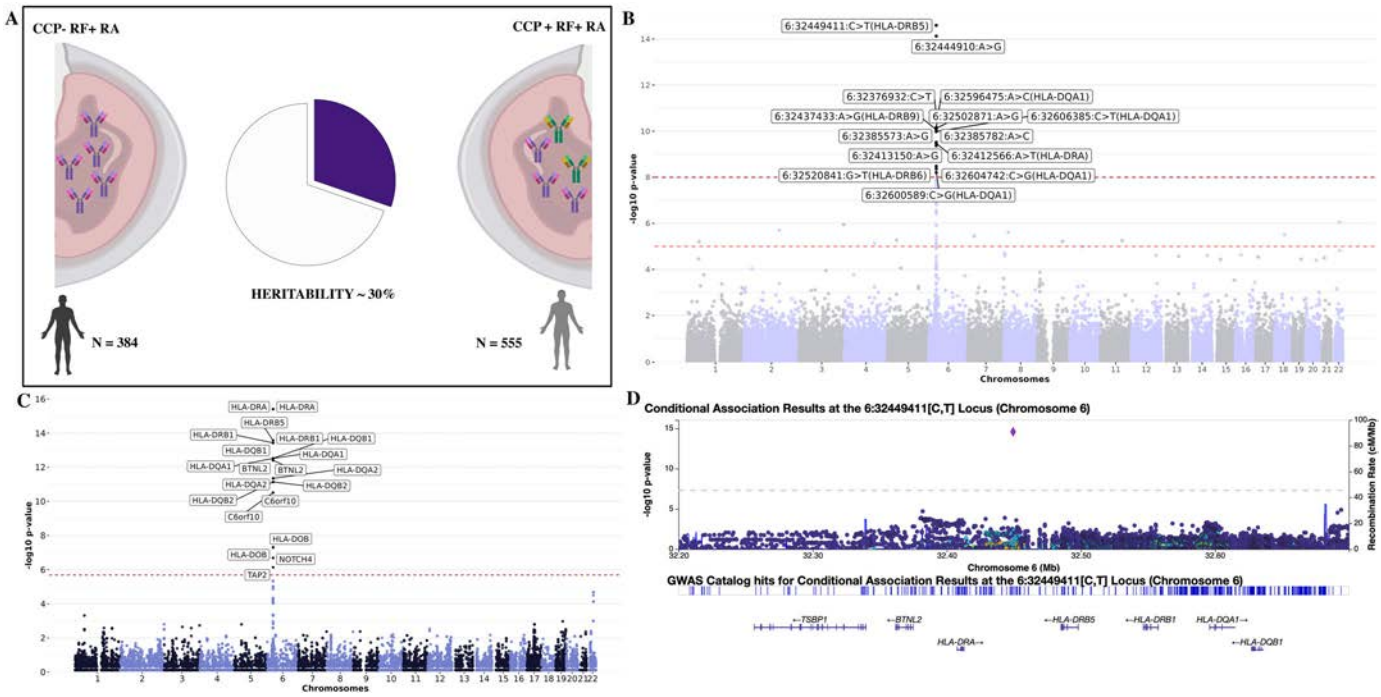

Figure 2. Genetic loci identified using conventional GWAS do not explain the difference in heritability between CCP+/RF+ and CCP–/RF+ RA. (A) Difference in heritability between CCP+/RF+ and CCP–/RF+ RA within the Rheumatoid Arthritis Comparative Effectiveness Research cohort. (B) Manhattan plot for GWAS, corrected for covariates with one principal component and biologic sex, comparing CCP+/RF+ and CCP –/RF+ RA in which single nucleotide polymorphisms with significant association statistics are labeled. (C) Manhattan plot for gene-based association analyses, corrected for covariates with one principal component and biologic sex, comparing CCP+/RF+ and CCP–/RF+ RA in which genes with significant association statistics are labeled. CCP, anti–cyclic citrullinated peptide; GWAS, genome-wide association study; RA, rheumatoid arthritis; RF, rheumatoid factor.

for five principal components, sex, and age (Supplementary Figures 1B and 1C). The results were comparable across both models, indicating that the first covariate setting was sufficient. Our analysis identified 2,441 genetic variants with associated *P* values meeting the Bonferroni-corrected significance threshold of 5×10^{-8}. All the genome-wide significant variants were confined to the HLA region on chromosome 6, and a handful of additional variants surpassed a nominal *P* value threshold of 5×10^{-5} (Figure 2B).

To dissect association signals within the HLA region, we performed stepwise regression followed by conditional analyses using GCTA-COJO,[25] which identified *HLA-DRB5* as the primary driver of the strong HLA association. The lead variant 6:32449411:C>T captured the core genetic effect and markedly attenuated residual signals after conditioning (Figure 2C). Although this finding is consistent with the central role of HLA class II alleles in RA susceptibility[37] and prior GWAS comparing CCP+/RF+ and CCP–/RF+ RA cases, significant GWAS SNPs explained only about 3% (ie, only 10% of the ~30% heritability difference between the two groups), indicating substantial false negatives due to stringent false discovery rate control (Figure 2B). Univariate gene-based association tests using LDAK identified significant associations with *HLA-DRB1*, *HLA-DRB5*, and *HLA-DRA* within the HLA region (Figure 2B) but remained largely locus confined and are inherently underpowered because they do not account for intergene relationships or joint effects (Figure 2D).

Network GWAS unveils additional loci underlying the phenotypic differences between CCP+/RF+ and CCP –/RF+ RA. With this cohort size, a conventional GWAS was underpowered to detect associations beyond the HLA locus. To address this, we adopted a network-based GWAS approach that integrates genetic association data with biologic networks to identify genes implicated for a given phenotype. High-scoring genes that are randomly distributed across the network may not reflect meaningful biologic associations. In contrast, moderately scoring genes that are highly proximal within the network are more likely to indicate a real signal because they often participate in the same pathways and contribute to the same traits. This approach is based on the premise that interacting proteins usually operate in similar molecular pathways and are commonly linked to the same trait.[20]

We used LDAK REML to estimate a comprehensive gene-centric score that account for coding variants and noncoding variants that modulate gene expression (Figure 3A), accounting for the underlying linkage disequilibrium structure. We then propagated these scores over a high-quality reference protein

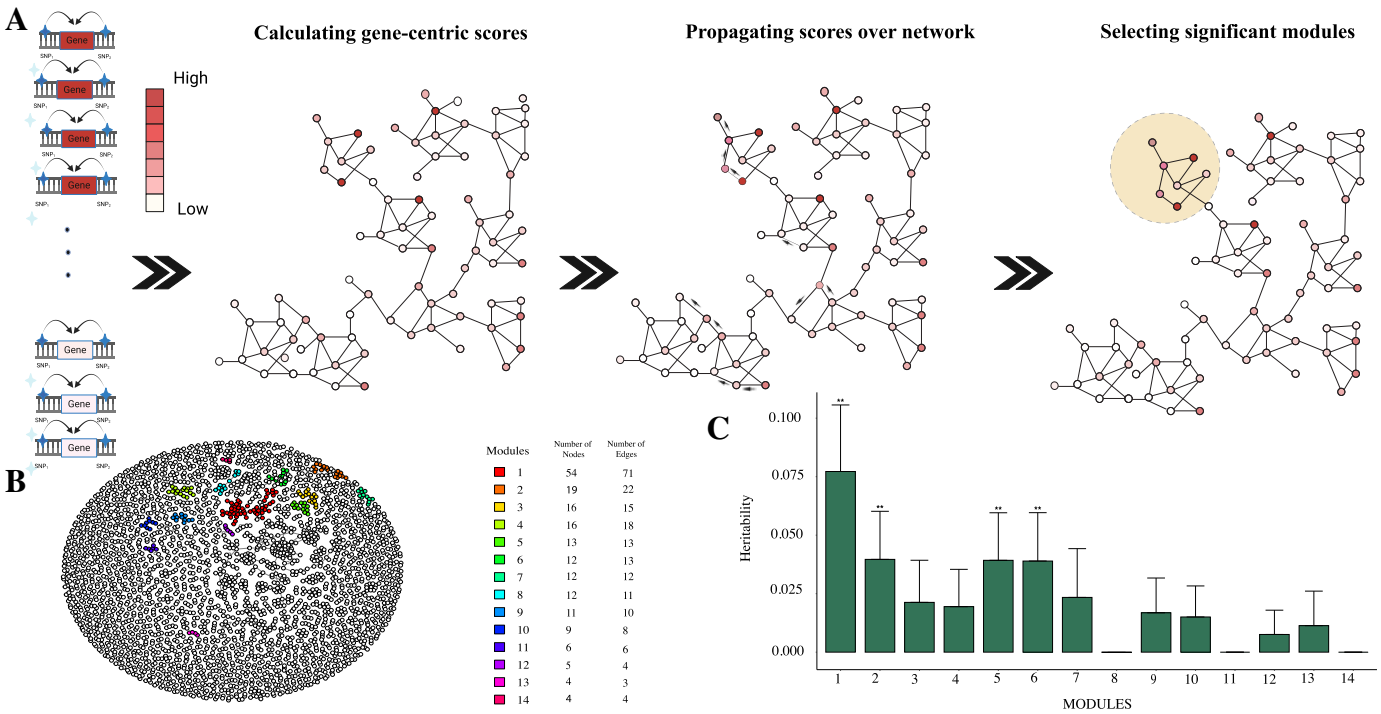

Figure 3. Network genome-wide association study identifies additional associations underlying genotypic differences between CCP+/RF+ and CCP−/RF+ RA. (A) Schematic representation of how network propagation was used to identify genetic loci underlying the phenotypic differences between CCP+/RF+ and CCP−/RF+ RA. (B) Network-based genome-wide association study analysis identifies 14 significant modules as candidates explaining genotypic and heritability differences between CCP+/RF+ and CCP−/RF+ RA. (C) Bar plot showing per-module contribution to the difference in heritability between CCP+/RF+ and CCP−/RF+ RA, where ** represents significant contributions as measured by the LDAK restricted maximum likelihood *P* value. CCP, anti–cyclic citrullinated peptide; RA, rheumatoid arthritis; RF, rheumatoid factor; SNP, single nucleotide polymorphism.

interactome[28] using a random walk with restart algorithm.[29] Critically, the network used here reflects connectivity at the functional level between proteins encoded by these genes and not at the locus level. The incorporation of multiscale (genetic and functional associations) and multiomic (genomic and interactome) data enables the identification of gene modules missed by a conventional GWAS. To determine both the number and size of significant gene modules, we applied a permutation-based statistical test (Supplementary Notes). Using this approach, we identified 14 statistically significant network modules (Supplementary Figure 2). These modules comprised 193 genes (Figure 3B), including genes from the HLA region and a wide array of other molecular pathways, which have not been previously implicated in the phenotypic differences between CCP+/RF+ and CCP−/RF+ RA.

Our analyses identified modules that significantly correlate with phenotypic differences between CCP+/RF+ and CCP−/RF+ RA. To move beyond correlations, we interrogated these modules in terms of their ability to explain heritability partitioning as well as against several functional genomic data sets. This multistep prioritization system helped identify the functional significance of the modules using multiple orthogonal analyses and data sets. The use of a combination of multiple layers of evidence (genetic, cellular, and molecular) from different data sets helped us converge on the most robust and biologically meaningful modules that explain heterogeneity between these two subtypes of RA.

Candidate gene modules explain the difference in heritability. To assess the relative importance of each gene module, we estimated module-specific heritability contributions using LDAK REML. Conventional GWAS SNPs, limited to the HLA locus, explained only approximately 3% (~10% of the ~30%) of the heritability difference between subgroups. In contrast, combining heritability across network modules recapitulated an approximately 31% difference, comparable to genome-wide estimates, enabling prioritization of modules by genetic contribution. Beyond the HLA module (module 1; $h^2 = 0.075$), modules 2, 5, and 6 showed significant independent contributions (Figure 3C).

Multivariate analysis using sorted bulk RNA-seq data reveals cell type–specific signals for candidate gene modules. In addition to explaining heritability, we hypothesized that functionally important network modules would

correspond to genes whose expression programs are significantly different between doubly and singly seropositive RA. So, we performed an orthogonal validation analysis using a data set of bulk RNA-seq from the Accelerating Medicines Partnership RA phase I data.[31] Interestingly, although this cohort included patients with CCP+/RF+ RA, most of the singly seropositive patients were CCP+/RF– and a few were CCP–/RF+. However, in the RACER cohort, the singly seropositive patients were CCP –/RF+. Despite this difference, the analysis allows us to evaluate whether the identified modules are overall discriminatory between doubly and singly seropositive RA.

We tested whether the expression of genes encoding proteins within the identified network modules could significantly discriminate CCP+/RF+ RA from other subtypes across different cell types, using AUC as the performance metric. We performed permutation testing by randomly selecting size-matched gene sets from all genes in the bulk RNA-seq data. In fibroblasts, the interferon signaling and extracellular matrix remodeling (ECM) module (module 1) was discriminatory between doubly versus singly seropositive RA (Figure 4A). Genes coding for proteins comprising the immune response and inflammation modulation and complement system activation and regulation modules (modules 4 and 5, respectively) were found to be discriminatory in T cells (Figure 4B). The cytokine signaling and immune response modulation module (module 7) was significant in B cells (Figure 4C), and the interferon signaling and ECM, TGF-β/BMP signaling in developmental processes, protein folding and glycosylation in the endoplasmic reticulum, and chemokine-mediated signaling in immune response modules (modules 1, 2, 10, and 13, respectively) were significant in monocytes (Figure 4D).

Multivariate analysis using imputed expression from RACER cohort prioritizes specific candidate gene modules. To further validate our findings at the expression level, we imputed the expression levels of genes in the 14 modules for subjects in the RACER cohort based on their individual genotypes. We used PrediXcan,[30] a regularized regression approach that leverages individual genetic variation to predict corresponding expression levels for each subject. This is an orthogonal but equally important approach because we used imputed matched (at a per-subject level) gene expression in this analysis as opposed to an orthogonal cohort in the prior analysis. By using the PrediXcan model, we were able to impute expression levels for both adipose tissue and whole blood. Consistent with the prior transcriptomic analysis using data from the AMP cohort, this assessment revealed that several of the 14 identified modules were again significantly discriminatory between CCP+/RF+ and CCP–/RF+ RA in adipose tissue and whole blood (Figure 4E).

Network GWAS identifies cell type–specific modules that stratify disease endotypes. Our study introduced a robust and innovative method for identifying genetic factors underlying the phenotypic difference between patients with CCP +/RF+ and CCP–/RF+ RA. Using a network-based GWAS approach, we identified 14 candidate gene modules (Figure 5A). Five of these modules, interferon signaling and ECM (module 1, Figure 5B), complement system activation and regulation (module 5, Figure 5C), TGF-β/BMP signaling in developmental processes (module 2, Figure 5D), protein folding and glycosylation in the endoplasmic reticulum (module 10, Figure 5D), and protein processing and cellular transport (module 6, Supplementary Figure 2), successfully passed two of the three stringent validation analyses.

We were able to assign cell-type specificity for four of the five modules, and we consider these the final validated modules for downstream functional analyses and biologic interpretation using a large-language model–based approach[38] (Figure 5B–5D). We were unable to specify cell-type specificity for one module, which may be interesting for future follow-up (module 6, Supplementary Figure 2). Together, these modules comprise 107 genes. The largest module, comprising 54 genes, included genes from within the HLA region and other immune signaling genes. The other modules encompassed a wide range of biologic processes. Despite the vast search space of >17,000 proteins in the entire network, our method demonstrates a high level of specificity (Figure 5A). Interestingly, these modules contain genes with both high and low gene scores, highlighting the potential of our approach to identify genes that may be overlooked in traditional GWAS analyses.

Our analysis identified a significant module comprising complement system genes, including *C9*, *C8A*, *C8B*, *C7*, and *C6* (Figure 5C). The complement system is a crucial part of the innate immune response, and its dysregulation has been implicated in autoimmune diseases such as RA. Notably, the presence of complement genes encoding components of the membrane attack complex in module 5 (complement system activation and regulation) indicates a potential involvement of complement-mediated cytotoxicity and subsequent tissue damage mechanisms in RA (Figure 5C). Overall, our findings shed new light on the complex interplay of genes and proteins in the mechanism of RA and open new avenues for further research and potential therapeutic interventions.

Gene modules represent structured subnetworks rather than merely groups of unrelated genes. To highlight the importance of this connectivity structure within our identified modules, we compared the performance of candidate gene modules against "distribution-matched" control modules (Supplementary Notes). Permutation testing against random size-matched modules showed that for two of the four modules, addition of connectivity structure improved discriminatory power (AUC) beyond gene membership alone, whereas for the other two modules, gene membership alone was sufficient (Figure 5E). Even with this stringent test, we observed

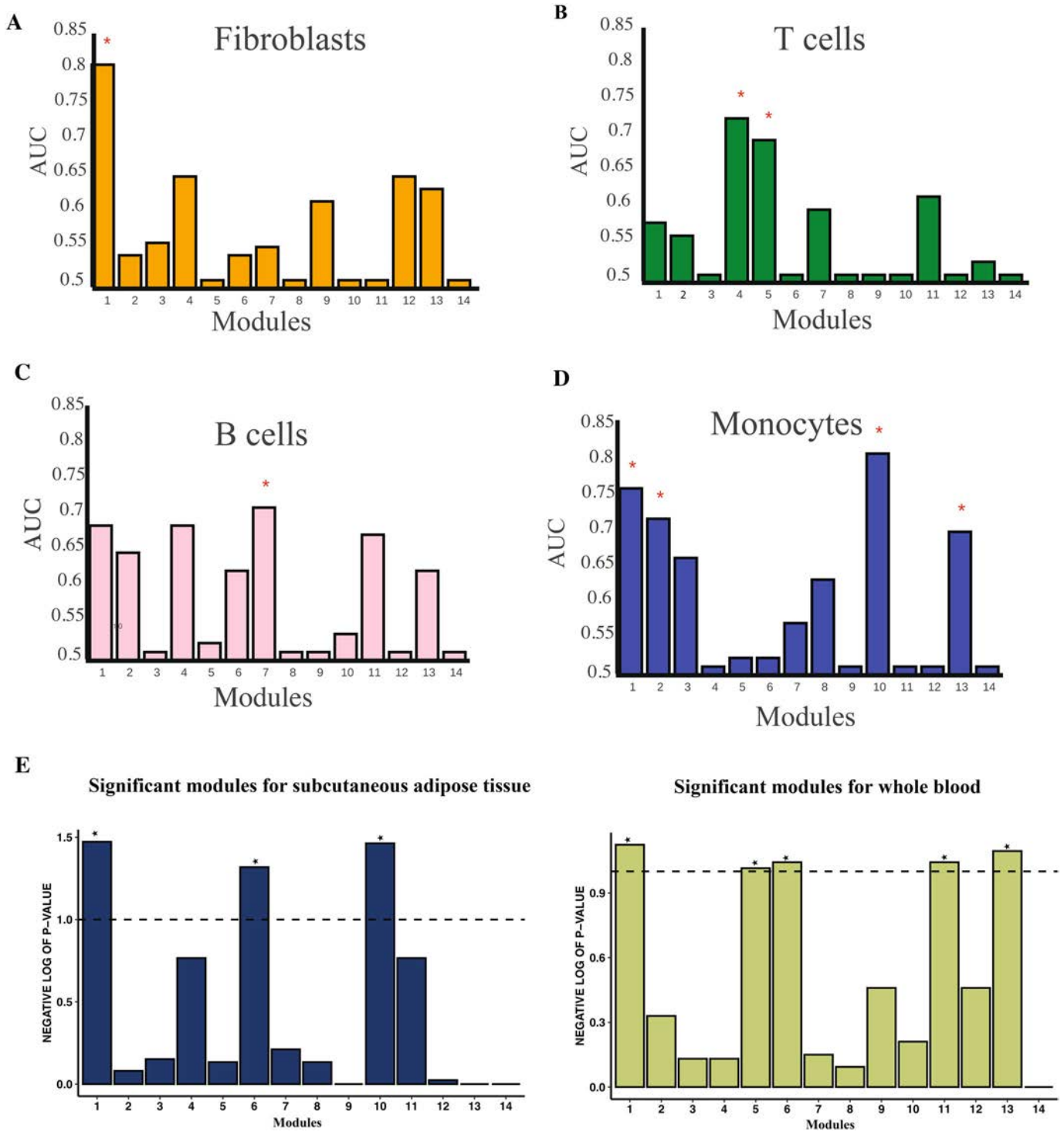

Figure 4. Multivariate analyses of sorted bulk RNA-sequencing data and imputed gene expression data reveal cell type and tissue specificity of candidate gene modules. (A–D) Bar plot showing the discriminative ability of a multivariate logistic regression model based on gene expression profiles for each module in fibroblasts (A), T cells (B), B cells (C), and monocytes (D), where AUC values represent the model's ability to discriminate anti–cyclic citrullinated peptide+/rheumatoid factor+ rheumatoid arthritis from other rheumatoid arthritis subsets and * represents the model's performance against a score distribution-matched module. (E) Bar plot showing the discriminative ability of a multivariate logistic regression model based on predicted gene expression for each module in subcutaneous adipose tissue, where –log(*P* values) represent the discriminatory power of the modules and * represents models with –log(*P* value) ≥ 1. AUC, area under the receiver operating characteristic curve.

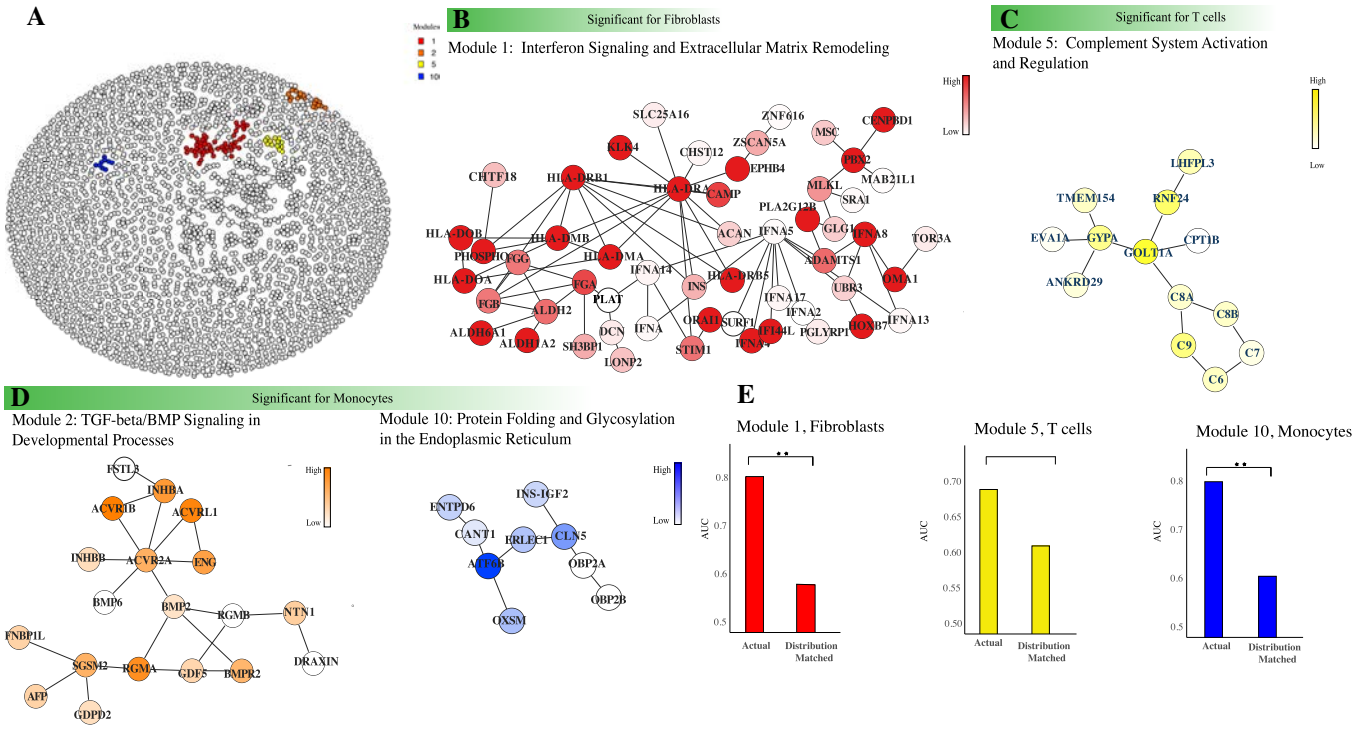

Figure 5. Prioritized gene modules reveal novel cross-talk between HLA–type 1 interferon underlies the phenotypic differences seen between anti–cyclic citrullinated peptide+/rheumatoid factor+ and other rheumatoid arthritis subsets. (A) Visualization of prioritized gene modules in the overall network (prioritized modules are colored). (B) Module with significant performance in multivariate analysis using expression data from fibroblasts. (C) Module with significant performance in multivariate analysis using expression data from T cells. (D) Module with significant performance in multivariate analysis using expression data from monocytes. (E) Gene modules showing significantly higher discriminatory power compared to random distribution-matched gene sets. AUC, area under the receiver operating characteristic curve.

significant differences in the predictive power of our modules compared to the "distribution-matched, size-matched" controls. Specifically, these differences were notable for the interferon signaling and ECM module (module 1) in T cells and the protein folding and glycosylation in the endoplasmic reticulum module (module 10) in monocytes. Together, these results indicate that the identified modules underlie key phenotypic differences in doubly versus singly seropositive RA.

Validation of selected gene modules using orthogonal genetic data from the All of Us cohort. To independently validate the gene modules identified from network GWAS of the RACER cohort, we leveraged genotype and phenotype data from the All of Us cohort.[32] We restricted our analysis to European ancestry individuals who were RF+ (RF > 20 IU/mL), yielding a cohort of 248 patients with RA, a population composition like that of the RACER cohort. These samples were further stratified based on anti-CCP antibody status into double-positive (CCP+/RF+; n = 93) and single-positive (CCP–/RF+; n = 155) subgroups, with CCP values >20 IU/mL considered positive (Supplementary Figure 3A). A GWAS comparing these two groups revealed significant enrichment at the HLA class II locus on chromosome 6 (Figure 6A), consistent with findings in the RACER cohort (Figure 2B). We used LDAK to aggregate SNP scores for each gene and compared the scores of genes from our modules to distributions derived from random, size-matched gene sets. Notably, two modules—interferon signaling and ECM (module 1) and complement system activation and regulation (module 5)—showed significantly higher genetic scores relative to random expectations (Figure 6B), highlighting the robustness of our findings and the importance of these genes in shaping the phenotypic differences between the endotypes.

Prioritized gene modules capture molecular processes that explain heterogeneity in RA beyond seroprevalence of autoantibodies. Beyond serotype-based heterogeneity, patients with RA also display additional clinical variation, one aspect of which is captured by CTAPs.[33] CTAPs reflect distinct synovial inflammatory microenvironments, ranging from lymphocyte rich (CTAP-TB and CTAP-TF) to myeloid- or fibroblast-dominated profiles (CTAP-M, CTAP-F, and CTAP-EFM) and have been shown to predict differential treatment responses. We next sought to test whether the gene modules identified through network GWAS as distinguishing CCP+/RF+ and CCP–/RF+ RA endotypes also contribute to the phenotypic differences between CTAPs. To do this, we performed functional

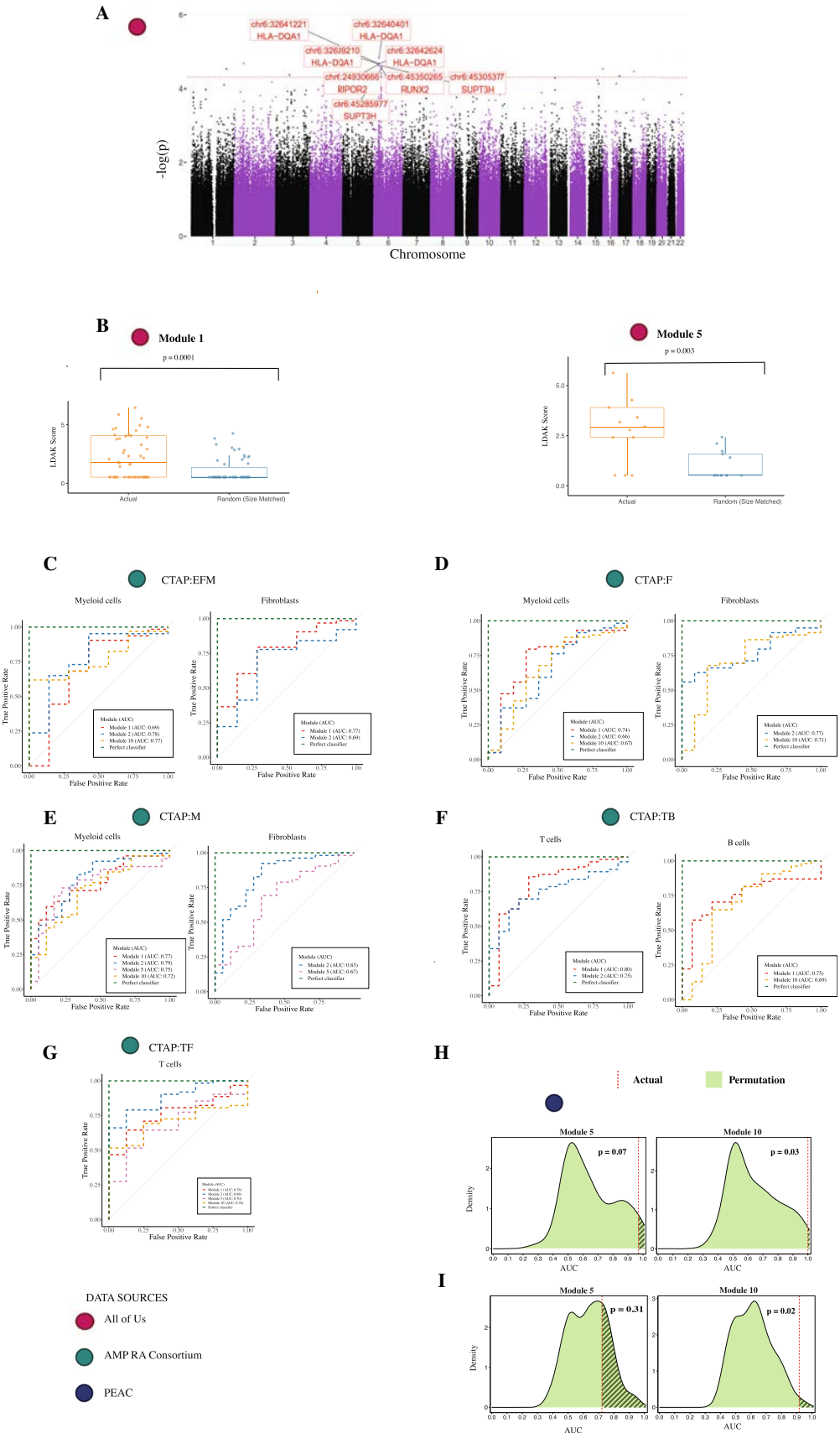

Figure 6. Legend on next page.

validation using scRNA-seq data from sorted synovial cell populations. We evaluated the discriminatory power of the modules in distinguishing individual CTAPs (Figure 6C–6G). The modules exhibited CTAP-specific discriminatory performance, with interferon signaling and ECM TGF-β/BMP signaling modules differentiating stromal- and lymphocyte-enriched CTAPs across relevant cell types (Supplementary Additional Clinical Findings).

Further, predicting patient response to specific therapeutic regimens remains a significant clinical challenge in RA. We investigated whether cell-type–specific gene modules from our network-based GWAS could discriminate between patients showing inadequate responses to methotrexate or TNF inhibitors (TNFi) (Supplementary Figure 3B). Indeed, the identified gene modules were discriminatory between different treatment responses across multiple cell types (Supplementary Additional Clinical Findings).

Multivariate analysis using whole-blood RNA-seq data from the Pathobiology of Early Arthritis cohort validates candidate gene modules. To provide orthogonal validation of the candidate gene modules in a larger cohort, we analyzed whole-blood RNA-seq data from the Pathobiology of Early Arthritis[39] cohort (n = 67). This larger data set enabled us to both validate the robustness of the prioritized modules and determine whether their signals specifically distinguished CCP +/RF+ from CCP–/RF+ RA, beyond general RF-associated effects.

First, restricting the analysis to blood-derived samples, we evaluated whether expression of genes from the selected modules could discriminate between patients with doubly and singly seropositive RA. We observed strong discriminator performance, particularly for module 5 (complement system activation and regulation) and module 10 (protein folding and glycosylation in the endoplasmic reticulum; Figure 6H, Supplementary Figure 3C). We then repeated the analysis comparing only RF+ and RF– patients in the same data set. We found that module 5 is specific to the contrast between doubly seropositive (CCP+/RF+) and singly seropositive (CCP–/RF+) RA (Figure 6I, Supplementary Figure 3D). Together, these analyses demonstrate that certain network modules represent very specific differences between CCP+/RF+ and CCP–/RF+, whereas others uniquely define the molecular signatures of doubly seropositive RA relative to singly seropositive RA.

DISCUSSION

Differences in seroprevalence for autoantibodies such as CCP represent a major source of clinical heterogeneity in RA, reflecting not only phenotypic variation but distinct disease states. Multiple studies have shown that CCP+/RF+ and CCP–/RF+ RA are driven by different genetic architectures, but most of these studies were conducted using only CCP+/RF+ or CCP–/RF+ RA samples.[8–10] Traditional GWASs have identified both shared and distinct loci across CCP+ and CCP– RA, including *ANKRD55*, *STAT4*, *C5orf30*, *PTPN22*, *ELMO1*, *RUNX1*, and *BLK*.[40–42] Within the HLA region, *HLA-DR4* has been associated with CCP+/RF+ RA[43] and *HLA-DR3* with CCP–/RF+ RA.[44] To date, only one case-case GWAS between CCP+/RF+ and CCP –/RF+ RA has been reported.[11] However, due to limited sample size, this study could not identify loci beyond the HLA region. Although HLA loci contribute to phenotypic differences, they fail to explain the observed heritability gap, motivating the use of a network-based GWAS approach to identify additional loci underlying disease heterogeneity.

Using a novel network propagation-based approach, we identified 14 significant gene modules. Further validation using heritability partitioning and functional genomic data sets prioritized five modules, which were replicated in an independent cohort and captured additional clinical heterogeneity between the two endotypes, including CTAPs and variability in treatment response. Our systems-level approach can partly help explain why CCP+/RF+ and CCP–/RF+ patients—although treated with the same first-line therapies such as methotrexate or TNFi—often follow divergent therapeutic trajectories. Moreover, we observed that these endotype-specific gene modules are not confined to the synovium; rather, some of the same modules are also detectable in peripheral blood. This makes our approach clinically valuable for patient stratification and precision medicine in RA.

Figure 6. Functional validation of CCP-associated gene modules. (A) Manhattan plot for genome-wide association study comparing CCP+/RF+ and CCP–/RF+ RA in the All of Us cohort. (B) Comparison of LDAK scores for prioritized gene modules versus size-matched random gene sets in the All of Us cohort. (C) ROC curves evaluating the ability of gene modules to distinguish CTAP-EFM from other CTAP phenotypes using scRNA-seq data. (D) ROC curves evaluating the ability of gene modules to distinguish the CTAP-F from other CTAP phenotypes using scRNA-seq data. (E) ROC curves evaluating the ability of gene modules to distinguish the CTAP-M from other CTAP phenotypes using scRNA-seq data. (F) ROC curves evaluating the ability of gene modules to distinguish the CTAP-TB from other CTAP phenotypes using scRNA-seq data. (G) ROC curves evaluating the ability of gene modules to distinguish the CTAP-TF from other CTAP phenotypes using scRNA-seq data. (H) Distribution of AUC values from 10-fold cross-validation distinguishing CCP+/RF+ from CCP–/RF+ RA. The null distribution was obtained by permutation testing, wherein seropositivity labels were randomly shuffled. (I) Distribution of AUC values from 10-fold cross-validation distinguishing patients with RF+ from RF– RA. The null distribution was obtained by permutation testing, wherein group labels (CCP & RF status) were randomly shuffled. AMP, Accelerating Medicines Partnership; AUC, area under the receiver operating characteristic curve; CCP, anti–cyclic citrullinated peptide; CTAP, cell-type abundance phenotype; PEAC, Pathobiology of Early Arthritis cohort; RA, rheumatoid arthritis; RF, rheumatoid factor; ROC, receiver operating characteristic; scRNA-seq, single-cell RNA-sequencing.

These identified modules recapitulate known mechanisms of RNA pathogenesis and provide novel insights. For example, understanding the role of complement system activation in RA, particularly in the context of the complement system activation and regulation module (module 5), could open new avenues for therapeutic intervention. Targeting the components of the membrane attack complex or modulating its activity may offer a strategy to mitigate tissue damage and inflammation in RA, particularly in those with CCP+ disease.[29,30] Overall, this study demonstrates that network-based GWAS coupled to functional genomics can help characterize interaction-specific molecular phenotypes[45,46] linked to disease pathogenesis missed by conventional GWAS approaches.

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AUTHOR CONTRIBUTIONS

All authors contributed to at least one of the following manuscript preparation roles: conceptualization AND/OR methodology, software, investigation, formal analysis, data curation, visualization, and validation AND drafting or reviewing/editing the final draft. As corresponding author, Dr Das confirms that all authors have provided the final approval of the version to be published and takes responsibility for the affirmations regarding article submission (eg, not under consideration by another journal), the integrity of the data presented, and the statements regarding compliance with institutional review board/Declaration of Helsinki requirements.

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Spondyloarthritis Preceding and Following Inflammatory Bowel Disease Diagnosis and Risk Factors: A Temporal Trends Analysis in a Population-Based Cohort

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Objective. Spondyloarthritides (SpA) and inflammatory bowel disease (IBD) are immune-mediated diseases with overlap in clinical and immunologic features. However, temporal correlation of SpA and IBD in individual patients and risk factors are not well characterized.

Methods. We conducted a nationwide population-based study between January 1, 1998, and July 31, 2022, to determine SpA prevalence preceding IBD diagnosis and its incidence following IBD diagnosis. Using cross-linked register data, we identified individuals with IBD diagnosis and matched them to individuals without IBD. Using logistic regression, we determined the odds of SpA preceding IBD diagnosis, and using Cox regression, we determined the hazard of new-onset SpA following IBD diagnosis.

Results. Of 102,648 individuals included in the study, 17,108 (16.7%) individuals were diagnosed with IBD. The adjusted odds ratios of SpA in the eight-year period preceding IBD, Crohn disease (CD), and ulcerative colitis (UC) diagnosis, compared to matched individuals, were 1.95 (95% confidence interval [CI] 1.78–2.14), 2.84 (95% CI 2.43–3.32), and 1.61 (95% CI 1.43–1.81), respectively. The adjusted hazard ratios of SpA following IBD, CD, and UC diagnosis, compared to matched individuals, were 2.51 (95% CI 2.34–2.70), 3.17 (95% CI 2.81–3.59), and 2.24 (95% CI 2.05–2.45), respectively. SpA prevalence demonstrated temporal variability, with an increase during the few years around IBD diagnosis. Associations were stronger for axial SpA and among women and young adults following IBD diagnosis.

Conclusion. In a population-based cohort, we report that SpA diagnosis is associated with IBD preceding and following its diagnosis. We demonstrate temporal variability and highlight clinical variables associated with SpA in IBD.

INTRODUCTION

Axial and peripheral spondyloarthritis (SpA) are immune-mediated inflammatory arthritides associated with disability and adverse individual and societal impact.[1–4] Similarly, inflammatory bowel disease (IBD), including Crohn disease (CD) and ulcerative colitis (UC), is an immune-mediated disease of the intestinal tract with substantial morbidity, disability, and health care costs.[5,6] SpA can coexist with IBD and other immune-mediated inflammatory diseases.[1] In fact, features of axial and peripheral joint involvement have been found on detailed rheumatologic evaluation of 17% and 50% of individuals with newly diagnosed IBD, respectively.[7,8] However, the temporal correlation of the development of SpA and IBD in individual patients remains a knowledge gap. Simultaneously, delay in the diagnosis of axial SpA is common, with the mean delay ranging from two to six years, leading

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The study is based on data from the Danish Nationwide Registers (https://sundhedsdatastyrelsen.dk). The register data are protected by the Danish Act on Processing of Personal Data and are accessed through application to and approval from the Danish Data Protection Agency and the Danish Health Data Authority.

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to progressive joint damage and disability.[9,10] Similarly, delay in CD diagnosis up to a few years, with associated disease progression and complications, is also common.[11,12] Therefore, an understanding of clinical and phenotypic features of individuals with SpA who later develop IBD, as well as individuals with IBD at risk of developing SpA, is highly relevant for clinical monitoring of patients toward screening for and early recognition of symptoms, application of diagnostics, and specialist referral. Early diagnosis is critical for early treatment, prevention of progression of both SpA and IBD, and improved patient outcomes.[10,12] Further, a better understanding of the relationship between the two immune-mediated diseases will help select and implement therapeutic strategies that target both diseases for harmonized treatment. Therefore, in this study, our aim was to explore the association between SpA and IBD, with a specific focus on the temporal relationship between the two diagnoses and associated risk factors.

METHODS

Study design. We conducted a nationwide cohort study for which the source population included all residents of Denmark between January 1, 1998, and July 31, 2022. We identified study participants using the Danish Civil Registration System (CRS), a prospective register for demographic and vital data with continuous updates, cross-linked to the Danish National Patient Register (DNPR) through a unique personal identification number (CPR number).

Study participants. Of all individuals included in the CRS, we excluded those with prior diagnoses of the immune-mediated diseases rheumatoid arthritis, lupus, and sarcoidosis and those who lived outside Denmark for more than one year in total out of the eight years before the date of IBD diagnosis.

Exposure. We identified IBD cases in the DNPR, which includes all inpatient and outpatient hospital contacts since 1977 and 1995, respectively. We defined incident IBD cases based on *International Classification of Diseases, Tenth Revision* (ICD-10) codes for CD and UC diagnoses (K50 and 51, respectively) and registration date. The latter refers to either the date of an outpatient visit or the start of an inpatient contact. Any outpatient visit registered under an outpatient contact and any inpatient contact associated with a primary or secondary IBD diagnosis are considered to be an IBD-related registration. To minimize the risk of misdiagnosis, we included individuals with at least two IBD-related registrations within a two-year period. The date of the initial IBD contact, henceforth index date, was assigned as the date of IBD diagnosis. We excluded all individuals with an IBD registration before the start of the inclusion period. Both IBD contacts were required to occur between January 1, 2006, and July 31, 2014, to allow for data on eight years before and eight years after the date of IBD diagnosis. In the event that the two IBD-related registrations diagnoses were disparate (CD and UC), the later diagnosis was recorded.

Every defined case of IBD was matched 1:5 on age (in one-year intervals), sex, and municipality of residence to individuals from the pool of individuals without IBD living in Denmark eight years before the matching date (with an allowed absence of up to one year in total during that period) using risk set matching, referred to as reference individuals.[13] For each reference individual, the second of the two IBD contacts was used as time of matching to mitigate immortal-time bias.

Outcome. The outcome was defined as a single registration of SpA, with the registration being either a primary or a secondary related registration code, based on ICD-10 codes in the DNPR (Supplementary Table 1). Registrations used were both inpatient contacts and outpatient visits but not emergency department contacts. The positive predictive value of a single ICD registration code for SpA is estimated to be between 70% and 89% in the Swedish National Patient Register.[14]

Covariates. We included age at index date, sex, and calendar period as adjustment covariates.

Statistical analysis. All individuals in this study cohort were observed from the start of the study until the date of SpA diagnosis, emigration, death, or end of the follow-up period, whichever occurred first. We calculated the incidence rate of SpA in individuals with IBD compared to their corresponding references. Prevalence between the eight years preceding and the eight years following the index date was calculated by looking at each month over the follow-up period and defining incident SpA if an individual had a new or ongoing contact for SpA. We conducted multivariable logistic regression analysis to analyze the prevalence odds ratio (OR) for SpA preceding IBD diagnosis in individuals with IBD compared with reference individuals. Next, we conducted adjusted Cox proportional hazards regression analysis to determine the hazard ratio (HR) for SpA following IBD diagnosis. Furthermore, we conducted interaction analysis to study whether variables such as age, sex, and calendar period had any interaction effect on the association between SpA and IBD diagnosis. Statistical significance of the interaction term in regression models was evaluated using a likelihood ratio test comparing the models with and without the interaction term.

To further investigate the temporal relationship between SpA and IBD, we analyzed ORs and HRs in the time intervals of zero to two, two to four, and four to eight years preceding and following IBD diagnosis, respectively. Lastly, we conducted a sensitivity analysis excluding enthesitis as part of the outcome, analyzing ankylosing spondylitis and sacroiliitis separately, and requiring two registrations, with a primary or secondary related registration code, of the same subtype diagnosis of SpA. For Cox regression

analyses, individuals with contacts for SpA in the eight years preceding the index date were excluded, and in the scenario of reference individuals being diagnosed with IBD during the follow-up, they were censored at the time of diagnosis. All analyses were conducted using R (version 4.4.2), and the threshold for statistical significance for all tests was set at 0.05.

Ethics statement. The register data are protected by the Danish Act on Processing of Personal Data and are accessed through application to and approval from the Danish Data Protection Agency and the Danish Health Data Authority.

RESULTS

Cohort characteristics. Of 5,417,081 individuals living in Denmark between January 1, 2006, and July 31, 2014, 17,108 individuals were diagnosed with IBD. These individuals were matched 1:5 on age at matching date, sex, and municipality of residence to include 85,540 individuals without IBD. This study population was used for analysis of SpA preceding IBD diagnosis. After excluding persons with SpA diagnosis in the eight years preceding the index date, 16,468 individuals with IBD and 83,870 reference individuals remained in the study and were included in the analysis of SpA following IBD diagnosis. The study flowchart is described in Figure 1.

Among individuals with IBD, 5,043 (29.5%) individuals were diagnosed with CD, whereas the remaining 12,065 (70.5%) individuals were diagnosed with UC. Baseline characteristics of the study population are included in Table 1.

Prevalence of SpA before and after IBD diagnosis. The prevalence curves for SpA overall and the subtypes axial and peripheral SpA in individuals with IBD, CD, and UC and reference individuals are demonstrated in Figure 2. At all time points from the eight preceding years to the eight years following IBD, CD, and UC diagnosis, the prevalence of SpA was higher among those with IBD compared to the reference individuals. There was a sharp increase in SpA prevalence in the one year before IBD diagnosis and up to two years following IBD diagnosis, after which SpA prevalence plateaued. SpA prevalence was especially higher in individuals with CD.

Odds of SpA up to eight years before IBD diagnosis. The odds of SpA overall were increased in individuals with IBD, CD, and UC within the eight years preceding IBD diagnosis compared to reference individuals (adjusted OR [aOR] 1.95 [95% confidence interval (CI) 1.78–2.14], aOR 2.84 [95% CI 2.43–3.32], and aOR 1.61 [95% CI 1.43–1.81], respectively; Figure 3). The OR for axial SpA was higher relative to the OR for peripheral SpA in those with IBD compared to reference individuals (aOR 4.65 [95% CI 3.63–5.95] and aOR 1.74 [95% CI 1.58–1.93], respectively), and it was highest in individuals who were later diagnosed with CD (aOR 11.49, 95% CI 7.55–17.92).

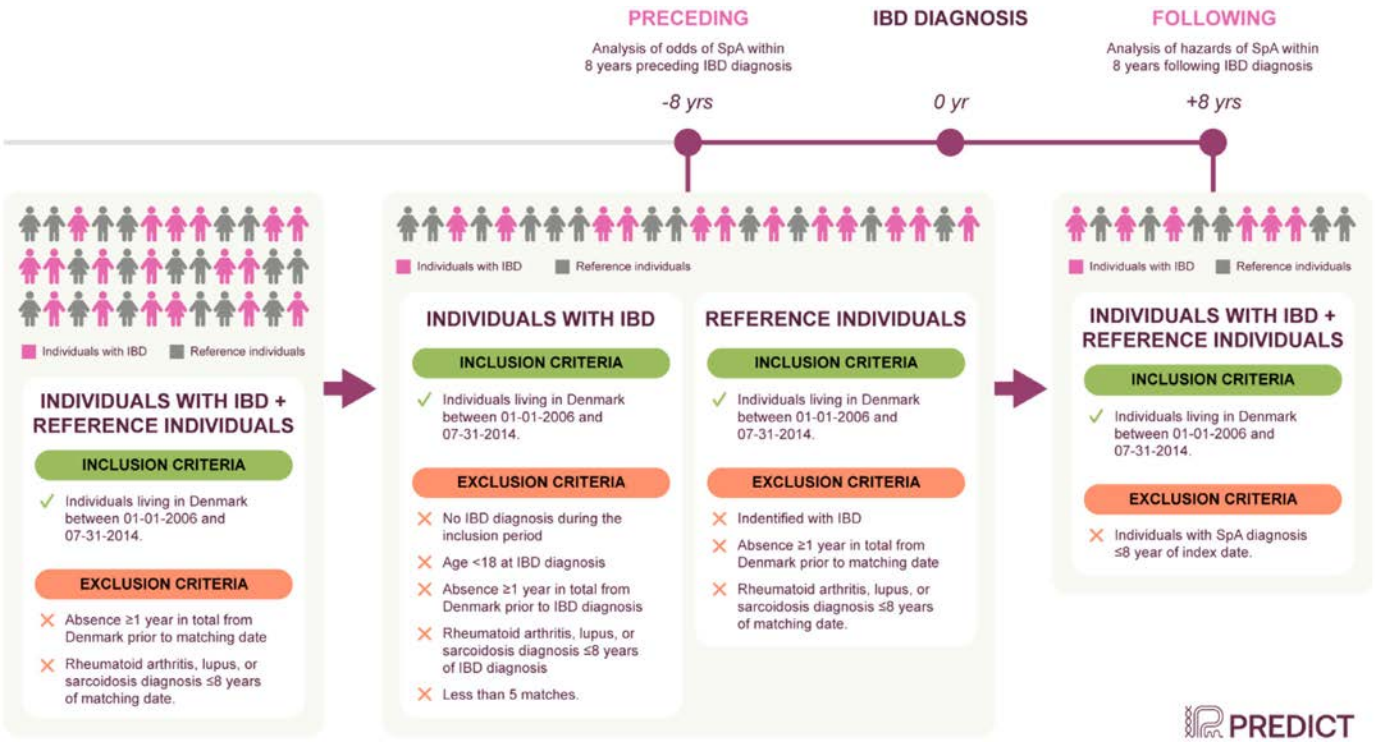

Figure 1. Flowchart for derivation of the study population. IBD, inflammatory bowel disease; SpA, spondyloarthritis.

Table 1. Baseline characteristics of the study population (N = 102,648)*

Baseline characteristics	Individuals with IBD (n = 17,108; 16.7%)	Reference individuals (n = 85,540; 83.3%)
IBD subtype, n (%)		
Crohn disease	5,043 (29.5)	–
Ulcerative colitis	12,065 (70.5)	–
Sex, n (%)		
Female	9,119 (53.3)	45,595 (53.3)
Period of birth, n (%)		
Before 1950	4,453 (26.0)	22,265 (26.0)
1950–1970	5,472 (32.0)	27,360 (32.0)
1971–1990	6,403 (37.4)	32,015 (37.4)
After 1990	780 (4.6)	3,900 (4.6)
Age at index date, n (%)		
<30 y	4,315 (25.2)	21,575 (25.2)
30–49 y	5,866 (34.3)	29,330 (34.3)
50–70 y	4,905 (28.7)	24,525 (28.7)
>70 y	2,022 (11.8)	10,110 (11.8)
Calendar period, n (%)		
2006–2008	5,682 (33.2)	28,410 (33.2)
2009–2011	6,386 (37.3)	31,930 (37.3)
2012–2014	5,040 (29.5)	25,200 (29.5)

* IBD, inflammatory bowel disease.

Hazards of SpA eight years after IBD diagnosis. Next, we estimated the adjusted HRs (aHRs) for SpA among those with IBD, CD, and UC compared to reference individuals. We found that the risk of SpA was increased in individuals with IBD, CD, and UC (aHR 2.51 [95% CI 2.34–2.70], aHR 3.17 [95% CI 2.81–3.59], and aOR 2.24 [95% CI 2.05–2.45], respectively; Figure 4). The highest aHR was for axial SpA in individuals with CD, compared to reference individuals, during the follow-up period (aHR 8.28, 95% CI 5.95–11.51).

Odds and hazards of SpA in specific time intervals. The odds of SpA (overall, axial, and peripheral) were increased in individuals with IBD, CD, and UC compared to reference individuals (Supplementary Figure 1A). The aORs generally decreased with increasing temporal distance from the date of IBD diagnosis. A similar trend was seen with the HRs of SpA following IBD diagnosis (Supplementary Figure 1B).

Stratified analysis. We found no evidence of effect modifiers in sex, age (in relevant groups), or calendar period with SpA (overall, axial, or peripheral) diagnosis preceding IBD diagnosis (Supplementary Figure 2). In analysis of SpA diagnosis following IBD diagnosis, the hazards of SpA (overall, axial, and peripheral) were higher among women and in the age group 18 to 45 years (Supplementary Figure 3).

Sensitivity analysis. We conducted sensitivity analyses excluding the SpA subtype enthesitis, changing the SpA diagnosis definition to two registrations of the same subtype of SpA instead of one, and analyzing ankylosing spondylitis and sacroiliitis separately. Across all analyses, estimates were consistent and numerically higher in a majority (Supplementary Figures 4–6).

DISCUSSION

In this nationwide population-based cohort study with analysis of data from over two decades, we found that SpA and IBD diagnoses were associated with each other in the eight years preceding and following IBD diagnosis. Compared to matched reference individuals, individuals with IBD were more likely to have been diagnosed with SpA preceding IBD diagnosis. Similarly, the hazards of SpA following IBD diagnosis were increased among individuals with IBD, relative to reference individuals. These associations were stronger for CD than UC and for axial SpA than peripheral SpA. The probability of SpA diagnosis remained higher in those with IBD throughout the study period but with temporal variability, rising sharply in the few years preceding and following IBD diagnosis and plateauing thereafter. Following IBD diagnosis, variables such as sex and age at IBD diagnosis were associated with interaction effects, with a higher probability of SpA preceding IBD diagnosis among women and young adults. To our knowledge, this is the first study to examine the temporal relationship between IBD and SpA, with emphasis on incidence cases, in a population-based cohort with over two decades of follow-up and the role of relevant clinical variables in this relationship.

Our finding of SpA diagnosis preceding IBD diagnosis has clinical, epidemiologic, and mechanistic relevance: first, individuals with SpA, both axial and peripheral but especially the former, are likely to be at risk for developing IBD. Therefore, regular screening for gastrointestinal symptoms, inflammatory biomarker testing such as fecal calprotectin, and prompt subspecialist referral, as indicated, are warranted to facilitate early IBD diagnosis. This is especially relevant for CD, which was more strongly associated with SpA in our analysis, relative to UC. CD is also associated with protean symptoms and delay in diagnosis, and its early diagnosis and treatment are critical to mitigate disease progression and complications.[12] Epidemiologically, subgroups that are at increased risk of IBD following SpA diagnosis, such as women and young adults, warrant close clinical monitoring for symptoms. Finally, these insights provide impetus to unravel the immunologic and inflammatory pathways that are common across these immune-mediated diseases.[15]

Our findings are consistent with previous reports that demonstrate a relationship between SpA and intestinal inflammation. In a retrospective analysis of 180 individuals with SpA and without IBD, fecal calprotectin levels were elevated in 16% of individuals, and on digital chromoendoscopy, a substantial proportion of individuals had evidence of intestinal inflammation.[16] In a systematic review of seven studies, 21.2% to 70.7% of patients with SpA had elevated fecal calprotectin levels.[17] Endoscopic and

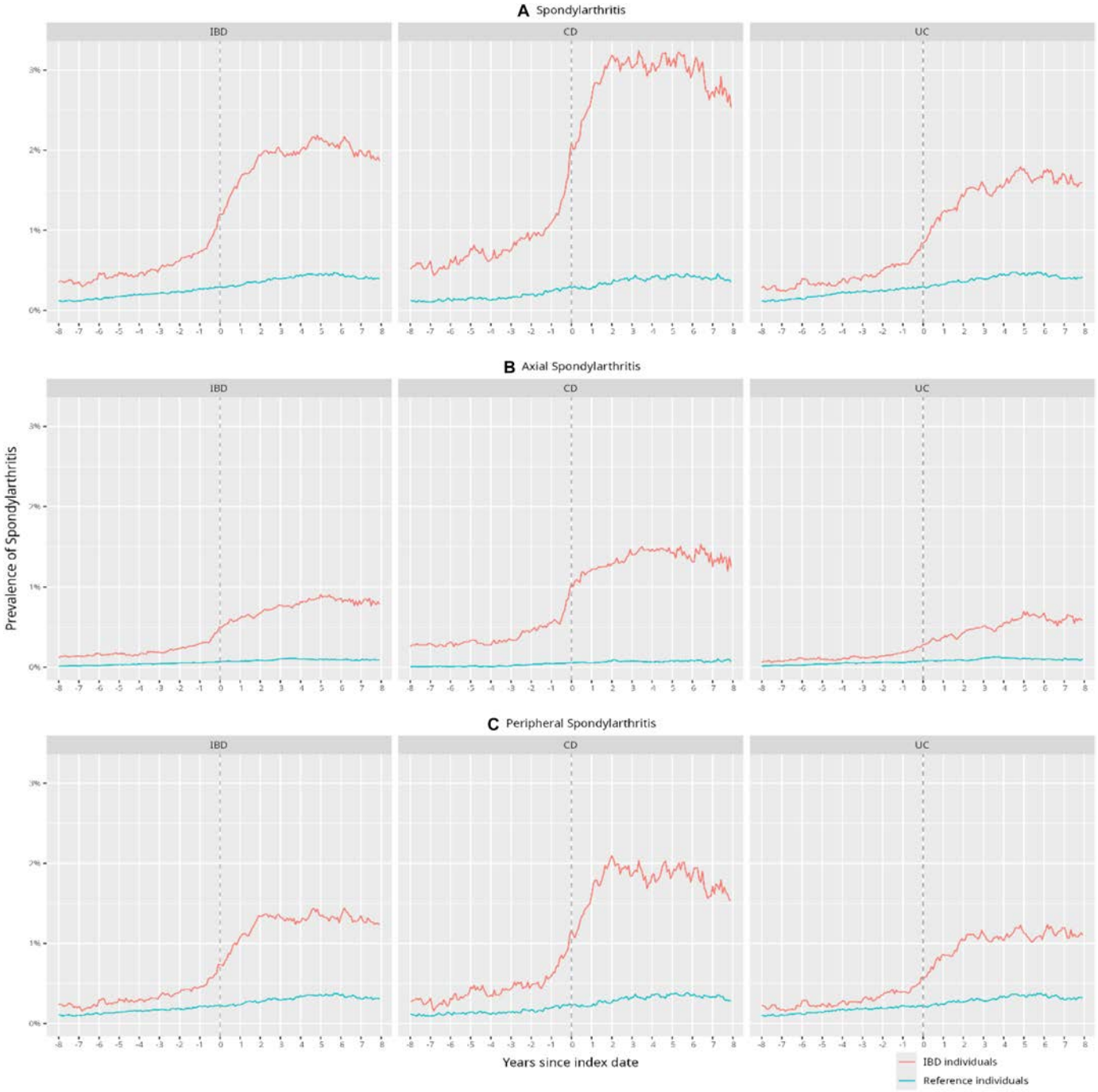

Figure 2. Monthly prevalence for SpA in individuals with IBD, CD, and UC compared to matched reference individuals. Monthly prevalence of (A) overall, (B) axial, and (C) peripheral SpA in individuals with IBD, CD, and UC preceding and following IBD diagnosis compared to matched references. An incident of SpA in each month for calculation of prevalence was defined as a new or ongoing outpatient visit or inpatient contact. Any outpatient visit registered under an outpatient contact and any inpatient contact associated with a primary or secondary IBD diagnosis were included. CD, Crohn disease; IBD, inflammatory bowel disease; SpA, spondyloarthritis; UC, ulcerative colitis. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/art.70095/abstract.

histologic evidence of intestinal inflammation is reported in a majority of individuals in association with SpA across studies.[18,19] At a molecular level, commonality across immune-mediated diseases is represented in genetic susceptibility, environmental triggers, targeting of end organs by activated immune cells, and disrupted cytokine responses.[15] The trajectory of SpA, particularly closer to IBD diagnosis, mirrors that of several preclinical biomarkers, further supporting overlap across immune-mediated diseases.[20]

Following IBD diagnosis, the risk of SpA is increased as well. This is especially true for disease subtypes axial SpA and CD. Others have reported consistent findings. In a systematic

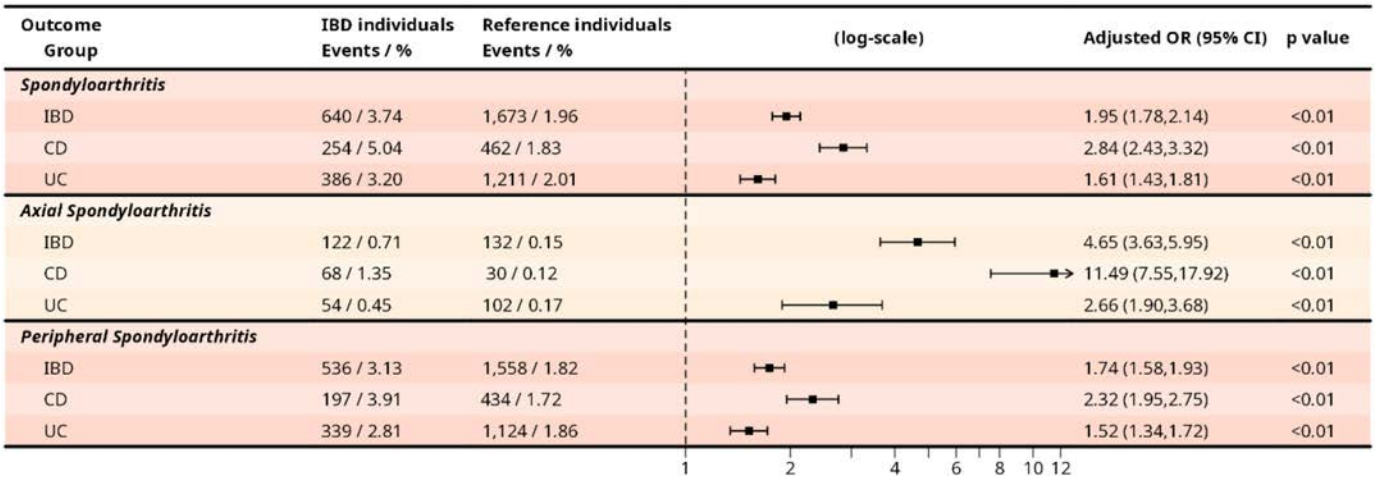

Figure 3. ORs of SpA within the eight years preceding IBD diagnosis. ORs and 95% CIs for SpA (overall, axial, and peripheral) in individuals with IBD, CD, and UC within the eight years preceding IBD diagnosis/index date when compared to matched references. All models were adjusted for age at index date, sex, and calendar period. CD, Crohn disease; CI, confidence interval; IBD, inflammatory bowel disease; OR, odds ratio; SpA: spondyloarthritis; UC, ulcerative colitis. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/art.70095/abstract.

review and meta-analysis of 71 prevalence studies and 3 incidence studies, Karreman et al reported that axial and peripheral SpA occurred in up to 13% of individuals with IBD.[21] However, it is important to note that although some of the estimates in our analysis were large, the number of events were relatively few, and therefore the absolute risk is likely to be not that large. Our findings have clinical implications. Regular screening for musculoskeletal symptoms and further testing, as indicated, are warranted and can help with early diagnosis and early management of SpA. A sharp increase in risk after diagnosis followed by a plateau may reflect uncontrolled inflammation early on and subsequently a beneficial impact of appropriate advanced therapies, many of which are used to treat both IBD and SpA.

Further, we report additional original information. SpA was associated with both CD and UC, with higher estimates for CD. Although others have reported on SpA and CD, our finding of a relationship of SpA with UC is less well known and highlights the importance of monitoring for extraintestinal manifestations across both IBD subtypes. Next, we found that the diagnosis of SpA was higher in the few years preceding and following IBD diagnosis. This may be related in part to increased contact with the health care system during this period. However, we note that the increase in the SpA slope was sharper for the outcome in CD than UC, even though UC is associated with more overt symptoms and therefore possibly more contact with the health care system than CD. This suggests that there may be a true increase in SpA incidence in the peri-IBD diagnosis period; during this period, closer follow-up of individuals with IBD may be warranted. We also report interaction effects; female sex and younger age at CD diagnosis are associated with higher hazards of SpA

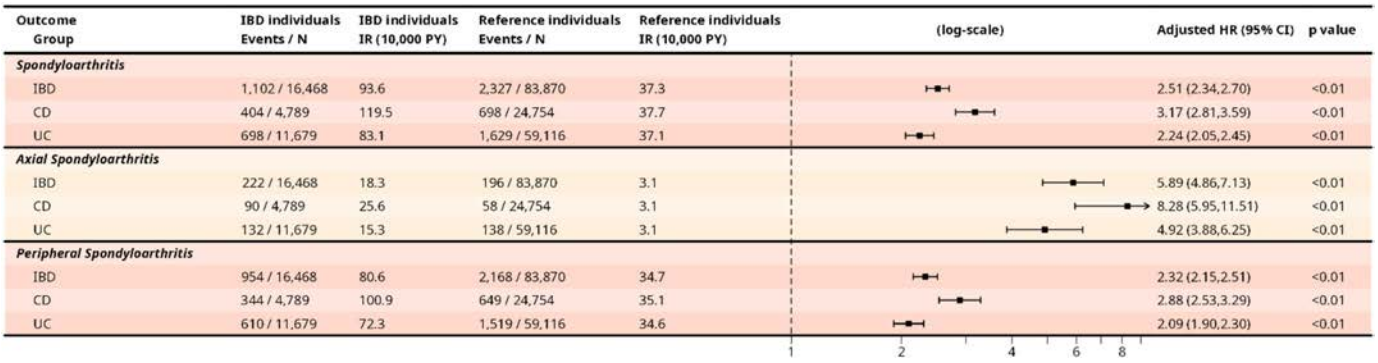

Figure 4. HRs of SpA within the eight years following IBD diagnosis. HRs and 95% CIs for SpA (overall, axial, and peripheral) in individuals with IBD, CD, and UC within the eight years following IBD diagnosis/index date when compared to matched references. Individuals with an SpA diagnosis before their index date were excluded. All models were adjusted for age at index date, sex, and calendar period. CD, Crohn disease; CI, confidence interval; HR, hazard ratio; IBD, inflammatory bowel disease; IR, incidence rate; PY, person-years; SpA, spondyloarthritis; UC, ulcerative colitis. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/art.70095/abstract.

following IBD diagnosis. These variables can inform clinical practice and warrant further study to understand underlying mechanisms. However, it is important to acknowledge that the individuals in the oldest age group are more likely to represent a healthier subset of the population within that age range, as the analysis following IBD diagnosis was limited to incident SpA cases.

There are considerable overlaps between SpA and IBD, including shared genetic and nongenetic risk factors, waxing and waning disease course with progressive end-organ injury, disordered immune response with infiltration of target tissue, and complications.[15] In fact, it has been proposed that a cytokine-based classification of immune-mediated diseases may better represent pathotypes and has greater therapeutic utility over an organ-based classification.[15] The tumor necrosis factor α (TNFα) pathway represents a common effector pathway across both diseases, and TNF inhibitors are effective in both SpA and IBD.[10,12] JAK inhibition, which blocks several cytokine pathways, is also effective in both diseases.[22] In contrast, interleukin-17 (IL-17) and IL-23 blockades are effective SpA and IBD treatments, respectively, but not of the converse disease.[15]

Strengths of our study include use of a population-based cohort with long-term follow-up, application of validated definitions for IBD and SpA, and effect modification analysis for relevant covariates. Our study also has limitations. Our two study populations estimating SpA prevalence ORs in IBD using logistic regression and estimating HRs for SpA in survival analyses are distinct and not directly comparable even though they were derived from the same population-based cohort. The absolute number of events for specific subgroups is small, and there is a risk of unmeasured confounding. Although the former is a limitation, it can also be seen as a strength in this study because for rare outcomes, such as SpA, ORs and HRs approximate each other and provide comparable clinical information.[23] Another limitation is a risk of misclassification bias; however, our definitions of IBD, CD, and UC in the DNPR have a positive predictive value of 95%.[24]

In summary, we report on the epidemiologic relationship between IBD and SpA and the trajectory of SpA and IBD alongside each other in a nationwide temporal trends analysis. We provide actionable clinical guidance to improve early diagnosis and treatment and highlight knowledge gaps. Shared mechanisms across IBD and SpA in the preclinical period warrant further exploration.

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AUTHOR CONTRIBUTIONS

All authors contributed to at least one of the following manuscript preparation roles: conceptualization AND/OR methodology, software, investigation, formal analysis, data curation, visualization, and validation AND drafting or reviewing/editing the final draft. As corresponding author, Dr Agrawal confirms that all authors have provided the final approval of the version to be published and takes responsibility for the affirmations regarding article submission (eg, not under consideration by another journal), the integrity of the data presented, and the statements regarding compliance with institutional review board/Declaration of Helsinki requirements.

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Efficacy and Safety of Guselkumab in Participants With Active Psoriatic Arthritis After Inadequate Response to One Prior Tumor Necrosis Factor Inhibitor: Week-24 Results of a Phase 3, Randomized, Placebo-Controlled Study

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Objective. To evaluate the efficacy and safety of guselkumab, an interleukin-23p19 subunit inhibitor, in participants with active psoriatic arthritis (PsA) and inadequate response (inadequate efficacy and/or intolerance) to one prior tumor necrosis factor (TNF) inhibitor.

Methods. In SOLSTICE (phase 3b, randomized, multicenter, double-blind, placebo-controlled study), enrolled adults with active PsA (three or more swollen joints; three or more tender joints; C-reactive protein ≥ 0.3 mg/dL) and inadequate response to one prior TNF inhibitor were randomized to guselkumab 100 mg every 4 weeks (Q4W), guselkumab 100 mg at weeks 0 and 4 and then Q8W, or placebo with crossover to guselkumab Q4W at week 24. The primary endpoint was ≥20% improvement in American College of Rheumatology criteria (ACR20) at week 24. Secondary endpoints included ACR50, ACR70, Investigator's Global Assessment of psoriasis (IGA) score of 0 or 1 with ≥2-grade improvement, ≥90% improvement in Psoriasis Area and Severity Index (PASI90), and minimal disease activity (MDA) at week 24 and were analyzed by intention-to-treat.

Results. Analyses included 451 randomized participants (Q4W n = 150; Q8W n = 151; placebo n = 150). At week 24, significantly greater proportions of guselkumab (Q4W/Q8W)-treated participants versus placebo-treated participants, respectively, achieved ACR20 (primary endpoint: 58.6%/62.2% vs 34.8%), ACR50 (31.4%/32.1% vs 12.2%), ACR70 (17.5%/17.3% vs 2.0%), IGA 0/1 response (50.0%/57.3% vs 17.4%), PASI90 (49.4%/45.5% vs 12.0%), and MDA (18.8%/23.9% vs 5.4%) (all $P < 0.001$). Through week 24, 46.7%, 53.6%, and 48.3% of participants receiving guselkumab Q4W, guselkumab Q8W, and placebo, respectively, had one or more adverse event. One death occurred (myocardial infarction).

Conclusion. Comparable efficacy was observed with both guselkumab regimens in participants with active PsA and inadequate response to one prior TNF inhibitor; safety findings were consistent with the known profile of guselkumab in patients with psoriatic disease.

INTRODUCTION

Psoriatic arthritis (PsA) is characterized by chronic inflammation affecting the joints and skin and is notable for the heterogeneity in symptom presentation, including peripheral arthritis, axial inflammation, enthesitis, dactylitis, and psoriatic skin plaques and nail disease.[1–3] Treatment selection for patients with PsA can be challenging and may be influenced

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by several factors such as active PsA domains, comorbidities, contraindications, and patient preferences. Current international treatment guidelines recommend selecting therapies to effectively address active domains in the individual patient while also taking into consideration possible contraindications.[1–3] For patients with relatively mild disease, treatment may begin with nonsteroidal anti-inflammatory drugs (NSAIDs) or conventional synthetic disease-modifying antirheumatic drugs (csDMARDs). However, for those with persistently active disease or poor prognostic indicators, advanced therapy with biologic DMARDs (bDMARDs) or targeted synthetic DMARDs (tsDMARDs) is generally recommended.

Tumor necrosis factor (TNF) inhibitors were the first advanced therapies approved for patients with active PsA and, historically, have been the first bDMARDs prescribed for these patients.[4] Although TNF inhibitors are highly efficacious for many patients, a substantial proportion do not respond within six months (~40%–80%) or lose response over time, with decreasing duration of persistence with each subsequent TNF inhibitor.[4] Currently, bDMARDs targeting interleukin-12/23p40 (IL-12/23p40),[5] IL-23p19,[6,7] and IL-17[8–10] are approved for patients with active PsA. Treatment guidelines from the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA), EULAR, and the American College of Rheumatology (ACR)/National Psoriasis Foundation provide comprehensive recommendations that are appropriate for the majority of patients with PsA when considering optimal therapies to address active domains and related conditions.[1–3] However, to date, there are no evidence-based recommendations that specifically address the optimal sequence of therapies and whether or not patients with PsA should switch to another mechanism of action for those who have experienced inadequate efficacy or intolerance to an initial TNF inhibitor.

Guselkumab, the only fully human, dual acting,[11] selective IL-23p19 subunit inhibitor, administered subcutaneously every four or eight weeks (Q4W/Q8W) demonstrated significant multidomain efficacy in the phase 3, randomized, placebo-controlled DISCOVER-1[12] and DISCOVER-2[13] studies. Across both studies, the majority of participants were biologic-naive; 118 (31%) in DISCOVER-1 were TNF inhibitor–experienced, with 44 (37%) of those having discontinued their prior TNF inhibitor due to inadequate response (TNFi-IR). In the subsequent phase 3b COSMOS study, guselkumab demonstrated efficacy in TNFi-IR participants with active PsA; however, only the Q8W dosing regimen was evaluated.[14] Post hoc analyses of TNF inhibitor–experienced DISCOVER-1 participants suggested that TNFi-IR patients may derive incremental benefit from the more frequent Q4W dosing regimen, particularly for achieving stringent response outcomes such as ≥50% or ≥70% improvement in the ACR response criteria (ACR50/70) and minimal disease activity (MDA).[12,15] Thus, SOLSTICE was designed to evaluate the efficacy and safety of both guselkumab dosing regimens in TNFi-IR participants with active PsA;[16] primary efficacy and safety results through week 24 are reported herein.

PATIENTS AND METHODS

Participants and study design. SOLSTICE is an ongoing, phase 3, multicenter, randomized, placebo-controlled study that enrolled adults (≥18 years) with a PsA diagnosis for at least six months meeting the Classification Criteria for Psoriatic Arthritis (CASPAR).[16,17] Eligible participants had active PsA (three or more swollen joints; three or more tender joints; C-reactive protein [CRP] ≥ 0.3 mg/dL) and either documented history of psoriasis or at least one psoriatic plaque (≥2 cm diameter) and/or nail changes consistent with psoriasis. All participants had an inadequate response (inadequate efficacy and/or intolerance) to only one prior TNF inhibitor. Inadequate efficacy was defined as a lack of benefit (documented by the treating physician) with one prior TNF inhibitor after ≥12 weeks of adalimumab, certolizumab pegol, etanercept, or golimumab (or biosimilars) or ≥14 weeks of infliximab (or biosimilars). Documented lack of benefit included inadequate improvements in swollen or tender joint count (SJC/TJC), physical function, or disease activity. Participants could not have other inflammatory diseases that might confound efficacy assessments, including but not limited to rheumatoid arthritis, nonradiographic or radiographic axial spondyloarthritis (not including patients with a primary PsA diagnosis with spondylitis), systemic lupus erythematosus, or Lyme disease (confirmed by Western blot). Participants also could not have unstable cardiac disease or current malignancy or history of malignancy within the past five years (except nonmelanoma skin cancer or cervical cancer in situ that was adequately treated with no evidence of recurrence for three or more months).

Concomitant therapy at stable doses (three or more months) was permitted with one of the following csDMARDs: methotrexate (MTX; ≤25 mg/week), sulfasalazine (≤3 g/day), hydroxychloroquine (≤400 mg/day), or leflunomide (≤20 mg/day). Stable concomitant treatment was also permitted with NSAIDs or other analgesics for PsA and/or oral glucocorticoids (≤10 mg/day prednisone, two or more weeks). Participants could not have received the following TNF inhibitors (or biosimilars) within the specified timeframe before the first study agent administration: infliximab or intravenous golimumab (eight weeks); subcutaneous golimumab, adalimumab, or certolizumab pegol (six weeks); and etanercept (four weeks). Prior treatment with more than one TNF inhibitor (or their biosimilars), other bDMARDs, or a Janus kinase (JAK) inhibitor was not permitted. Participants also could not have received systemic immunosuppressants; apremilast; csDMARDs other than MTX, sulfasalazine, hydroxychloroquine, or leflunomide; epidural, intra-articular, intramuscular, or intravenous glucocorticoids; or phototherapy or systemic treatments that could affect psoriasis evaluations within four weeks before first study agent administration. Topical treatments that could affect

psoriasis evaluations were prohibited within two weeks of the first study agent adminstration.

Participants were centrally randomized using an interactive web response system, with computer-generated permuted blocks and stratified by baseline csDMARD use (yes or no), to receive guselkumab 100 mg Q4W; guselkumab 100 mg at weeks 0 and 4 and Q8W thereafter; or placebo with crossover to guselkumab Q4W at week 24. At week 16, participants with <20% improvement from baseline in both SJC and TJC were eligible for early escape and could initiate or increase the dose of one permitted concomitant medication, up to the maximum protocol-specified dose. Study agents were identical in appearance and provided as prefilled syringes. Participants in the Q8W group received placebo injections at 8-week intervals beginning at week 8 to maintain the blind. The final efficacy and safety visits will be at weeks 100 and 112, respectively. As specified in the protocol, study investigators and participants will remain blinded to treatment group assignment through week 112. Therefore, only aggregate results are presented herein.

SOLSTICE is being conducted in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines. The protocol was approved by an institutional review board or ethics committee for each site. All participants provided written informed consent.

Assessments. At baseline, weight and body mass index were collected by the investigators, and participants self-identified their race and ethnicity by selecting from a fixed set of categories. Disease activity assessments included SJC (0–66), TJC (0–68), and physician global assessment of disease activity (PhGA; visual analog scale [VAS] 0–10). Enthesitis was assessed using the Leeds Enthesitis Index (LEI; 0–6)[18] and the Spondyloarthritis Research Consortium of Canada (SPARCC) enthesitis score (0–16);[19] dactylitis was evaluated using the dactylitis severity score (DSS; 4-point score of 0 = none to 3 = severe for each digit; total of 0–60).[20,21] Psoriatic skin disease activity was assessed using the Investigator's Global Assessment of psoriasis (IGA; 0 [clear] to 4 [severe])[22] and the Psoriasis Area and Severity Index (PASI; 0–72),[23] both among participants with ≥3% psoriatic body surface area (BSA) and IGA ≥2 at baseline. Independent joint assessors at each site who were blinded to all other disease activity assessments evaluated SJC, TJC, enthesitis, and dactylitis. Skin assessments were performed by the treating physician (or designee).

Participants rated their global assessment of disease activity (arthritis and arthritis+psoriasis; both VAS 0–10), pain (VAS 0–10), and physical function (Health Assessment Questionnaire–Disability Index [HAQ-DI]; 0–3).[24] They rated their fatigue using the Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-Fatigue) tool (0–52).[25] Participants also reported their overall health-related quality of life (HRQoL) with the 36-item Short-Form Health Survey physical component summary (SF-36 PCS)[26] score. MDA and very low disease activity (VLDA) were defined as achieving five or all seven, respectively, of the following criteria: SJC ≤ 1, TJC ≤ 1, PASI ≤ 1, patient-reported pain ≤ 15 (VAS 0–100), patient global assessment ≤ 20 (VAS 0–100), HAQ-DI ≤ 0.5, and one or less tender entheseal points.[27]

Participants were monitored for adverse events (AEs). AEs of interest included serious AEs (SAEs), AEs resulting in discontinuation of study agent, infections (including serious and opportunistic infections and active tuberculosis), malignancies, major adverse cardiovascular events (MACEs; cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke), and injection site reactions. Serum samples were collected at regular intervals for chemistry and hematology laboratory assessments, determining serum guselkumab concentrations, and detecting antibodies to guselkumab. The presence of antibodies to guselkumab was assessed using a validated, sensitive, drug-tolerant electrochemiluminescence immunoassay.

Statistical analyses. The primary endpoint was the proportion of participants achieving an ACR20 response at week 24. Based on week-24 ACR20 response rates in the DISCOVER-1 (Q4W 59.4%; Q8W 52.0%; placebo 22.2%)[12] and COSMOS (Q8W 44.4%; placebo 19.8%)[14] studies, a sample size of 150 participants in each treatment group was predicted to provide >90% power (two sided; $\alpha = 0.05$) to detect statistically significant differences between each guselkumab group and the placebo group. Multiplicity-controlled secondary endpoints (all at week 24) were tested in the following order: IGA 0/1 response (IGA of 0 or 1 and ≥2-point improvement), ≥90% improvement in PASI score (PASI90), change from baseline in HAQ-DI, change from baseline in SF-36 PCS, change from baseline in FACIT-Fatigue, and achievement of MDA. The proportions of participants achieving ACR20 at week 16, ACR50 at weeks 16 and 24, and ACR70 at week 24 were weakly controlled endpoints that were not part of the sequential testing process but were prespecified to be tested upon achievement of statistical significance for the primary endpoint; therefore, *P* values generated for these endpoints are not considered nominal. Other secondary endpoints included response rates for achieving VLDA, HAQ-DI improvement ≥0.35[28] (among participants with baseline HAQ-DI ≥0.35), and FACIT-Fatigue improvement ≥4 at week 24 and ACR20/50/70 over time. Additionally, outcomes related to enthesitis and dactylitis were determined among participants with a baseline score >0: proportions of participants with LEI, SPARCC enthesitis score, and DSS of 0 at week 24 and least squares (LS) mean changes from baseline to week 24 in these scores.

Efficacy analyses were summarized by randomized treatment group. Participants were considered nonresponders or to have no change from baseline if they met the following treatment failure rules: discontinuation of study agent for any reason other than natural disaster (COVID-19 site restrictions) or major disruption (Russia and Ukraine crisis), initiation of or increase in dose of

csDMARDs or oral glucocorticoids above baseline doses (including participants meeting early escape criteria), or initiation of protocol-prohibited PsA therapies. Severe treatment noncompliance was defined as missing >30% of the planned doses from week 0 up to and including a given time point (ie, two or more doses for week-24 endpoints). For ACR20/50/70, IGA 0/1, PASI90, MDA, VLDA, HAQ-DI, and FACIT-Fatigue responses, after applying treatment failure rules, data from participants who discontinued study agent or had severe noncompliance due to natural disaster or major disruption were imputed by multiple imputation (MI) at all subsequent time points (study agent discontinuation) or the next time point (severe noncompliance). Other missing data were imputed using nonresponder imputation (NRI). For continuous secondary endpoints, after applying treatment failure rules, data after participants discontinued study agent or had severe noncompliance due to natural disaster or major disruption were not used; all missing data were imputed by MI. Treatment group differences were assessed using the combined standardized Wilson–Hilferty transformation of the Cochran–Mantel–Haenszel test, stratified by baseline csDMARD use (yes or no), for categorical endpoints and analysis of covariance (including baseline score, treatment group, and baseline csDMARD use [yes or no]) for continuous variables.

For achievement of enthesitis (LEI and SPARCC) and dactylitis resolution, after applying treatment failure rules, data after participants discontinued study agent or had severe noncompliance due to natural disaster or major disruption were not used, and any other missing data were imputed using NRI. Response rates and nominal *P* values were determined using a generalized linear mixed model including treatment group, visit, an interaction term of visit with treatment group, and baseline csDMARD use (yes or no).

AEs were summarized by actual treatment received for all participants who received one of more administration of study agent. Pharmacokinetic and immunogenicity analyses included all participants who received one or more guselkumab administration. ACR20 and ACR50 response rates were determined by guselkumab concentration quartiles for both dosing regimens.

Data availability. The data sharing policy of Johnson & Johnson is available at https://www.jnj.com/innovativemedicine/our-innovation/clinical-trials/transparency. As noted on this site, requests for access to the study data can be submitted through the Yale Open Data Access Project site at http://yoda.yale.edu.

RESULTS

Participant disposition. Data for these analyses were collected from September 28, 2021, through October 28, 2024; 729 individuals were screened. One enrolled participant was randomized and received study agent at two sites simultaneously and was therefore excluded from all efficacy and safety analyses. The final study population comprised 451 participants (Q4W n = 150; Q8W n = 151; placebo n = 150) from 103 sites in 12 countries. One participant in the placebo group withdrew before receiving any study agent. Through week 24, an additional 26 participants (5.8%; Q4W n = 8 [5.3%]; Q8W n = 7 [4.6%]; placebo n = 11 [7.4%]) discontinued study agent (Figure 1), 5 (Q4W n = 1; Q8W n = 1; placebo n = 3) due to an AE. The most common

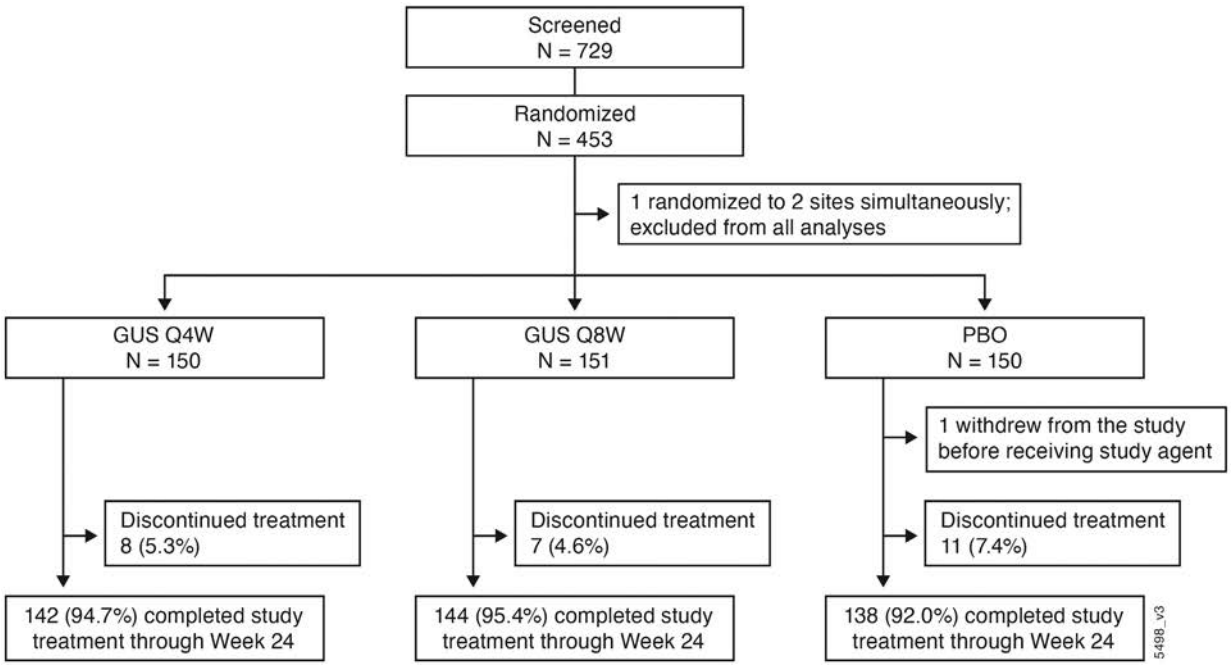

Figure 1. Participant disposition through week 24 of the SOLSTICE study. GUS, guselkumab; PBO, placebo; Q4W, every 4 weeks; Q8W, every 8 weeks.

Table 1. Baseline characteristics of SOLSTICE participants*

	Guselkumab 100 mg		
	Q4W (N = 150)	Q8W (N = 151)	Placebo (N = 150)
Demographics			
Age, years	50.6 ± 13.3	51.9 ± 12.9	49.2 ± 12.6
Sex			
Female	75 (50.0)	77 (51.0)	85 (56.7)
Male	75 (50.0)	74 (49.0)	65 (43.3)
Race			
White	141 (94.0)	143 (94.7)	141 (94.0)
Black or African-American	5 (3.3)	6 (4.0)	4 (2.7)
Asian	3 (2.0)	0	1 (0.7)
American Indian or Alaska Native	1 (0.7)	0	2 (1.3)
Not reported/unknown	0	2 (1.3)	2 (1.3)
Ethnicity			
Hispanic or Latino	18 (12.0)	18 (11.9)	22 (14.7)
Not Hispanic or Latino	132 (88.0)	128 (84.8)	127 (84.7)
Not reported	0	5 (3.3)	1 (0.7)
Weight, kg	86.5 (20.8)	89.5 (19.8)	85.9 (21.1)
BMI, kg/m^2	30.0 (6.5)	30.9 (6.6)	30.0 (7.3)
Disease characteristics			
PsA duration, years	8.8 ± 8.3	8.3 ± 7.5	7.0 ± 6.6
SJC, 0–66	10.7 ± 7.8	10.3 ± 6.6	10.2 ± 6.4
TJC, 0–68	18.1 ± 12.6	17.1 ± 11.2	16.8 ± 11.6
Patient's assessment of pain, VAS, 0–10	6.1 ± 2.0	6.2 ± 2.0	6.2 ± 2.0
Patient's global assessment (arthritis), VAS, 0–10	6.1 ± 2.1	6.2 ± 2.1	6.2 ± 1.9
Physician's global assessment, VAS, 0–10	6.5 ± 1.5	6.7 ± 1.6	6.5 ± 1.6
HAQ-DI, 0–3	1.3 ± 0.6	1.3 ± 0.6	1.3 ± 0.6
CRP, mg/dL	1.2 ± 1.6	1.3 ± 1.7	1.4 ± 1.9
Participants with BSA ≥3% and IGA ≥2, N	92	89	86
IGA, 0–4			
2	44 (47.8)	39 (43.8)	39 (45.3)
3	37 (40.2)	45 (50.6)	42 (48.8)
4	11 (12.0)	5 (5.6)	5 (5.8)
PASI, 0–72	10.4 ± 9.5	10.1 ± 9.4	9.0 ± 6.5
Participants with LEI >0	84/149 (56.4)	84/151 (55.6)	79/148 (53.4)
LEI, 1–6	2.7 ± 1.5	2.6 ± 1.6	2.5 ± 1.5
Participants with SPARCC enthesitis score >0	95/149 (63.8)	97/151 (64.2)	93/148 (62.8)
SPARCC enthesitis score, 1–16	5.6 ± 4.0	5.2 ± 3.9	5.1 ± 3.8
Participants with dactylitis	54/149 (36.2)	42/151 (27.8)	52/147 (35.4)
DSS, 1–60	5.8 ± 5.7	6.3 ± 9.0	6.5 ± 7.4
DAPSA[a]	42.2 ± 19.8	41.2 ± 17.8	40.8 ± 17.6
PASDAS, 0–10	6.2 ± 0.9	6.2 ± 1.0	6.2 ± 0.9
SF-36 PCS, 0–100	34.2 ± 8.0	33.6 ± 7.6	33.9 ± 7.5
FACIT-Fatigue, 0–52	28.3 ± 10.1	28.2 ± 11.6	27.6 ± 10.6
Prior TNF inhibitor			
Adalimumab	92 (61.3)	81 (53.6)	92 (61.3)
Certolizumab pegol	5 (3.3)	5 (3.3)	4 (2.7)
Etanercept	26 (17.3)	29 (19.2)	24 (16.0)
Golimumab	20 (13.3)	31 (20.5)	22 (14.7)
Infliximab	7 (4.7)	5 (3.3)	8 (5.3)
Reason for discontinuing prior TNF inhibitor			
Inadequate response	126 (84.0)	121 (80.1)	118 (78.7)
Intolerance	20 (13.3)	30 (19.9)	28 (18.7)
Inadequate response and intolerance	4 (2.7)	0	4 (2.7)

(Continued)

Table 1. (*Cont'd*)

	Guselkumab 100 mg		
	Q4W (N = 150)	Q8W (N = 151)	Placebo (N = 150)
Concomitant medications			
csDMARDs	88 (58.7)	86 (57.0)	84 (56.0)
MTX	75 (50.0)	69 (45.7)	72 (48.0)
Dose, mg/week	17.4 ± 4.2	16.2 ± 4.6	16.8 ± 4.3
Oral glucocorticoids	17 (11.3)	22 (14.6)	17 (11.3)
NSAIDs	71 (47.3)	70 (46.4)	69 (46.0)

* Data presented as n (%), n/N (%), or mean ± SD unless otherwise noted. BMI, body mass index; BSA, body surface area; CRP, C-reactive protein; csDMARD, conventional synthetic disease-modifying antirheumatic drug; DAPSA, Disease Activity Index for Psoriatic Arthritis; DSS, dactylitis severity score; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy–Fatigue; HAQ-DI, Health Assessment Questionnaire–Disability Index; IGA, Investigator's Global Assessment of psoriasis; LEI, Leeds Enthesitis Index; MTX, methotrexate; NSAID, nonsteroidal anti-inflammatory drug; PASDAS, Psoriatic Arthritis Disease Activity Score; PASI, Psoriasis Area and Severity Index; PsA, psoriatic arthritis; Q4W, every 4 weeks; Q8W, every 8 weeks; SF-36 PCS, 36-item Short-Form Health Survey physical component summary; SJC, swollen joint count; SPARCC, Spondyloarthritis Research Consortium of Canada; TJC, tender joint count; TNF, tumor necrosis factor; VAS, visual analog scale.
[a] DAPSA disease activity categories defined as the following: remission (≤4); low disease activity (>4 to ≤14); moderate disease activity (>14 to ≤28); high disease activity (>28).

reason for study agent discontinuation was withdrawal of consent (Q4W n = 3; Q8W n = 5; placebo n = 4).

At week 16, 58 participants met the early escape criteria (Q4W n = 14 [9.3%]; Q8W n = 8 [5.3%]; placebo n = 36 [24.0%]). Of these, 19 (32.8%) initiated or increased the dose of permitted medications (Q4W n = 6 of 14 [42.9%]; Q8W n = 2 of 8 [25.0%]; placebo n = 11 of 36 [30.6%]). One participant discontinued study agent due to evacuation from Ukraine (major disruption); no participant discontinued study agent due to COVID-19 restrictions. A total of 37 participants (8.2%; Q4W n = 13 [8.7%]; Q8W n = 12 [7.9%]; placebo n = 12 [8.0%]) were classified as having severe treatment noncompliance due to natural disaster or major disruption.

Baseline characteristics. Baseline demographic and disease characteristics were well-balanced among the treatment groups (Table 1). Baseline scores for clinical characteristics and HRQoL were consistent with moderately to severely active PsA. Across the treatment groups, the mean age was 49 to 52 years, 50% to 57% were female, and 94% to 95% were White. The mean SJC and TJC ranged from 10.2 to 10.7 and 16.8 to 18.1, respectively; 53.4% to 56.4% had an LEI >0 (mean: 2.5–2.7), 62.8% to 64.2% had a SPARCC >0 (mean: 5.1–5.6), and 27.8% to 36.2% had dactylitis (mean DSS: 5.8–6.5). Patient-reported outcomes were indicative of substantial impairment of physical function and HRQoL and high levels of fatigue. Additionally, 11 participants (Q4W n = 3 [2.0%]; Q8W n = 5 [3.3%]; placebo n = 3 [2.0%]) reported a medical history of fibromyalgia.

The most common prior TNF inhibitor was adalimumab (53.6%–61.3%), followed by etanercept, golimumab (either intravenous or subcutaneous), infliximab, and certolizumab pegol (Table 1). Most participants (78.7%–84.0%) cited inadequate response as the reason for discontinuing their prior TNF inhibitor. Concomitant csDMARD use was reported by just over half of participants in each treatment group, and among these, nearly all were receiving MTX (mean dose: 16–17 mg/week). At baseline, 11% to 15% of participants were receiving oral glucocorticoids, and 46% to 47% were receiving NSAIDs.

Efficacy. At week 24, 58.6% of participants in the Q4W group and 62.2% in the Q8W group achieved an ACR20 response (primary endpoint) versus 34.8% in the placebo group ($P < 0.001$ for both; Table 2). Significantly greater proportions of participants in the Q4W and Q8W groups than in the placebo group achieved an ACR20 at week 16 (51.1% and 56.5% vs 29.1%, respectively; $P < 0.001$ for both) and an ACR50 at weeks 16 (23.8% [$P < 0.001$] and 28.0% [$P = 0.001$] vs 9.4%, respectively) and 24 (31.4% and 32.1% vs 12.2%, respectively; $P < 0.001$). Separation from placebo was observed as early as weeks 4 (Q4W) and 8 (Q8W) for achieving ACR20, weeks 8 (Q8W) and 12 (Q4W) for achieving ACR50, and week 12 for achieving ACR70 (Figure 2). Among participants with ≥3% BSA and IGA ≥2 at baseline, significantly greater proportions of guselkumab-treated participants achieved clear or almost clear skin at week 24 when assessed by IGA 0/1 response (Q4W 50.0% and Q8W 57.3% vs placebo 17.4%; $P < 0.001$ for both) and PASI90 (Q4W 49.4% and Q8W 45.5% vs placebo 12.0%; $P < 0.001$ for both; Figure 3).

Among the 247 participants with a baseline LEI score >0, greater proportions of those receiving guselkumab Q4W (51.7%; nominal $P = 0.004$) and Q8W (45.0%; nominal $P = 0.048$) versus placebo (29.8%) achieved resolution at week 24, and LS mean changes from baseline at week 24 were −1.5 (nominal $P = 0.007$), −1.3 (nominal $P = 0.066$), and −0.9, respectively (Table 2). Among participants with a baseline SPARCC enthesitis score >0 (n = 285), response rates for achieving resolution at

Table 2. Efficacy results at week 24 in SOLSTICE*

	Guselkumab 100 mg		
	Q4W (N = 150)	Q8W (N = 151)	Placebo (N = 150)
ACR20, %	58.6	62.2	34.8
Difference vs placebo (95% CI)	23.8 (12.7–35.0)	27.4 (16.4–38.4)	
P value	<0.001	<0.001	
ACR50, %	31.4	32.1	12.2
Difference vs placebo (95% CI)	19.3 (10.1–28.4)	20.0 (10.9–29.0)	
P value	<0.001	<0.001	
ACR70, %	17.5	17.3	2.0
Difference vs placebo (95% CI)	15.5 (9.0–22.0)	15.2 (8.9–21.6)	
P value	<0.001	<0.001	
IGA 0/1 response,[a,b] %	50.0	57.3	
Difference vs placebo (95% CI)	32.6 (19.7–45.5)	39.9 (26.9–52.8)	17.4
P value	<0.001	<0.001	
PASI90,[a] %	49.4	45.5	12.0
Difference vs placebo (95% CI)	37.5 (25.1–49.9)	33.6 (21.2–45.9)	
P value	<0.001	<0.001	
MDA, %	18.8	23.9	5.4
Difference vs placebo (95% CI)	13.4 (6.2–20.7)	18.5 (10.8–26.1)	
P value	<0.001	<0.001	
VLDA, %	4.7	6.6	0.7
Difference vs placebo (95% CI)	4.0 (0.4–7.6)	6.0 (1.8–10.1)	
P value[c]	0.032	0.006	
HAQ-DI			
LS mean change	−0.42	−0.40	−0.24
LS mean difference vs placebo (95% CI)	−0.18 (−0.30 to −0.06)	−0.16 (−0.28 to −0.04)	
P value	0.003	0.008	
Improvement ≥0.35,[d] %	55.0	52.8	35.4
Difference vs placebo (95% CI)	19.7 (8.1–31.4)	17.5 (6.0–29.0)	
P value[c]	0.001	0.004	
SF-36 PCS			
LS mean change	7.0	7.0	3.7
LS mean difference vs placebo (95% CI)	3.3 (1.6–5.1)	3.3 (1.5–5.0)	
P value	<0.001	<0.001	
FACIT-Fatigue			
LS mean change	8.4	7.8	3.9
LS mean difference vs placebo (95% CI)	4.5 (2.5–6.6)	3.9 (1.9–5.9)	
P value	<0.001	<0.001	
Improvement ≥4, %	62.8	63.7	37.7
Difference vs placebo (95% CI)	25.1 (14.0–36.3)	25.9 (14.9–37.0)	
P value[c]	<0.001	<0.001	
LEI[e]			
Resolution of enthesitis, %	51.7	45.0	29.8
Difference vs placebo (95% CI)	21.9 (6.8–37.0)	15.2 (0.2–30.2)	
P value[c]	0.004	0.048	
LS mean change	−1.5	−1.3	−0.9
LS mean difference vs placebo (95% CI)	−0.6 (−1.0 to −0.2)	−0.4 (−0.8 to 0.03)	
P value[c]	0.007	0.066	
SPARCC enthesitis score[f]			
Resolution of enthesitis, %	43.7	42.0	24.5
Difference vs placebo (95% CI)	19.2 (5.6–32.9)	17.5 (4.1–31.0)	
P value[c]	0.006	0.011	
LS mean change	−3.0	−2.6	−1.9
LS mean difference vs placebo (95% CI)	−1.2 (−2.0 to −0.3)	−0.8 (−1.6 to 0.03)	
P value[c]	0.006	0.060	

(Continued)

Table 2. (*Cont'd*)

	Guselkumab 100 mg		
	Q4W (N = 150)	Q8W (N = 151)	Placebo (N = 150)
DSS[g]			
Resolution of dactylitis, %	65.5	82.7	43.1
Difference vs placebo (95% CI)	22.5 (2.9–42.0)	39.6 (20.9–58.4)	
P value[c]	0.024	<0.001	
LS mean change	−4.8	−5.8	−3.7
LS mean difference vs placebo (95% CI)	−1.1 (−2.3 to 0.2)	−2.1 (−3.4 to −0.7)	
P value[c]	0.094	0.003	

* ACR20/ACR50/ACR70, ≥20%/≥50%/≥70% improvement in American College of Rheumatology response criteria; BSA, body surface area; CI, confidence interval; DSS, dactylitis severity score; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy–Fatigue; HAQ-DI, Health Assessment Questionnaire–Disability Index; IGA, Investigator's Global Assessment of psoriasis; LEI, Leeds Enthesitis Index; LS, least squares; MDA, minimal disease activity; PASI90, ≥90% improvement in Psoriasis Area and Severity Index; Q4W, every 4 weeks; Q8W, every 8 weeks; SF-36 PCS, 36-item Short-Form Health Survey physical component summary; SPARCC, Spondyloarthritis Research Consortium of Canada; VLDA, very low disease activity.
[a] Among participants with ≥3% BSA affected by psoriasis and a baseline IGA ≥2: Q4W n = 92; Q8W n = 89; placebo n = 86.
[b] IGA 0/1 response defined as IGA of 0 or 1 and ≥2-grade improvement from baseline.
[c] Nominal *P* value.
[d] Among participants with a baseline HAQ-DI ≥0.35: Q4W n = 138; Q8W n = 143; placebo n = 144.
[e] Among participants with LEI >0 at baseline: Q4W n = 84; Q8W n = 84; placebo n = 79.
[f] Among participants with SPARCC enthesitis score >0 at baseline: Q4W n = 95; Q8W n = 97; placebo n = 93.
[g] Among participants with DSS >0 at baseline: Q4W n = 54; Q8W n = 42; placebo n = 52.

week 24 were greater for those in the Q4W (43.7%; nominal $P = 0.006$) and Q8W (42.0%; nominal $P = 0.011$) groups versus placebo (24.5%); LS mean changes from baseline at week 24 were –3.0 (nominal $P = 0.006$), –2.6 (nominal $P = 0.060$), and –1.9, respectively (Table 2). Among the 148 participants with dactylitis at baseline, those receiving guselkumab had higher response rates for achieving resolution at week 24 (Q4W 65.5% [nominal $P = 0.024$] and Q8W 82.7% [nominal $P < 0.001$] vs placebo 43.1%); the LS mean change from baseline in DSS was –4.8 (nominal $P = 0.094$) in the Q4W group, –5.8 in the Q8W group (nominal $P = 0.003$), and –3.7 in the placebo group (Table 2).

LS mean changes in HAQ-DI from baseline to week 24 were significantly greater in the guselkumab groups versus placebo (Q4W –0.42 [$P = 0.003$] and Q8W –0.40 [$P = 0.008$] vs –0.24). Among participants with a baseline HAQ-DI ≥0.35, 55.0% of Q4W- and 52.8% of Q8W-treated participants achieved a meaningful improvement (≥0.35) at week 24 compared with 35.4% in the placebo group (nominal $P = 0.001$ and 0.004, respectively; Table 2). Participants in the guselkumab groups also had significantly greater LS mean improvements at week 24 compared with the placebo group in FACIT-Fatigue (Q4W 8.4 and Q8W 7.8 vs placebo 3.9) and SF-36 PCS (Q4W 7.0 and Q8W 7.0 vs placebo 3.7) scores (all $P < 0.001$) and greater response rates for achieving meaningful improvement (≥4) in FACIT-Fatigue score at week 24 (Q4W 62.8% and Q8W 63.7% vs placebo 37.7%; both nominal $P < 0.001$; Table 2).

At week 24, greater proportions of participants in the Q4W and Q8W groups than in the placebo group achieved MDA (18.8% and 23.9% vs 5.4%; both $P < 0.001$) and VLDA (4.7% [nominal $P = 0.032$] and 6.6% [nominal $P = 0.006$] vs 0.7%; Table 2).

Safety. Aggregate safety results are reported herein to maintain the blinding (per protocol) through week 112 in this ongoing study. Through week 24, 46.7%, 53.6%, and 48.3% of participants in the Q4W, Q8W, and placebo groups, respectively, reported one or more AEs; infections were the most common (23.3%, 28.5%, and 29.5%, respectively; Table 3). Two participants experienced a serious infection (laryngitis [n = 1] and pyelonephritis [n = 1]). Four participants (Q4W 1 [0.7%]; Q8W 2 [1.3%]; placebo 1 [0.7%]) had an injection site reaction; all were mild. One malignancy occurred; a participant with no personal or family history of malignancy had a scalp lesion mistakenly assumed to be psoriasis but was subsequently diagnosed as nodular basal cell carcinoma. The lesion was removed, and the participant continued in the study with no change to study treatment. There were no opportunistic infections, cases of tuberculosis, or anaphylactic or serum sickness reactions.

Across treatment groups, 12 participants reported an SAE; all were singular events, including myasthenia gravis, pulmonary embolism and deep vein thrombosis (both in one participant), colitis, atrial fibrillation, gastritis, and pyelonephritis. One death occurred; an elderly participant with a history of type 2 diabetes, hypertension, and prior tobacco use had a fatal myocardial infarction (MACE) 17 days after the week-12 study agent administration.

The rates of hepatic laboratory abnormalities (based on National Cancer Institute–Common Terminology Criteria for Adverse Events) through week 24 were low. Four participants

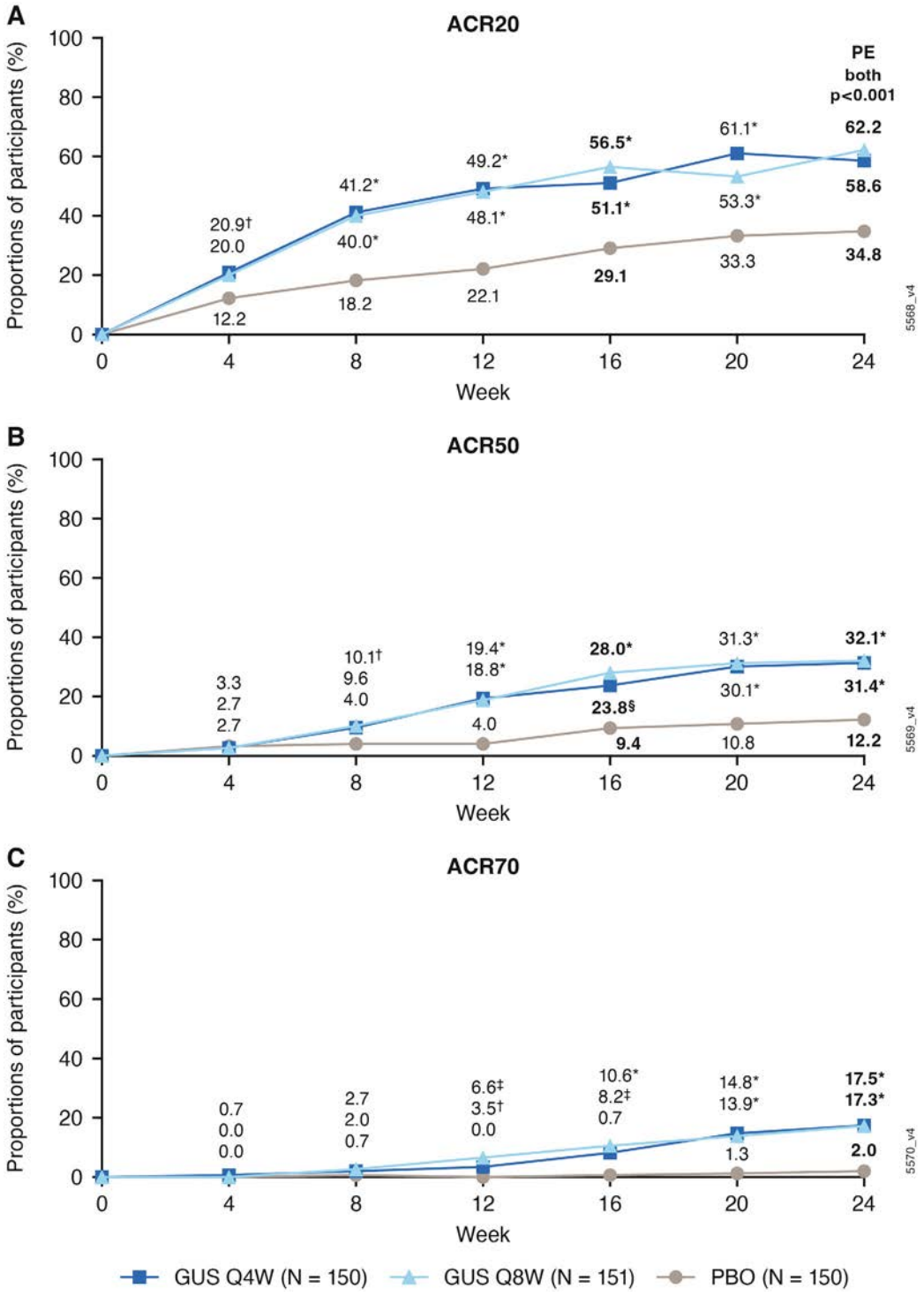

Figure 2. Proportions of participants achieving (A) ACR20, (B) ACR50, and (C) ACR70 over time in the SOLSTICE study. Response rates for achieving (A) ACR20 at week 16, (B) ACR50 at weeks 16 and 24, and (C) ACR70 at week 24 were weakly controlled endpoints that were not part of the sequential testing process but were prespecified to be tested upon achievement of statistical significance for the PE; therefore, *P* values generated for these endpoints are not considered nominal. Bolded values represent the multiplicity-controlled PE (ACR20 at week 24) and weakly controlled endpoints; all other *P* values are nominal. $^{*}P < 0.001$; $^{\S}P = 0.001$; $^{\ddagger}P < 0.01$; $^{\dagger}P < 0.05$. ACR20/ACR50/ACR70, ≥20%/≥50%/≥70% improvement in American College of Rheumatology response criteria; GUS, guselkumab; PBO, placebo; PE, primary endpoint; Q4W, every 4 weeks; Q8W, every 8 weeks.

experienced a Grade-2 increase in alanine aminotransferase (ALT; Q4W 3 [2.0%]; placebo 1 [0.7%]), and one experienced a Grade-3 ALT increase. No participant had a Grade-4 increase in ALT or aspartate aminotransferase (AST) or met the criteria for Hy's law, and no increase in ALT or AST was classified as an SAE. The incidence of increases in ALT and AST was similar regardless of concomitant MTX use (data not shown).

Pharmacokinetics and immunogenicity. Among guselkumab-randomized participants, 149 in each group received one or more guselkumab administrations and had one or more available postbaseline serum samples. Median trough serum guselkumab concentrations reached steady state by approximately week 12 in the Q4W group (2.86 μg/mL; interquartile range: 1.87–4.55) and approximately week 20 in the Q8W group (0.78 μg/mL; interquartile range: 0.44–1.30). No apparent exposure-response relationship was observed for achievement of ACR20 or ACR50 responses at week 24 across trough guselkumab concentration quartiles at week 20 (data not shown). Through week 24, the incidence of antibodies to guselkumab was low (Q4W 17 [11.4%]; Q8W 6 [4.0%]; of these participants, six were positive for neutralizing antibodies).

DISCUSSION

Through week 24 of SOLSTICE, both guselkumab Q4W and Q8W performed similarly in improving the signs and symptoms of active PsA in participants who had either inadequate efficacy with or intolerance to one prior TNF inhibitor. Response rates for achieving substantial improvements in joint-related symptoms, clear or almost clear skin, and overall MDA at week 24 were statistically significantly greater with guselkumab versus placebo. Although serum trough guselkumab concentrations were higher with the Q4W than with the Q8W dosing regimen, comparable efficacy was observed overall between guselkumab groups. Additionally, exploratory analyses found no relationship between ACR20 and ACR50 response rates and serum guselkumab concentrations, consistent with prior analyses from DISCOVER-1 and -2.[29] Although previous analyses from the TNF inhibitor–experienced subgroup in DISCOVER-1 suggested potential differences in dose response, the sample size was much smaller relative to SOLSTICE, and analyses from DISCOVER-1 and -2 showed similar pharmacodynamic effects in reducing cytokine levels with both guselkumab dosing regimens through 24 weeks of treatment.[30] More recent in vitro analyses demonstrated that guselkumab is uniquely able to potently bind both CD64 on the surface of myeloid cells and the IL-23 secreted from these cells, thereby potentially neutralizing inflammation at the cellular source in inflamed tissue sites.[11]

At week 24, guselkumab Q4W- and Q8W-treated participants had greater mean improvements in HAQ-DI, FACIT-Fatigue, and SF-36 PCS scores than those receiving placebo. For all three scores, the LS mean changes for both guselkumab groups from baseline to week 24 exceeded the level of change considered meaningful for individual patients (HAQ-DI: ≥0.35; FACIT-Fatigue: ≥4; SF-36 PCS: ≥5). Response rates for achieving meaningful improvements in physical function, fatigue, and overall HRQoL were greater in the guselkumab groups compared with placebo and comparable across the guselkumab dosing regimens. The improvements in physical function, fatigue, and overall HRQoL observed with guselkumab treatment in SOLSTICE are consistent with earlier findings from DISCOVER-1 and DISCOVER-2 using the HAQ-DI, FACIT-Fatigue, and SF-36 instruments in addition to the Patient-Reported Outcomes Measurement Information System (PROMIS)–29 domains of fatigue, physical function, and social participation (DISCOVER-1).[15,31–33]

Guselkumab-treated participants had greater response rates for achieving resolution of enthesitis and dactylitis versus placebo at week 24. However, the treatment effect of guselkumab in LS mean changes in LEI, SPARCC enthesitis, and DSS scores was not consistent between the dosing regimens. Evaluating dactylitis and enthesitis can be subjective and may be confounded by comorbidities such as fibromyalgia. Additionally, the entheseal insertion sites evaluated varied according to the scoring system being used; the SPARCC enthesitis score includes 16 anatomical sites, whereas the LEI includes only 6.[18,19]

The results from SOLSTICE build upon the smaller phase 3b COSMOS study[14] and corroborate those of real-world analyses. Among patients in the CorEvitas Psoriatic Arthritis/Spondyloarthritis Registry who initiated guselkumab with a dosing regimen consistent with US Food and Drug Administration–approved labeling, nearly 80% remained persistent at six months.[34] On average, this cohort had significant improvements from baseline to six months in clinical Disease Activity Index for Psoriatic Arthritis (cDAPSA) scores (excluding the CRP component), PhGA scores, patient-reported pain, and percentage of affected BSA. Of note, 73% of these patients had received prior therapy with at least one TNF inhibitor.[34] Previous US claims-based analyses evaluated persistence with on-label dosing regimens in patients with active PsA initiating guselkumab or a subcutaneous TNF inhibitor[35] or an IL-17A inhibitor.[36] Those initiating guselkumab (~50% had received at least one prior bDMARD) were more likely to remain persistent with on-label therapy through 12 months than those initiating a TNF inhibitor (~3×) or IL-17A inhibitor (~2×). Direct comparisons of the efficacy of guselkumab with other IL-23 and IL-17 inhibitors are precluded by a lack of head-to-head studies. However, in general, response rates for achieving the stringent ACR50 and ACR70 responses at week 24 in SOLSTICE were similar with those previously reported for risankizumab,[37] ixekizumab,[38] secukinumab,[39] bimekizumab (week 16),[40] and upadacitinib[41] in participants with an inadequate response to prior therapy with TNF inhibitors or other biologics.

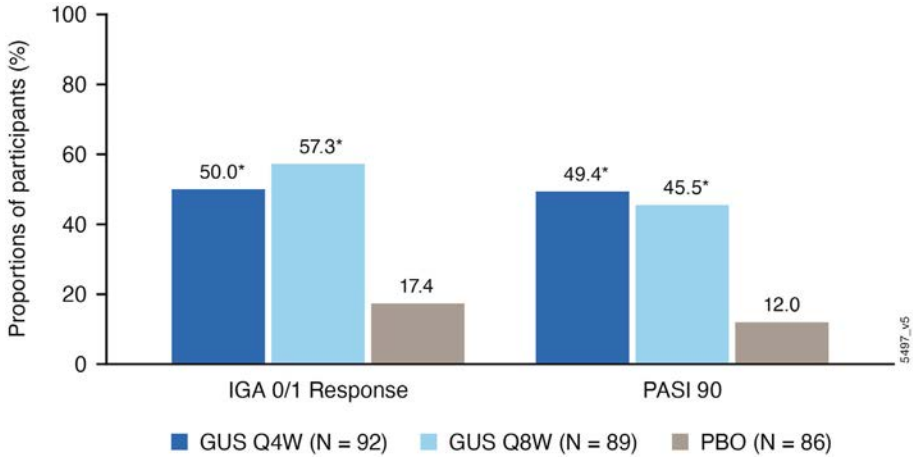

Figure 3. Proportions of participants achieving an IGA 0/1 response[a] and PASI 90 at week 24 in the SOLSTICE study among participants with ≥3% body surface area affected by psoriasis and a baseline IGA ≥2. *$P < 0.001$. GUS, guselkumab; IGA, Investigator's Global Assessment of psoriasis; PASI 90, ≥90% improvement in Psoriasis Area and Severity Index; PBO, placebo; Q4W, every 4 weeks; Q8W, every 8 weeks.
[a]IGA 0/1 response defined as IGA of 0 or 1 and ≥2-grade improvement from baseline.

Safety findings through week 24 were consistent with the known safety profile of guselkumab Q4W and Q8W in patients with psoriatic disease. The types and frequencies of AEs were generally comparable between the guselkumab dosing groups, with no apparent dose-effect on safety outcomes. Infections were the most common type of AE; there were no serious or opportunistic infections and no cases of active tuberculosis. The incidence of hepatic abnormalities identified through routine testing was similar between participants who did and did not receive concomitant MTX. There were no Grade-4 increases in ALT or AST, no increase was classified as an SAE, and no participant met the criteria for Hy's law. There were few SAEs, and all were singular events.

Limitations of the SOLSTICE study include the requirement that participants had prior exposure to only one TNF inhibitor; therefore, findings may not be generalizable to patients who have experienced inadequate efficacy or intolerance with more than one TNF inhibitor, bDMARDs using other mechanisms of action (eg, IL-17 inhibitors), or tsDMARDs (eg, JAK inhibitors). Additionally, eligibility criteria for SOLSTICE required a washout period before the first study agent administration, which may not be consistent with switching medications in real-world clinical practice. The placebo response was relatively high for ACR response outcomes, reflecting an increasingly common concern in randomized controlled studies globally.[42] As noted by Kerschbaumer et al, the trend toward higher placebo responses over time may be a result of the expansion of clinical trials across regions and countries with more varied socioeconomic characteristics.[42] In regions with limited access to standard medical care and advanced biologics, the frequency of interactions with health care providers and more stringent adherence to permitted concomitant therapies (eg, MTX) required for clinical trial participation may have influenced the higher placebo responses observed in SOLSTICE. The current analyses from this ongoing study are restricted to six months; planned analyses through later time points will allow evaluation of maintenance of response with both guselkumab dosing regimens in TNFi-IR patients.

Findings from SOLSTICE demonstrated that both the Q4W and Q8W dosing regimens of guselkumab are efficacious in improving the signs and symptoms of active PsA through six

Table 3. AEs through week 24 of SOLSTICE*

	Guselkumab 100 mg		
	Q4W (N = 150)	Q8W (N = 151)	Placebo (N = 149)
Mean follow-up, weeks	24.0	23.7	23.6
Participants with ≥1 AE	70 (46.7)	81 (53.6)	72 (48.3)
Participants with ≥1 SAE	2 (1.3)	4 (2.6)	6 (4.0)
Participants with ≥1 infection	35 (23.3)	43 (28.5)	44 (29.5)
Serious infections	0	0	2 (1.3)
Opportunistic infections	0	0	0
Participants with ≥1 injection site reaction	1 (0.7)	2 (1.3)	1 (0.7)

* Data presented as n (%) unless otherwise noted. AE, adverse event; Q4W, every 4 weeks; Q8W, every 8 weeks; SAE, serious AE.

months in a population of participants who had either inadequate efficacy with or intolerance to one prior TNF inhibitor. Both guselkumab dosing regimens demonstrated similar efficacy and safety results in this TNFi-IR population.

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AUTHOR CONTRIBUTIONS

All authors contributed to at least one of the following manuscript preparation roles: conceptualization AND/OR methodology, data collection, formal analysis, and data curation AND drafting or reviewing/editing the final draft. As corresponding author, Dr Ogdie confirms that all authors have provided the final approval of the version to be published and takes responsibility for the affirmations regarding article submission (eg, not under consideration by another journal), the integrity of the data presented, and the statements regarding compliance with institutional review board/Declaration of Helsinki requirements.

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BRIEF REPORT

Successful Spontaneous Pregnancies and Healthy Neonates After Dual-Target CAR–T Cell Therapy in Systemic Lupus Erythematosus

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Objective. Dual-target CAR–T cell therapy targeting BCMA and CD19 is an emerging and promising treatment for systemic lupus erythematosus (SLE). However, its effects on fertility and neonatal safety are largely unknown. This report describes the outcomes of two successful pregnancies and deliveries in a patient with SLE treated with BCMA/CD19 CAR–T cell therapy.

Methods. A 24-year-old woman with class IV lupus nephritis received BCMA/CD19 CAR–T cell therapy. The patient achieved sustained molecular remission of SLE and became pregnant spontaneously at 6-months and 21-months postinfusion. We monitored for CAR–T cell presence in maternal and neonatal samples and assessed the health of the infants.

Results. Lupus activity remained minimal without flares throughout both pregnancies. The patient had two term vaginal deliveries of healthy female infants. Serial digital polymerase chain reaction analysis of the patient's blood, breast milk, and placenta, as well as the infants' blood at birth and during follow-up, were all uniformly negative for CAR–T cell DNA. Both infants showed normal growth, neurodevelopment, and immune function at follow-up, with no evidence of CAR–T cell transmission. The patient's self-reported quality of life also improved significantly after the therapy.

Conclusion. This case suggests that BCMA/CD19 CAR–T cell therapy may induce sustained remission (over 30 months) in SLE, preserve fertility, and result in healthy pregnancies and neonates. This finding highlights the need for evidence-based guidelines for patients considering pregnancy after CAR–T cell therapy.

INTRODUCTION

Systemic lupus erythematosus (SLE) predominantly affects women of reproductive age, and although ovarian reserve itself may not differ from healthy controls, multiple factors contribute to impaired fertility in SLE. Cytotoxic agents used for severe SLE, notably cyclophosphamide, are the major non–age-related cause of infertility. High-dose glucocorticoids and other medications may further disrupt menstrual function. In addition, antiphospholipid antibodies in lupus are strongly linked to recurrent pregnancy loss and obstetric complications. Thus, active disease flares and traditional lupus treatments are known risk factors for reduced fertility and higher pregnancy morbidity.[1–3] CAR–T cell therapies targeting B cell antigens have revolutionized treatment for refractory autoimmune conditions.[4,5] Our previous study of dual-target BCMA/CD19 CAR–T cells in lupus nephritis demonstrated deep humoral immune reset; patients achieved eradication of pathogenic autoantibodies, normalization of complement, and sustained remission.[6] Notably, this potent immunotherapy has been well tolerated, generally causing only mild cytokine release syndrome.

However, the long-term effects of CAR–T cells on fertility and on offspring are poorly understood. CAR–T cells usually persist

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only weeks to months but can occasionally survive for years.[7] Transplacental passage of maternal T cells and their presence in breast milk raise concerns regarding fetal and neonatal safety.[8] In oncology cases, CAR–T cell DNA has been detected in maternal serum and breast milk for years after infusion, although infants in those reports showed no engraftment.[9] Meanwhile, recent studies highlight that fertility guidance around CAR–T cell therapy is currently lacking and that patients often receive no counseling on timing of conception.[10]

To our knowledge, there are few published reports of pregnancy in patients with SLE after CAR–T cell therapy. Here, we describe a case of a young woman with refractory lupus nephritis who underwent experimental BCMA/CD19 CAR–T cell therapy, achieved sustained remission (over 30 months), and later experienced two healthy spontaneous pregnancies. Importantly, our data also reveal that this patient maintained disease stability throughout both pregnancies and reported sustained improvements in physical and emotional well-being following BCMA/CD19 CAR–T cell therapy. Given the high reproductive burden faced by this population, such findings point toward the broader use of CAR–T cells in addressing both immunologic and quality-of-life goals in SLE.[11,12] Herein, we present detailed maternal and neonatal outcomes, including immune monitoring, to assess the safety of conception and lactation after CAR–T cell therapy in patients with SLE.

MATERIALS AND METHODS

The patient, a 24-year-old nulliparous woman, was diagnosed with SLE at age 20 years and developed class IV-G (A/C) lupus nephritis confirmed by renal biopsy. Despite standard immunosuppression (high-dose prednisone taper, methotrexate, hydroxychloroquine, and thalidomide), she experienced disease relapse with SLE Disease Activity Index 2000 (SLEDAI-2K) of 14. She enrolled in a phase I trial of BCMA/CD19 CAR–T cells (ClinicalTrials.gov identifier: NCT05474885), discontinuing all immunosuppressants before lymphodepleting chemotherapy and CAR–T cell infusion.[6] Peripheral blood $CD19^+$ B cell counts were monitored by flow cytometry to assess B cell recovery. Serum levels of cytokines, levels of antinuclear antibody (ANA), anti–double-stranded DNA (anti-dsDNA) antibody, and complement components C3 and C4 were measured using standard clinical immunoassays as previously described.[6] The persistence of CAR–T cells in peripheral blood was quantified by droplet digital polymerase chain reaction (ddPCR). The frequency of CAR-positive cells within the total $CD3^+$ T cell population was determined using flow cytometry. Written informed consent was obtained from the patient. The study was approved and monitored by the local ethics committee of Zhongshan City People' s Hospital (K2025-055).

Flow cytometry. The peripheral blood mononuclear cells (PBMCs) were isolated from heparinized whole blood using Histopaque density gradient under the biosafety level 2+ facility. To isolate PBMCs, blood 1:1 diluted in phosphate-buffered saline (PBS) was layered over in Histopaque in a SepMate tube and centrifuged for 30 minutes at 400 g. The PBMC layer was collected by quickly pouring the content into a new 50-ml round-bottom polystyrene tube. The cells were washed twice with PBS to remove any remaining Histopaque and to remove platelets and then adjusted to a concentration of 1×10^6 cells/mL. For lymphocyte subsets detection, PBMC underwent surface staining for 30 minutes at 4°C with antibody cocktails containing a combination of following antibodies: APC anti-CD19, APC-AF750 anti-CD8, PE-Cy7 anti-CD4, PerCP-Cy5.5 anti-CD45, FITC anti-CD3, and PE anti-CD16+56 (BioLegend). For CAR detection, cells were stained with biotin-labeled polyclonal goat anti-mouse-F(ab)2 antibodies (Jackson ImmunoResearch) and then stained with phycoerythrin-labeled streptavidin (BD Biosciences) and PerCP anti-CD3 (BioLegend). After wash, stained cells were recorded on flow cytometer (DxFLEX, Beckman Coulter) and analyzed by FlowJo software version 10.8.1 software (FlowJo).

ddPCR. Genomic DNA (gDNA) was prepared from peripheral blood, breast milk, and placenta with DNeasy Blood and Tissue Kit (QIAGEN), following the manufacturer's protocols. CAR–T cell–specific copy numbers were analyzed by the ddPCR system (Forevergen Biotechnology) using woodchuck hepatitis virus posttranscriptional regulatory element (WPRE) and albumin (ALB) genes as reference. Final concentrations of primers (900 nM) and probes (250 nM) followed the general Forevergen Biotechnology guidelines for ddPCR. Assays were repeated three times for each sample. For the calculation of CAR–T copy numbers per microgram of gDNA, the instrument's QuantaSoft software (version 1, Forevergen Biotechnology) output of copies per microliter for each channel (CAR–T and ALB) was used. In detail, the following primer sets were used for dd-PCR reactions:

WPRE: forward primer GGCACTGACAATTCCGTGGT, reverse primer AGGGACGTAGCAGAAGGACG.

probe: FAM-ACGTCCTTTCCATGGCTGCTCGC-BHQ.

ALB: forward primer GCTGTCATCTCTTGTGGGCTGT, reverse primer ACTCATGGGAGCTGCTGGTTC.

probe: HEX-CCTGTCATGCCCACACAAATCTCTCC-BHQ.

Histopathology. Full-thickness placental tissue and representative fetal membrane (amnion–chorion) samples were collected immediately after delivery. From each placenta, we sampled at least three full-thickness blocks from the central parenchyma (including chorionic plate and basal plate) and one roll of fetal membranes. Tissue specimens were placed in 10% neutral-buffered formalin at room temperature for 24 to 48 hours and then processed for paraffin embedding. Paraffin-embedded tissue blocks were trimmed and cut into 4-μm–thick sections

using a standard microtome. Sections were mounted onto glass slides, air-dried, and baked at 60°C for 30 to 60 minutes before staining. Hematoxylin and eosin (H&E) staining was performed using standard histologic procedures. In brief, sections were deparaffinized in xylene and rehydrated through a graded ethanol series to distilled water. Slides were stained with hematoxylin according to the laboratory standard (followed by bluing in running tap water or bluing solution), rinsed, and counterstained with eosin. After counterstaining, slides were dehydrated through ascending alcohols, cleared in xylene, and coverslipped with a synthetic mounting medium. All reagent names, concentrations, and staining times were performed according to the manufacturer's instructions and recorded in the laboratory log. Stained slides were examined by bright-field light microscopy. Representative photomicrographs of placental parenchyma and fetal membranes were captured with a calibrated digital camera attached to the microscope. Representative images included fields from the first pregnancy and second pregnancy as presented in Supplementary Figures. Images were acquired at objective magnifications appropriate to illustrate the histologic features. Two perinatal pathologists (blinded to clinical pregnancy outcome and CAR–T cell status) independently reviewed all slides. Placental findings were assessed for features commonly associated with maternal and fetal placental injury and inflammation.

Data availability statement. The raw data supporting the conclusions of this article will be shared upon request.

RESULTS

CAR–T cell persistence and initial treatment response. At week six postinfusion, the patient achieved B cell full recovery (peripheral $CD19^+$ cell count within normal range; Figure 1), molecular remission, and normalization of complement and autoantibodies. No adverse events beyond grade I cytokine release syndrome occurred.[6] On day 10 after CAR–T cell infusion, peripheral blood digital PCR showed 17,171 copies/μg of CAR transgene, and flow cytometry indicated that the frequency of CAR–T cells in $CD3^+$ T cells was 14.7% (Table 1, Supplementary Figure 1).

Pregnancy outcomes. Without fertility assistance, the patient conceived naturally at 6 months and again at 21 months following CAR–T cell therapy. Both pregnancies remained clinically quiescent, with no lupus flares or new disease activity. Each pregnancy progressed to term, and she underwent uncomplicated vaginal deliveries of two female infants weighing appropriately for gestational age. Detailed placental and fetal membrane histology in both cases revealed no evidence of maternal vascular malperfusion, chronic villitis, or other inflammation (Supplementary Figure 2). At birth, both infants exhibited head circumference below first percentile of the mean for sex and gestational age but showed progressive catch-up growth and, by 3 months of age, had attained median anthropometric percentiles for sex and age (Supplementary Figure 3).

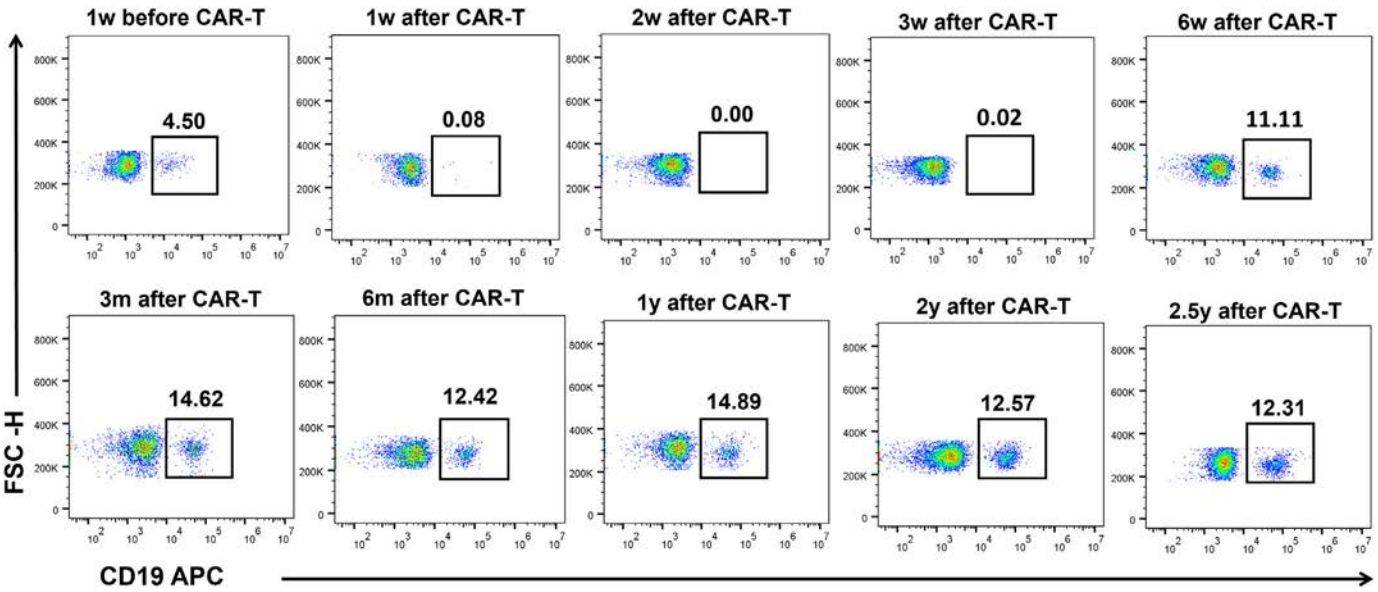

Figure 1. Longitudinal reconstitution of peripheral blood B cells following CAR–T cell therapy. Flow cytometry was used to quantify the proportion of $CD19^+$ B cells within the lymphocyte population at the indicated time points: one week before treatment (baseline), at one week, two weeks, three weeks, and six weeks postinfusion, followed by three months, six months, 1 year, 2 years, and 2.5 years after CAR–T cell therapy. The analysis demonstrates the dynamic depletion and subsequent recovery of the B cell lineage, culminating in sustained normalization of B cell levels within the physiologic range following the initial period of CAR–T cell activity. APC, allophycocyanin; FSC-H, forward scatter height; m, month; w, week; y, year.

Table 1. CAR-expressing T cells detected by flow cytometry and ddPCR*

Samples	ddPCR (copies/μg)	Flow cytometry (%)
Mother's blood at 10 days after CAR–T cell infusion	17,171.49105	14.7
Mother's blood at 50 days after CAR–T cell infusion	210.0193089	0.4
Mother's blood at 7 months after CAR–T cell infusion (at the beginning of the first pregnancy)	57.16719614	0
Mother's blood at 16 months after CAR–T cell infusion (three days before the first childbirth)	0	–
The first newborn's blood at 48 hours after birth	0	–
Colostrum of the first pregnancy	0	–
Placenta of the first pregnancy	0	–
Mother's blood at 31 months after CAR–T cell infusion (two days before the second childbirth)	0	–
The second newborn's blood at 48 hours after birth	0	–
Colostrum of the second pregnancy	0	–
Placenta of the second pregnancy	0	–

* ddPCR, droplet digital polymerase chain reaction.

Sustained immune remission and quality-of-life improvements supporting pregnancy after CAR–T cell therapy. Laboratory immunologic assessments demonstrated that, before CAR–T cell therapy, the patient presented with a markedly elevated interleukin-6 (IL-6) level (20.54 pg/mL) (Supplementary Table 1). However, before her first delivery, levels of multiple cytokines, including IL-6, had normalized, indicating that CAR–T cell–mediated immune resetting effectively suppressed systemic inflammation. Concurrently, high-titer ANA (from 71.28 to 8.04 RU/mL) and anti-dsDNA antibody (from 229.75 to 1.69 IU/mL) levels markedly decreased, accompanied by restoration of complement components C3 and C4 from low (0.63–0.05 g/L) to within normal ranges (1.10–0.12 g/L) (Supplementary Table 1). These findings reflect sustained immunosuppression of autoimmune activity during the follow-up period, consistent with the patient's maintained clinical remission after CAR–T cell therapy. In addition to clinical remission, the patient's quality of life improved at three months of treatment and remained stable during both pregnancies, highlighting the broader psychosocial benefits of immune resetting (Supplementary Table 2). Notably, during the second pregnancy, peripartum measurements showed elevation of several proinflammatory cytokines (Il-1β, IL-6, and IL-8) compared with pre-CAR–T cell baseline (Supplementary Table 1). These laboratory findings were not associated with clinical disease flares or adverse maternal–neonatal outcomes.

Maternal and neonatal monitoring. Prior studies demonstrated that, six months after CAR–T cell infusion, residual CAR–T cells were undetectable by flow cytometry in all patients[6]; therefore, subsequent surveillance employed ddPCR with a limit of detection of one copy per microgram. At seven months postinfusion (gestational week four), quantitative PCR of maternal peripheral blood identified 57 copies/μg of CAR–T DNA, indicating persistent circulating CAR–T sequences. At delivery (16-month and 31-month postinfusion) and in colostrum, placental tissue, and neonatal peripheral blood sampled at 48 hours, CAR–T cell DNA remained below the assay's detection threshold (0 copies/μg; Table 1), demonstrating absence of vertical transmission.

Follow-up assessments of the mother at 39 weeks' of the second gestation, the first child at one year, and the second child at three months revealed that growth percentiles, neurodevelopmental milestones, fundus examination, hearing screening, IgG, IgM, and IgA levels, complement components, and lymphocyte subsets ($CD3^+$, $CD4^+$, $CD8^+$, $CD19^+$, and natural killer cells) all fell within age-appropriate reference ranges (Supplementary Table 3–5, Supplementary Figure 3), indicating intact maternal and neonatal immune function. The first infant, exclusively breastfed for six months, experienced no adverse events during our follow-up period. Collectively, these results indicate that maternal CAR–T cell infusion does not compromise neonatal immune development nor does it engender autoimmune or infectious sequelae.

DISCUSSION

This case extends emerging observations of safe pregnancies after CAR–T cell therapy into the autoimmune domain. Our report shows that dual-target BCMA/CD19 CAR–T cell therapy may induce sustained remission in refractory SLE while preserving fertility. The patient achieved complete clinical and serologic remission, mirroring prior trial results.[6] Remarkably, she experienced two spontaneous term pregnancies without relapse, suggesting that the immune "reset" conferred by CAR–T cells remained stable even under the physiologic stresses of pregnancy.

Concerns regarding maternal CAR–T cell trafficking across the placenta or via breast milk have remained largely theoretical. Oncology studies reported CAR–T cell DNA in breast milk but not in cord blood or infant peripheral blood, sometimes leading clinicians to discourage breastfeeding.[9,13] In contrast, our study found no CAR transgene in breast milk or infants at any time point, and both children had normal immune ontogeny. Notably, the first infant was breastfed for six months without issue, suggesting that lactation may be feasible in this setting, although larger studies are

required to confirm safety. Combined with negative digital PCR results for CAR–T cell DNA, immunophenotyping of maternal and neonatal peripheral blood (mother at late pregnancy, first child at one year, and second child at 48 hours) demonstrates physiologically normal lymphocyte subset distributions and Ig levels, supporting both the absence of CAR–T cell transmission and robust immune development in the offspring. Several proinflammatory cytokines and inflammation-related cellular markers that were elevated in late second pregnancy were not accompanied by clinically apparent lupus flares, maternal complications, or adverse neonatal outcomes within the available follow-up. Nevertheless, future studies should prospectively monitor these signals in larger cohorts and with longer follow-up.

Pregnancies in patients with SLE traditionally carry elevated risks of placental inflammation, preeclampsia, and neonatal lupus.[14] In our patient, systematic placental pathology showed none of the vascular or inflammatory lesions, consistent with her clinically quiescent disease status following CAR–T cell therapy. These outcomes suggest an association between CAR–T cell–mediated immune quiescence and the potential mitigation of typical obstetric complications of SLE in this context.

Limitations of this case include its single-patient scope and the need for longer follow-up of the offspring to confirm sustained immunologic stability, normal vaccine responses, and the absence of late-onset autoimmune phenomena. Prospective multicenter registries should systematically collect fertility outcomes, CAR–T cell kinetics, and comprehensive neonatal immune profiling in larger cohorts of CAR–T cell recipients. Establishing evidence-based guidelines for the optimal timing of conception after CAR–T cell infusion and evaluating the safety of breastfeeding in this context will be critical to inform clinical practice and patient counseling.

In summary, this case report demonstrates that BCMA/CD19 CAR–T cell therapy did not impair reproductive outcomes or neonatal health in a patient with refractory SLE. Instead, it appeared to protect against lupus flares and placental disease during pregnancy while enabling two healthy offspring. These findings, along with prior reports, support the notion that fertility can be preserved and that maternal CAR–T cells pose minimal risk to neonates. Our case highlights the urgent need for expanded research in this area and the development of evidence-based recommendations for family planning after CAR–T cell therapy in autoimmune disease.

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AUTHOR CONTRIBUTIONS

All authors contributed to at least one of the following manuscript preparation roles: conceptualization AND/OR methodology, software, investigation, formal analysis, data curation, visualization, and validation AND drafting or reviewing/editing the final draft. As corresponding author, Dr Hong confirms that all authors have provided the final approval of the version to be published and takes responsibility for the affirmations regarding article submission (eg, not under consideration by another journal), the integrity of the data presented, and the statements regarding compliance with institutional review board/Declaration of Helsinki requirements.

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BRIEF REPORT

Anifrolumab Treatment Leads to Rapid Reduction in Urinary Biomarkers of Intrarenal Inflammation in Lupus Nephritis: Results From the Phase 2 Randomized Trial

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Objective. Lupus nephritis (LN) is one of the most severe manifestations of systemic lupus erythematosus (SLE) and is partially driven by type I interferon signaling. Anifrolumab, an approved treatment for patients with SLE, has been investigated in a phase 2 trial in patients with LN receiving standard therapy (TULIP-LN, ClinicalTrials.gov identifier NCT02547922). We studied the impact of anifrolumab treatment on urinary biomarker expression in patients with LN through proteomic analysis of samples from TULIP-LN.

Methods. Urine samples were collected at weeks 0, 12, and 48 from patients treated with the anifrolumab basic regimen (n = 35), intensified regimen (n = 42), or placebo (n = 35), in addition to standard therapy, and analyzed for the presence of 197 proteins. The impact of anifrolumab relative to placebo on prespecified biomarkers linked to histologic activity was assessed, and a comparison of responders versus nonresponders was conducted on proteins detected in ≥75% of samples.

Results. Anifrolumab treatment significantly reduced urinary CD163 and monocyte chemoattractant protein 1 expression at week 12 versus placebo, including in patients classified as proteinuric nonresponders across all regimens. By week 48, biomarker levels declined in all groups, indicating that standard therapy alone can eventually suppress intrarenal inflammation but with slower kinetics. Proteomic analyses further revealed that anifrolumab was superior to placebo in reducing the proteomic inflammatory signature, regardless of responder status.

Conclusion. Compared with placebo, anifrolumab treatment significantly reduced urinary biomarkers of renal histologic activity in patients with LN, which may accelerate the resolution of intrarenal inflammation, potentially preventing damage accrual.

INTRODUCTION

Lupus nephritis (LN) is one of the most frequent severe clinical manifestations of systemic lupus erythematosus (SLE), developing in approximately 40% of patients with SLE.[1] Patients with LN maintain signs of histologic activity and are at substantial risk of developing end-stage renal disease, even with treatment.[1] Activation of type I interferon (IFN) is a key characteristic of LN disease pathogenesis,[2] with type I IFN gene signatures (IFNGS) also linked to failure of immunosuppressive therapy.[3]

Currently, the definition of renal response in patients with LN centers around improvements in proteinuria.[4] However, proteinuria does not correlate well with changes in intrarenal inflammation or histologic activity and is considered a lagging indicator

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Data underlying the findings described herein may be obtained in accordance with AstraZeneca's data sharing policy described at https://www.astrazenecaclinicaltrials.com/our-transparency-commitments/. Reuse is permitted only with permission from AstraZeneca.

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owing to its persistence following the occurrence of renal damage.[4,5] Therefore, the possibility of urinary biomarkers in LN that correlate with histologic activity and change dynamically with renal response has been investigated. Urinary CD163 has been particularly promising, with a strong association with complete renal response (CRR), disease severity, and histologic activity.[5,6] Ongoing advances in proteomics are aiding in identification of potential candidates as diagnostic, monitoring, and prognostic biomarkers in LN; advances such as wider proteome coverage at increased sensitivity have the potential to redefine the use of urinary biomarkers for LN.[7]

Anifrolumab, a human monoclonal antibody that blocks type I IFN signaling, has been approved in multiple countries for the treatment of patients with moderate to severe SLE.[8] Anifrolumab has been studied in patients with LN in both the phase 2 TULIP-LN trial (ClinicalTrials.gov identifier NCT02547922)[9] and the ongoing phase 3 IRIS study (ClinicalTrials.gov identifier NCT05138133).[10] Previous mechanistic analyses of anifrolumab, using proteomic and transcriptomic analysis of blood samples from clinical studies in patients with SLE, indicated that anifrolumab treatment can reverse the immune cell imbalances commonly observed in patients with SLE.[11] Here, we aimed to determine the impact of two different anifrolumab dosing regimens compared with placebo on the expression of urinary biomarkers in patients with LN through proteomic analysis of urine samples from patients enrolled in the phase 2 TULIP-LN trial.[9]

PATIENTS AND METHODS

Study design. TULIP-LN was a multicenter, multinational, randomized, placebo-controlled, double-blind phase 2 trial that included patients aged 18 to 70 years who fulfilled four or more of the American College of Rheumatology 1997 SLE classification criteria,[12] had biopsy-proven diagnosis of class III or IV (with or without coexistent class V) LN, had a 24-hour urine protein–creatinine ratio (UPCR24) >1 mg/mg, and had an estimated glomerular filtration rate (eGFR) ≥35 mL/min/1.73 m^2.[9]

A total of 147 patients were randomized (1:1:1) to receive either the anifrolumab basic regimen (BR; 300 mg intravenously [IV] every 4 weeks [Q4W]; n = 45), the anifrolumab intensified regimen (IR; 3 × 900 mg, then 300 mg thereafter IV Q4W; n = 51), or placebo (IV Q4W; n = 49) for 52 weeks in addition to standard therapy.[9] Randomization was stratified according to UPCR24 at screening (≤3.0 vs >3.0 mg/mg) and IFNGS status (high or low). Primary results from the study have been reported.[9] The study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice Guideline.

Objectives. In this study, we aimed to determine the impact of anifrolumab treatment (BR, IR, and BR + IR) compared with placebo on the expression of preselected urinary biomarkers of renal histologic activity and the expression of urinary proteomic inflammatory signatures over time through proteomic analysis of urine samples from patients in the phase 2 TULIP-LN trial.

Sample collection and proteomics analysis. Urine samples were collected at baseline (week 0) and weeks 12 and 48. Samples were frozen within 24 hours of collection and stored at –80°C until analysis and assessed for the presence of 197 proteins (192 by Luminex; 5 by Simoa) by Rules-Based Medicine (Rules-Based Medicine, Inc). The five Simoa proteins assayed were B-lymphocyte chemoattractant, IFNα, interleukin-1β (IL-1β), IL-6, and tumor necrosis factor α (TNFα). Ten prespecified biomarkers selected based on their established link to histologic activity were assessed in a hypothesis-driven approach: CD163, IL-16, visfatin, monocyte chemoattractant protein 1 (MCP-1), macrophage inflammatory protein 1α (MIP-1α), MIP-1β, neuropilin 1, T cell–specific protein RANTES, kidney injury molecule 1 (KIM-1), and myeloperoxidase (MPO).[5] MPO, a neutrophil degranulation marker elevated in proliferative LN,[13] was selected in place of proteinase 3, as it was not included in the targeted proteomic panel. Protein concentrations were normalized to urinary 24-hour creatinine levels. Each protein was assessed for detectability and was required to be in the quantifiable range for >75% of patients.

The impact of anifrolumab on expression of urinary biomarkers of renal inflammation was assessed longitudinally. Change in protein concentration from baseline to week 12 was assessed quantitatively through a linear model adjusted for baseline UPCR24 (<3 or ≥3 mg/mg), IFNGS (low or high), and baseline protein concentration for seven proteins (CD163, MCP-1, MIP-1β, neuropilin 1, RANTES, KIM-1, and MPO). Urinary protein concentrations of IL-16, visfatin, and MIP-1α were detected in <75% of patients and were excluded from linear modeling; their trajectories were evaluated as percentage detected (yes/no) using Fisher's exact test. Expression of urinary protein biomarkers was also assessed in the context of CRR at week 12, per treatment group. CRR was defined as UPCR24 ≤ 0.7 mg/mg, eGFR ≥60 mL/min/1.73 m^2, or no decrease of ≥20% from baseline, no treatment discontinuation, and no use of restricted medications.

Multiplexed proteomic analyses were performed to evaluate the impact of (1) anifrolumab versus placebo and (2) responders versus nonresponders on the expression of urinary inflammatory biomarkers using the Wilcoxen test (false discovery rate [FDR] = 0.1). Additionally, biomarker responses to anifrolumab versus placebo were stratified by LN class and National Institutes of Health (NIH) Chronicity Index. The BR and IR arms were combined, and the effect size between treatment groups was analyzed descriptively; statistical testing was not appropriate owing to small subgroup sizes.

RESULTS

Patient demographics and characteristics. Of 147 patients randomized in the TULIP-LN trial,[9] 112 were included in the urine proteomics data set (anifrolumab BR, n = 35; anifrolumab IR, n = 42; placebo, n = 35). Overall, baseline demographics and clinical characteristics of patients in the proteomics data set were consistent with the overall study population in TULIP-LN. Most patients were female (83.0%), were White (44.6%), had class IV LN (58.9%), and had high IFNGS status at baseline (94.6%) (Table 1). In the anifrolumab IR cohort, fewer patients had low C3 levels (47.6%) at baseline versus the anifrolumab BR (71.4%) and placebo (85.7%) groups.

Impact of anifrolumab on selected urinary biomarkers of renal histologic activity. Ten prespecified biomarkers linked with histologic activity were assessed in a hypothesis-driven approach. Baseline levels of these biomarkers were comparable between treatment arms. Using a linear model adjusted for baseline UPCR, IFNGS, and protein concentrations at week 12, patients treated with anifrolumab IR versus placebo demonstrated reduced urinary CD163 (FDR < 0.1, adjusted P = 0.07; Figure 1A) and MCP-1 levels (FDR < 0.1, adjusted P = 0.07; Figure 1B). By week 48, placebo-treated patients achieved reduced urinary CD163 and MCP-1 concentrations to similar levels, indicating that anifrolumab IR induces an earlier reduction in these urinary biomarker levels. At week 12, IL-16 (Figure 1C) and visfatin (Figure 1D) were detected in 8% and 10% of patients receiving anifrolumab IR versus 26% and 32% of patients receiving placebo (P = 0.05 and P = 0.03, respectively). The proportion of patients with detectable urinary IL-16 and visfatin was also numerically lower with anifrolumab BR versus placebo at week 12 (13% vs 26% and 28% vs 32%, respectively). The remaining preselected biomarkers did not display any changes following treatment with anifrolumab BR or IR compared with placebo (Supplementary Figure S1).

When comparing the combined anifrolumab regimens (BR + IR) with placebo, urinary CD163 and MCP-1 protein concentrations were lower at week 12 with anifrolumab (BR + IR) (FDR < 0.1, adjusted P = 0.06; Supplementary Figure S2A); the proportions of patients with detectable urinary IL-16 and visfatin were also numerically lower with anifrolumab treatment (BR + IR) versus

Table 1. Baseline demographics and clinical characteristics of patients included in the urine proteomics data set*

	Total (N = 112)	Placebo (n = 35)	Anifrolumab BR (n = 35)	Anifrolumab IR (n = 42)	*P* value
Age, mean ± SD, y	34.5 ± 10.3	34.3 ± 9.8	35.2 ± 11.5	34.2 ± 10.0	0.91
Female, n (%)	93 (83.0)	25 (71.4)	29 (82.9)	39 (92.9)	0.042
Weight, mean ± SD, kg	65.9 ± 15.1	68.1 ± 14.0	61.8 ± 12.4	67.5 ± 17.5	0.15
BMI, mean ± SD	25.0 ± 5.0	25.2 ± 4.1	23.6 ± 3.9	26.1 ± 6.1	0.082
Race, n (%)					0.49
American Indian or Alaska Native	2 (1.8)	0	2 (5.7)	0	
Asian	18 (16.1)	4 (11.4)	8 (22.9)	6 (14.3)	
Black or African American	6 (5.4)	1 (2.9)	1 (2.9)	4 (9.5)	
Native Hawaiian or other Pacific Islander	1 (0.9)	0	1 (2.9)	0	
Other	35 (31.2)	13 (37.1)	9 (25.7)	13 (31.0)	
White	50 (44.6)	17 (48.6)	14 (40.0)	19 (45.2)	
Geographic region, n (%)					0.64
Asia Pacific	18 (16.1)	4 (11.4)	8 (22.9)	6 (14.3)	
Europe	29 (25.9)	10 (28.6)	7 (20.0)	12 (28.6)	
Latin America	44 (39.3)	15 (42.9)	11 (31.4)	18 (42.9)	
North America	21 (18.8)	6 (17.1)	9 (25.7)	6 (14.3)	
Lupus duration, mean ± SD, mo	42.1 ± 59.1	55.8 ± 62.1	28.1 ± 51.1	42.3 ± 61.3	0.15
Renal biopsy result, n (%)					0.30
Class III	15 (13.4)	1 (2.9)	7 (20.0)	7 (16.7)	
Class III and V	11 (9.8)	3 (8.6)	4 (11.4)	4 (9.5)	
Class IV	66 (58.9)	24 (68.6)	20 (57.1)	22 (52.4)	
Class IV and V	20 (17.9)	7 (20.0)	4 (11.4)	9 (21.4)	
UPCR24, mean ± SD, mg/mg	3.3 ± 2.6	3.9 ± 3.6	3.1 ± 2.4	3.0 ± 1.6	0.30
Baseline UPCR >3 mg/mg, n (%)	54 (48.2)	16 (45.7)	20 (57.1)	18 (42.9)	0.40
SLEDAI-2K, mean ± SD	10.7 ± 4.8	11.3 ± 4.3	10.3 ± 4.8	10.5 ± 5.2	0.63
Nonrenal SLEDAI-2K, mean ± SD	4.6 ± 2.9	4.7 ± 2.0	5.2 ± 3.6	4.1 ± 2.8	0.23
IFNGS high, n (%)	106 (94.6)	32 (91.4)	35 (100)	39 (92.9)	0.25
Low C3, n (%)	75 (67.0)	30 (85.7)	25 (71.4)	20 (47.6)	0.001
Low C4, n (%)	34 (30.4)	12 (34.3)	10 (28.6)	12 (28.6)	0.87
NIH Activity Index, mean ± SD	5.6 ± 4.0	5.7 ± 3.7	6.1 ± 4.2	5.1 ± 4.1	0.56
NIH Chronicity Index, mean ± SD	3.5 ± 2.4	3.5 ± 2.8	3.1 ± 1.9	3.8 ± 2.3	0.46

* BMI, body mass index; BR, basic regimen; IFNGS, type I interferon gene signature; IR, intensified regimen; NIH, National Institutes of Health; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000; UPCR24, 24-hour urine protein–creatinine ratio.

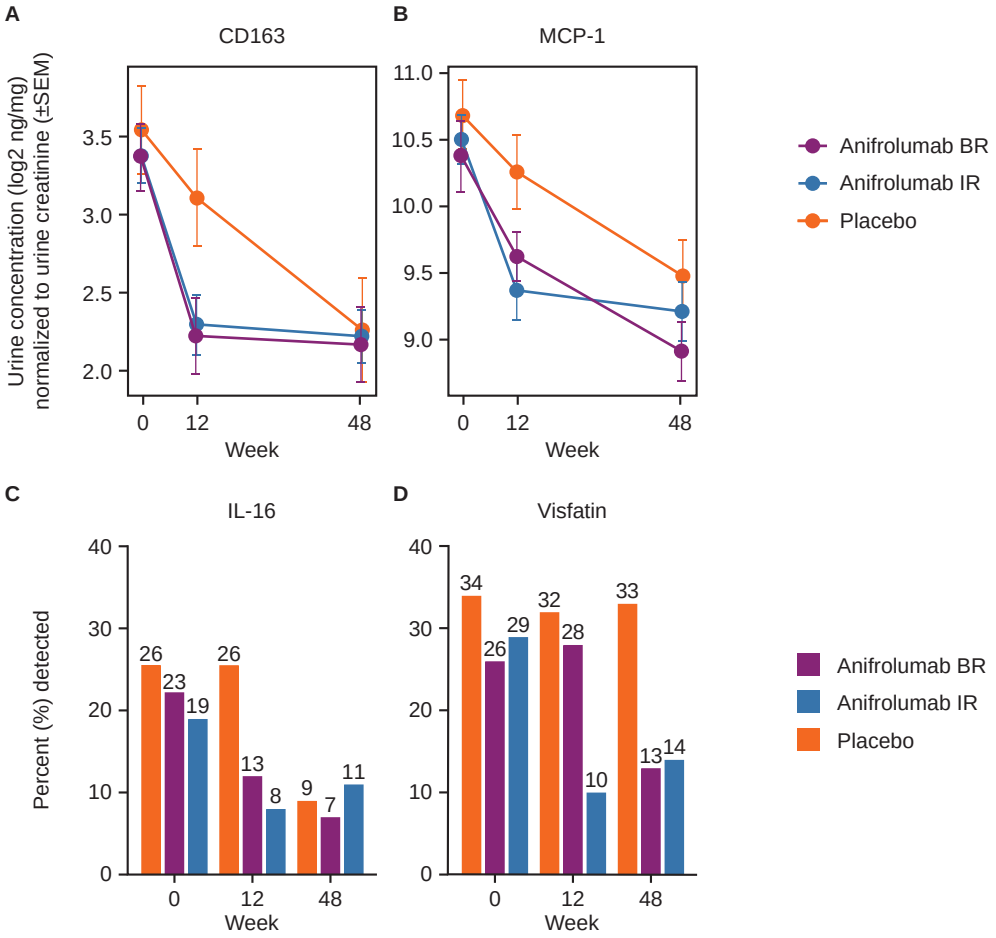

Figure 1. The impact of anifrolumab treatment on the expression of preselected urinary biomarkers of renal histologic activity in patients with LN. Longitudinal trajectories of prespecified biomarker (A) CD163 and (B) MCP-1 concentrations in patients at weeks 0, 12, and 48 receiving placebo (orange, n = 35), anifrolumab BR (purple, n = 35), or anifrolumab IR (blue, n = 42), shown as mean concentration in urine (±SEM), normalized to urine creatinine. (A) CD163 and (B) MCP-1 expression at week 12 anifrolumab IR versus placebo; adjusted $P = 0.07$ (FDR < 0.1). Trajectories of prespecified biomarkers (C) IL-16 and (D) visfatin in patients at weeks 0, 12, and 48 receiving placebo, anifrolumab IR, or anifrolumab BR, shown as percentage detected and evaluated using Fisher's exact test. (C) IL-16 and (D) visfatin at week 12 anifrolumab IR versus placebo; adjusted $P = 0.05$ and $P = 0.03$, respectively (FDR < 0.1). BR, basic regimen; FDR, false discovery rate; IL, interleukin; IR, intensified regimen; LN, lupus nephritis; MCP-1, monocyte chemoattractant protein 1.

placebo at week 12 but were not statistically significant (Supplementary Figure S2B).

Response status. We further assessed longitudinal concentrations of urinary CD163 and MCP-1 protein in CRR responders and nonresponders, per treatment group. In responders, the decrease in urinary CD163 and MCP-1 concentrations from baseline to week 12 was similar among treatment groups. In contrast, among nonresponders, treatment with anifrolumab BR (adjusted $P = 0.04$) and IR (adjusted $P < 0.01$) significantly decreased both urinary CD163 and MCP-1 concentrations from baseline to week 12 versus placebo (Figure 2A). Similar trends were observed with anifrolumab BR + IR treatment versus placebo (adjusted $P < 0.01$; Supplementary Figure S3), indicating an earlier improvement in biomarkers linked to renal histologic activity in nonresponders receiving anifrolumab versus placebo.

Multiplexed urinary proteomic analysis. To further evaluate the effect of anifrolumab on a broader set of urinary biomarkers, we focused on proteins in the panel detected in >75% of samples (n = 107). At week 12, only TRAIL-R3 expression was higher in patients receiving anifrolumab IR versus placebo (log_2 fold change 0.5, adjusted P value FDR < 0.1; Figure 2B, Supplementary Table S1). In contrast, several biomarkers of intrarenal inflammation were increased in patients receiving placebo versus anifrolumab IR (B2M, log_2 fold change –1.6; myoglobin, log_2 fold change –1.6; PPP, log_2 fold change –1.0; AAT, log_2 fold change –0.8; CD163, log_2 fold change –0.6; PGI, log_2 fold change –0.5; MMP3, log_2 fold change –1.1; BAFF, log_2

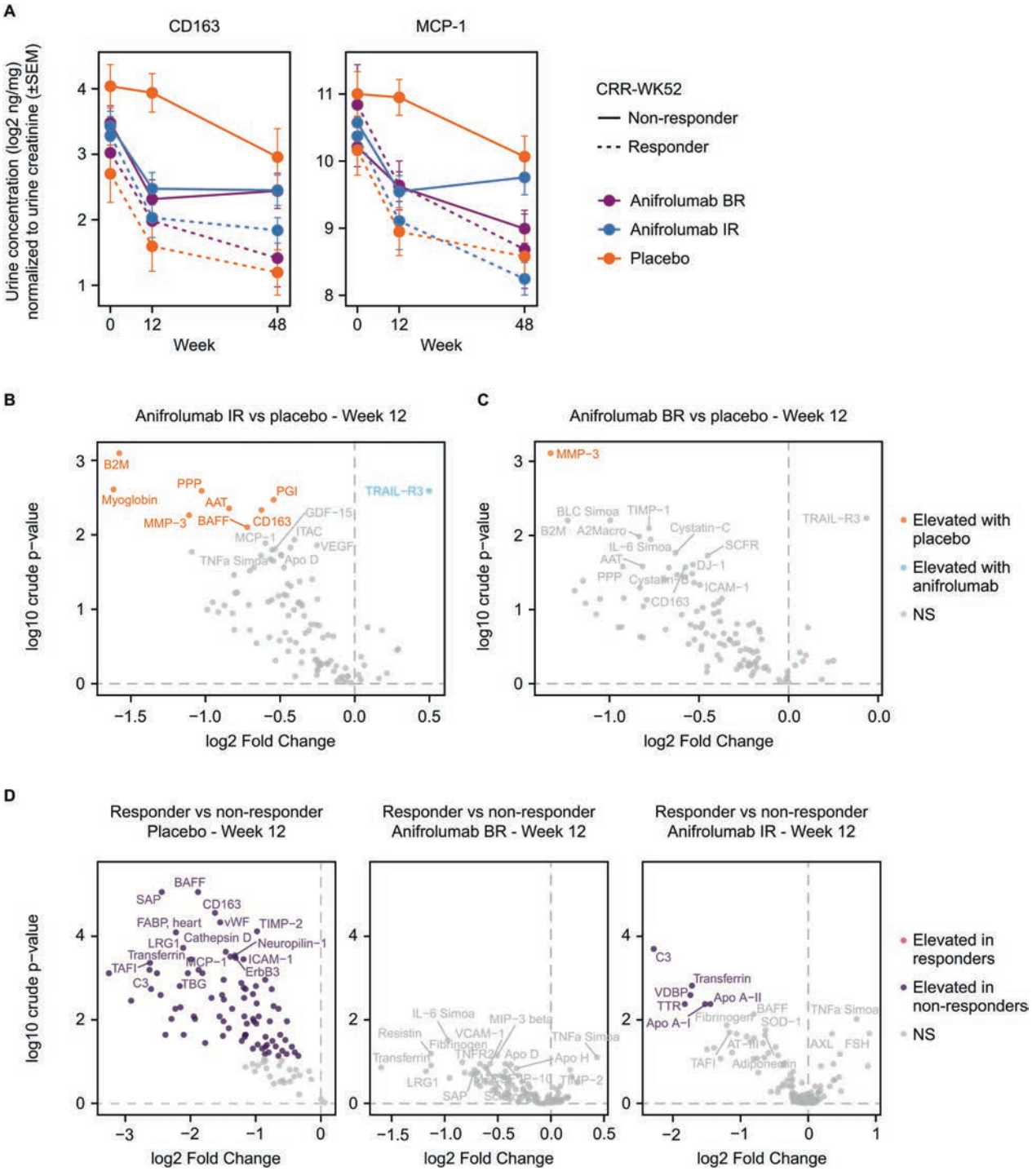

Figure 2. The impact of anifrolumab treatment on the expression of preselected urinary biomarkers of renal histologic activity in CRR responders and nonresponders and on a broader panel of urinary biomarkers in patients with LN. (A) Mean CD163 and MCP-1 protein concentrations in patients at week 0, 12, and 48, modeled in CRR responders and nonresponders and by treatment group and shown as mean concentration in urine (±SEM) normalized to urine creatinine. CD163 and MCP-1 expression at week 12; anifrolumab BR versus placebo, adjusted $P = 0.04$ (FDR < 0.1); anifrolumab IR versus placebo, adjusted $P < 0.01$ (FDR < 0.1). Volcano plots illustrate a comparison of protein concentrations at week 12 (B) in anifrolumab IR compared with placebo, (C) in anifrolumab BR compared with placebo, and (D) between nonresponders and responders to treatment with placebo (left panel), anifrolumab BR (middle panel), or anifrolumab IR (right panel). (B–D) Evaluated using the Wilcoxen test at week 12, including proteins expressed in at least 75% of patient samples. Colored dots represent an FDR-adjusted $P < 0.1$. (B–C) Orange indicates elevated expression with placebo, blue indicates elevated expression with anifrolumab treatment, and gray indicates nonsignificance. (D) Purple indicates elevated expression in nonresponders, and gray indicates nonsignificance. BR, basic regimen; CRR; complete renal response; FDR, false discovery rate; IR, intensified regimen; LN, lupus nephritis; MCP-1, monocyte chemoattractant protein 1; NS, nonsignificance.

fold change −0.7; adjusted *P* value [all] FDR < 0.1; Figure 2B, Supplementary Table S1); only MMP3 levels were higher in patients receiving placebo versus anifrolumab BR (log_2 fold change −1.3, adjusted *P* value FDR < 0.1; Figure 2C, Supplementary Table S1).

At week 12 with anifrolumab BR + IR treatment, only TRAIL-R3 was detected at greater concentrations versus placebo (log_2 fold change 0.5, adjusted *P* value FDR < 0.1). In contrast, several biomarkers were increased in patients receiving placebo versus anifrolumab BR + IR (Supplementary Figure S4A). No significant difference was detected when comparing the fold changes in biomarker levels at week 12 induced by IR versus placebo with those induced by BR versus placebo (Supplementary Figure S5).

In additional descriptive analyses by LN class, a trend toward stronger biomarker fold changes in mixed classes (III + V or IV + V) was observed versus pure proliferative forms (III/IV; Supplementary Figure S6A). By NIH Chronicity Index, biomarker reductions tended to be larger in patients with NIH Chronicity Index ≥4 versus <4 (Supplementary Figure S6B).

Response status. Placebo-treated nonresponders displayed elevated expression of many proteins (n = 82), including several biomarkers of intrarenal inflammation, when compared to responders at week 12 (TAFI, log_2 fold change −2.6; C3, log_2 fold change −2.6; SAP, log_2 fold change −2.4; FABP heart, log_2 fold change −2.2; LRG1, log_2 fold change −2.1; transferrin, log_2 fold change −2.0; TBG, log_2 fold change −1.9; BAFF, log_2 fold change −1.9; CD163, log_2 fold change −1.6; vWF, log_2 fold change −1.5; cathepsin D, log_2 fold change −1.5; MCP-1, log_2 fold change −1.4; neuropilin 1, log_2 fold change −1.3; ICAM-1, log_2 fold change −1.2; Erb3, log_2 fold change −1.3; TIMP-2, log_2 fold change −1.0; adjusted *P* value [all] FDR < 0.1; Figure 2D, left panel, Supplementary Table S1). There were no proteins that were differentially expressed between responders and nonresponders to anifrolumab BR (Figure 2D, middle panel, Supplementary Table S1). In patients treated with anifrolumab IR, only six proteins were detected at greater concentrations in nonresponders versus responders at week 12 (C3, log_2 fold change −2.3; TTR, log_2 fold change −1.8; VDBP, log_2 fold change −1.7; transferrin, log_2 fold change −1.7; Apo A-I, log_2 fold change −1.5; ApoA-II, log_2 fold change −1.4; adjusted *P* value [all] FDR < 0.1; Figure 2D, right panel, Supplementary Table S1). At week 12, nonresponders to anifrolumab BR + IR treatment had persistent expression of four proteins (transferrin, C3, fibrinogen, and IL-6 Simoa) versus responders, who demonstrated elevated TNFα Simoa levels alone (Supplementary Figure S4B). Taken together, these results demonstrate that patients with LN treated with anifrolumab have a reduced urinary proteomic inflammatory signature, regardless of responder status.

DISCUSSION

Here, we determined the impact of anifrolumab treatment on urinary biomarkers through proteomic analysis of urine samples from patients enrolled in the TULIP-LN phase 2 trial. Anifrolumab IR induced a more rapid reduction of preselected urinary biomarkers indicative of LN histologic activity, compared with placebo. These results were confirmed in a broader multiplexed proteomic analysis, which showed that anifrolumab reduced the expression of multiple biomarkers of intrarenal inflammation regardless of CRR responder status.

Anifrolumab IR more rapidly reduced CD163 and MCP-1 urinary biomarker levels versus placebo at week 12. CD163 is expressed by intrarenal macrophages in active LN and marks a profibrotic, anti-inflammatory phenotype.[14] Urinary CD163 levels are elevated in patients with active LN compared with patients with active extrarenal SLE, inactive SLE, or other glomerular diseases.[15] Increased urinary CD163 levels are correlated with proliferative LN and the NIH Activity Index, which quantifies histologic activity in SLE.[5,15] $CD163^+$ macrophages are the predominant immune cell type in LN kidneys and are implicated in LN pathogenesis.[14] Together, these findings suggest that urinary CD163 reflects the intrarenal inflammatory microenvironment.

MCP-1, a monocyte chemoattractant produced mainly by tubular epithelial cells and infiltrating macrophages, is also elevated in urine samples of patients with LN and is correlated with UPCR and renal disease activity score.[16] Reductions in levels of these biomarkers with anifrolumab treatment may modulate intrarenal myeloid inflammation early in the disease course.

Urinary BAFF and B2M levels were also reduced by anifrolumab by week 12. BAFF promotes B cell survival and differentiation and has been implicated in the pathogenesis of SLE; the anti-BAFF monoclonal antibody belimumab was the first approved biologic for SLE treatment,[17] with subsequent approval for LN. Patients with LN have significantly higher urinary BAFF bioactivity compared with patients with nonrenal SLE.[17] Serum B2M also correlates with SLE disease activity and damage, and is predictive of LN disease activity.[18]

Finally, anifrolumab also reduced IL-16, which strongly correlates with histologic activity in LN and was identified as one of the most widespread cytokines produced by kidney-infiltrating immune cells.[19] IL-16 is a proinflammatory cytokine implicated in kidney injury[19,20]; its urinary concentrations correlate with the presence of intrarenal $IL\text{-}16^+$ cells, supporting its specificity as a marker of local kidney inflammation.[19] Together, these observations indicate that many urinary biomarkers reflect intrarenal inflammatory processes specific to LN rather than systemic inflammation. Nevertheless, among the nearly 200 proteins analyzed here, it remains possible that some may derive from systemic immune activation rather than kidney-specific pathology.

Earlier reduction of urinary biomarker levels with anifrolumab may have clinical implications. The Accelerating Medicines Partnership demonstrated in a large multicenter cohort that CD163 levels predicted future loss of kidney function in LN.[21] Furthermore, an early decline in urinary CD163 and other markers of histologic activity after three months was predictive of subsequent

treatment response; CRR was defined as a reduction in UPCR to <0.5 mg/mg at one or two years, a threshold that has been associated with improved long-term preservation of kidney function in patients with LN.[5] As kidney survival is the main goal of treatment in patients with LN, these findings provide a potential link between early biomarker improvement and long-term kidney survival as well as prevention of damage accrual. Chronic kidney damage in proliferative LN follows a biphasic trajectory, with rapid accrual of higher NIH Chronicity Index score in the first nine months followed by a plateau.[22] However, damage can continue beyond this initial disease phase.[22] Because early damage accumulation in patients with LN is likely driven by inflammatory activity, an earlier reduction of urinary biomarkers linked to intrarenal inflammation, as observed by week 12 with anifrolumab IR, may attenuate the initial damage accrual phase, potentially preserving long-term kidney function.

Our findings indicate that anifrolumab IR reduced inflammatory biomarker levels, even in patients who did not achieve CRR. Although CRR responders in all treatment groups showed declines in CD163 and MCP-1 levels, nonresponders treated with anifrolumab demonstrated biomarker improvement not seen in placebo-treated nonresponders. This suggests that anifrolumab may suppress intrarenal inflammation even in the absence of reduction of proteinuria below a CRR target threshold. These findings highlight the potential limitations of traditional clinical CRR thresholds. However, for biomarker-based assessments to be clinically meaningful, a correlation with therapeutic benefit may need to be established. Proteomic analyses also revealed a broader reduction in inflammatory proteins among anifrolumab-treated patients versus standard therapy alone. Among CRR nonresponders, only 4 proteins were detected at greater concentrations with anifrolumab at 12 weeks, versus 82 in the placebo group. These findings are consistent with studies showing that up to 44% of patients achieving clinical response by proteinuria-based definitions may still display persistent histologic activity on biopsy, reinforcing the need for noninvasive tools to evaluate intrarenal disease activity more accurately.[23] Although anifrolumab led to relatively large reductions in biomarker levels versus placebo plus standard therapy as early as week 12, biomarker levels in the placebo group reduced to similar levels at week 48, indicating that standard therapy alone can eventually suppress intrarenal inflammation but with slower kinetics.

Our results suggest that urinary proteomics could refine proteinuria-based definitions of treatment response in patients with LN. Because proteinuria often lags behind histologic improvement,[4] urinary biomarkers such as CD163, MCP-1, and IL-16 may provide a more immediate reflection of intrarenal inflammation. Pending further validation and demonstration of their association with meaningful outcomes, such as kidney survival, the incorporation of these biomarker trajectories into future trials and clinical practice could enable earlier assessment of treatment efficacy, support timely therapeutic adjustments, and foster the development of mechanism-based end points in patients with LN.

This study has some important limitations. The sample size is relatively small, which limits statistical power and constrains our ability to draw definitive conclusions. The lack of long-term renal outcome data restricts our ability to draw firm conclusions about clinical significance of the observed changes in urinary proteomics. The lack of follow-up kidney biopsies after anifrolumab treatment limits our ability to correlate urinary biomarker changes with tissue-level inflammation.

This proteomic analysis using data from the phase 2 TULIP-LN trial provides novel insights into the timing and magnitude of intrarenal immune modulation following anifrolumab treatment and the longitudinal impact of anifrolumab on expression of biomarkers associated with renal histologic activity in patients with LN. Anifrolumab may induce earlier and potentially more meaningful immunologic changes than can be captured through proteinuria-based end points alone.

AUTHOR CONTRIBUTIONS

All authors contributed to at least one of the following manuscript preparation roles: conceptualization AND/OR methodology, software, investigation, formal analysis, data curation, visualization, and validation AND drafting or reviewing/editing the final draft. As corresponding author, Dr Ferrari confirms that all authors have provided the final approval of the version to be published and takes responsibility for the affirmations regarding article submission (eg, not under consideration by another journal), the integrity of the data presented, and the statements regarding compliance with institutional review board/Declaration of Helsinki requirements.

ROLE OF THE STUDY SPONSOR

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Nationwide Temporal Trends in Adverse Pregnancy Outcomes and Treatments in Systemic Lupus Erythematosus Pregnancy Over Two Decades in Sweden

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Objective. This nationwide descriptive study examined temporal trends in adverse pregnancy outcomes (APOs) and treatments in systemic lupus erythematosus (SLE) pregnancies in Sweden over 2003 to 2022.

Methods. Using nationwide Swedish registers, we identified 1,417 pregnancies of women with prevalent SLE and delivery dates in 2003 to 2022 and matched them to 14,133 non-SLE pregnancies from the general population on maternal age, delivery year, and parity. We assessed proportions of preeclampsia, preterm delivery, and small for gestational age (SGA) birth over time. Antimalarial, glucocorticoid, and low-dose aspirin use were examined during 2007 to 2022. Binomial generalized linear models with an identity link quantified mean annual absolute change (expressed in percentage points [pp]) in APO and treatment proportions.

Results. Overall, SLE pregnancies had 9.1% preeclampsia, 14.7% preterm delivery, and 6.9% SGA births (2003–2022). These outcomes remained stable in the general population but decreased in SLE pregnancies (preeclampsia from 14.1% in 2003–2004 to 9.6% in 2021–2022, –0.11 pp/y; preterm delivery from 25.9% to 11.2%, –0.63 pp/y; and SGA birth from 10.6% to 7.0%, –0.22 pp/y). Declines were more pronounced in nulliparous versus parous SLE pregnancies. APOs modestly decreased over time in SLE pregnancies with antiphospholipid syndrome. Antimalarial use during pregnancy increased from 23.9% in 2007-2008 to 76.5% in 2021-2022 (+3.3 pp/y). Low-dose aspirin use during pregnancy rose from 39.8% to 85.6% (+3.7 pp/y), whereas glucocorticoid use slightly decreased from 43.2% to 40.1% (–0.7 pp/y).

Conclusion. APOs in SLE pregnancies have decreased over the past two decades, potentially reflecting improved treatment strategies, particularly increased use of antimalarials and low-dose aspirin.

INTRODUCTION

Pregnant women with systemic lupus erythematosus (SLE) have elevated risks of adverse pregnancy outcomes (APOs), such as fetal loss, preterm delivery, fetal growth restriction, and hypertensive disorders of pregnancy compared to those without SLE.[1–4] Historically, pursuing pregnancy was not encouraged for women with SLE, especially those with severe or active disease or with organ involvement, because of the substantially high risk of APOs and limited knowledge of SLE and SLE pregnancy. Nowadays, with the advancement of care, more patients with SLE are having pregnancies.[5,6] However, managing SLE pregnancy remains a clinical challenge, especially regarding balancing the risks and benefits of pharmacological treatments for the patient and the fetus. Over the years, management guidelines for SLE, including SLE pregnancy, have been updated worldwide.[7–12]

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However, how recommendations have been implemented and whether the occurrence of pregnancy outcomes has declined over time remain unclear. Prior studies in SLE pregnancy most often reported the proportion of APOs and SLE treatments for the entire study period, with the overall APO proportions remaining high[1,4,13,14] and hydroxychloroquine (HCQ) being underused (ie, less than 50% of SLE pregnancies were treated with HCQ during pregnancy despite it being recommended).[15–18]

Information on changes in treatments and pregnancy outcomes over time is critical for informing health care providers and patients and identifying gaps for developing future guidelines. However, very few studies have described such time trends. One large study, including around 94,000 women with SLE in the United States, showed a considerable reduction in adverse outcomes (eg, in-hospital maternal mortality, fetal mortality) during 1998 to 2015.[5] HCQ use during pregnancy increased over time but overall remained suboptimal in several cohorts with SLE pregnancy.[17,18] Given the importance and scarcity of these data, we examined the temporal trends in the proportions of APOs and treatment in a nationwide cohort of SLE pregnancies in Sweden over two decades. To put the APO trends into context, we also compared the trends in pregnancies with SLE to those without SLE over the same period.

PATIENTS AND METHODS

Study design and population. This nationwide descriptive study included all singleton pregnancies leading to delivery from January 1, 2003, through December 31, 2022, in patients with prevalent SLE in Sweden and their matched non-SLE pregnancies from the general population. Figure 1 summarizes the study population selection.

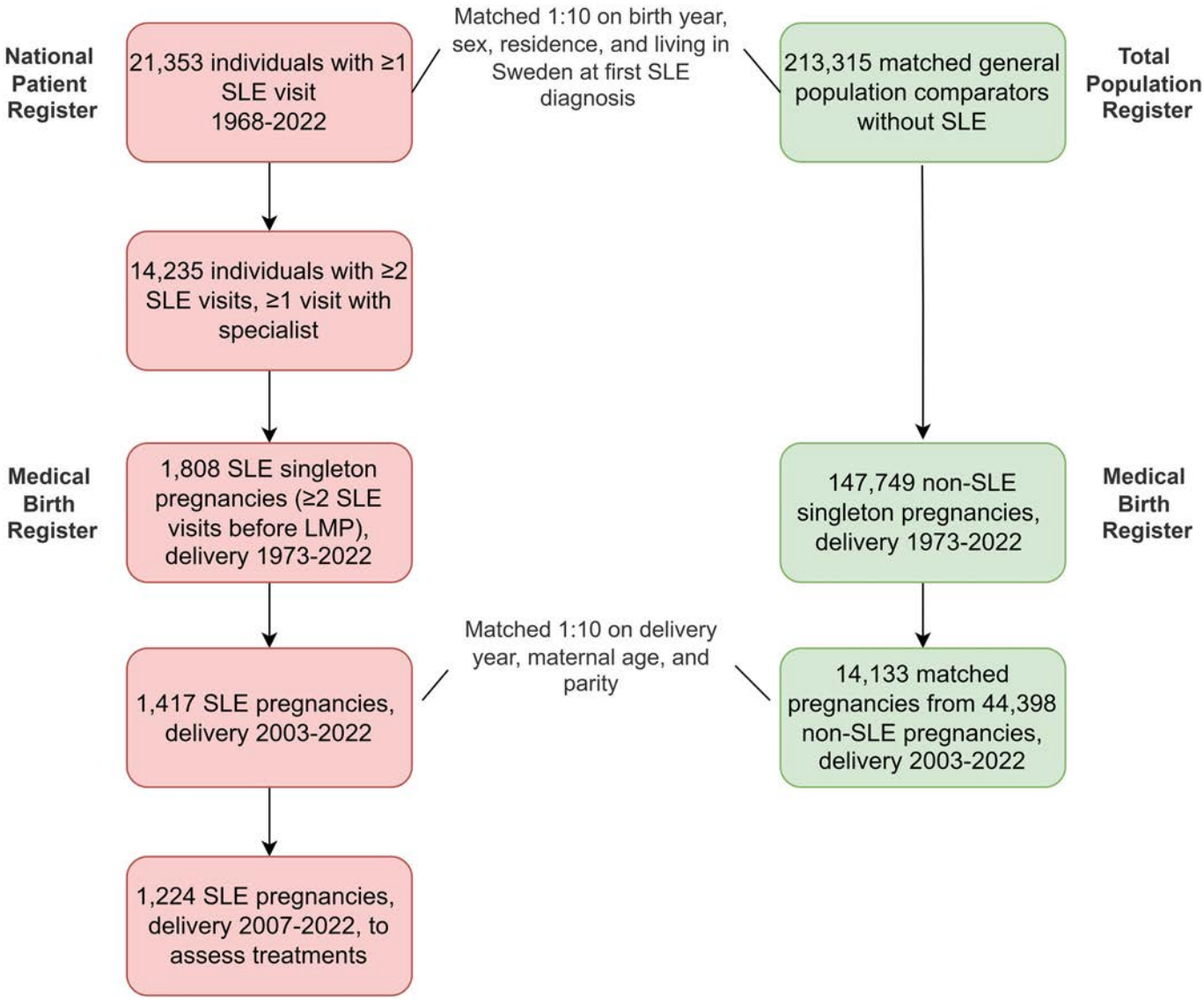

Figure 1. Selection of pregnancies in individuals with and without systemic lupus erythematosus (SLE). LMP, last menstrual period.

From the Swedish National Patient Register (NPR), which has data on hospitalizations since 1964 (nationwide since 1987) and outpatient specialist visits since 2001, individuals with a first visit listing an International Classification of Disease, 9th and 10th Revisions code for SLE (ICD9: 710A; ICD10: M32, excluding drug-induced SLE M32.0) were selected. For each SLE case, up to 10 comparators without SLE were randomly selected from the general population in Sweden, matched on birth year, sex, residence, and status of living in Sweden at the time of the first SLE diagnosis for the corresponding case. These individuals, with and without SLE, formed our original database. To improve the SLE case definition validity, we further required at least one additional inpatient or outpatient visit with an SLE diagnosis on a different date from the first and at least one of these two visits to be with a specialist who typically treats SLE (rheumatology, dermatology, nephrology, internal medicine, or pediatrics). This identification method has shown good accuracy.[19,20]

Using the maternal unique personal identity number, the defined SLE cases and general population comparators were linked to the Swedish Medical Birth Register (MBR) to identify SLE and non-SLE pregnancies leading to deliveries from 2003 to 2022. The MBR contains data on >98% of all deliveries in Sweden since 1973, including all live births regardless of gestational age and stillbirths from gestational week 28 before July 2008 and from gestational week 22 thereafter.[21] For SLE pregnancies, we required the two SLE-defining visits to occur before the last menstrual period (LMP) date to define prevalent SLE (cohort with SLE pregnancy). Non-SLE pregnancies were restricted to those from comparator women in our database who never had an SLE diagnosis before pregnancy. The LMP was estimated by subtracting gestational age at birth from the delivery date. Each SLE pregnancy was then matched to up to 10 non-SLE pregnancies on maternal age at delivery, delivery year, and parity (nulliparous/parous). Women could contribute multiple pregnancies to the study population. APO trends were examined in SLE and non-SLE pregnancies with delivery from 2003 to 2022. For treatment trends, because we needed data within six months preceding pregnancy and the Swedish Prescribed Drug Register, which includes all dispensed prescribed drugs at pharmacies, is available from July 2005, only SLE pregnancies with delivery from 2007 to 2022 were included. This study was approved by the Swedish Ethical Review Authority (2021-01148). Participant consent was waived for this study because it was a register-based study with pseudonymized data. We involved a person with lived experience in all aspects of the study, including conceptualization, shaping the research question and study methodology, choosing outcome measures, result interpretation, and writing up the study.

APOs. We examined the following APOs: preeclampsia, gestational hypertension, placental abruption, preterm delivery, and small for gestational age (SGA) birth, a commonly used proxy for fetal growth restriction. These conditions are important placenta-related pregnancy complications in SLE as well as in the general population. We also assessed Cesarean delivery (elective and emergency) because it has emerged as an important indicator of maternal morbidity and mortality compared with vaginal birth.[22]

For preeclampsia, we included diagnoses of preeclampsia, eclampsia, and pre-existing hypertension with superimposed preeclampsia from gestational week 20 + 0 to six weeks postpartum. Until 2019, preeclampsia was defined as hypertension (>140/90 mm Hg) in combination with excessive proteinuria. In October 2019, according to the Swedish Society of Obstetrics and Gynecology guideline, the criteria changed so that proteinuria became no longer obligatory if another organ impairment was present.[23] Preeclampsia, gestational hypertension, and placental abruption diagnoses were identified from the MBR and NPR, requiring at least one ICD code in the MBR maternal diagnoses or at least one ICD-coded NPR inpatient visit or at least two ICD-coded NPR outpatient visits (at least one for placental abruption). If a woman had both gestational hypertension and preeclampsia during the same pregnancy, she was classified as having preeclampsia only. Preterm delivery was defined as delivery before gestational week 37 + 0, categorized by onset into spontaneous or iatrogenic. SGA birth was defined as birthweight below two SDs of sex-specific mean weight per gestational age.[24] A composite outcome of any APOs (Cesarean delivery not counted) was also created.

SLE treatments. We retrieved dispensations of antimalarials (chloroquine and HCQ), glucocorticoids, azathioprine and other disease-modifying antirheumatic drugs, low-dose aspirin, and heparin and low molecular weight heparins (LMWHs). Use before pregnancy was defined as at least one dispensation within six months before LMP and use during pregnancy as at least one dispensation from LMP to delivery date. Supplementary Table S1 describes the definitions for all APOs, treatments, and other variables used in this study.

Other variables. Antiphospholipid syndrome (APS) and lupus nephritis were defined as at least one ICD-coded NPR inpatient or outpatient visit within five years before pregnancy. APS pregnancies were additionally identified if women had at least one dispensation for warfarin within one year before pregnancy or at least one dispensation for LMWH during pregnancy. We also included maternal age at delivery, first-trimester smoking and body mass index, education level one year before LMP, and country of birth.

Statistical analysis. We described maternal characteristics of SLE and matched non-SLE pregnancies. The annual number of deliveries per 1,000 women with SLE aged 15 to 49 from 2003 to 2022 was plotted along with the corresponding number

in the Swedish general population (retrieved from publicly available data from the National Board of Health and Welfare).[25] To analyze APO and treatment trends, we pooled data into two-year intervals because the number of SLE pregnancies per year was low (<100), especially before 2010, making the annual estimates unreliable. We calculated and visualized the proportions of APOs and treatments and their 95% confidence intervals over the whole study period and during each of the two-year intervals. In a sensitivity analysis, we grouped data into four-year intervals.

Modified Poisson models with robust variance estimators were used to assess temporal trends of APOs and treatments in SLE and non-SLE pregnancies separately (ie, dependent binary variables: APOs, treatments; independent variable: two-year calendar periods). This model directly regresses the log risk (log proportion) of binary outcomes on calendar period and provides *P* values for the relative change (risk ratio) of APO and treatment proportions per calendar period (hereafter referred to as *P* trend). The use of a robust variance estimator corrects for the overestimation of standard errors that arises when applying a Poisson distribution to binary outcomes and appropriately accounts for the correlation introduced by women contributing multiple pregnancies.[26,27] Differences in APO trends between SLE and non-SLE pregnancies were also assessed using modified Poisson models in the total study population with an interaction term between SLE (yes/no) and calendar intervals. To enhance the clinical interpretability of the temporal trend, we quantified the mean annual absolute changes in APO and treatment proportions, expressed as percentage points (pp), using binomial generalized linear models with the identity link.[28]

In SLE pregnancies, we performed trend analyses in subgroups defined by parity (nulliparous or parous) and in pregnancies with APS or with lupus nephritis because APO risks often differ by parity and both APS and lupus nephritis are major risk factors for APOs. The number of SLE pregnancies with APS (SLE+APS pregnancies) or with lupus nephritis was low; therefore, we grouped data into larger calendar periods. All analyses were performed with R version 4.3. It is not possible to publicly share the individual-level data used in this project due to the legal framework governing the raw data. For requests for study data, please contact the corresponding author.

RESULTS

The study population included 1,417 SLE pregnancies and 14,133 matched non-SLE pregnancies in Sweden from 2003 to 2022. The mean maternal age at delivery was 32 years, and 44% were nulliparous pregnancies (Table 1). There were slight differences in nonmatching characteristics, such as a higher proportion having an educational level of ≥13 years and a lower proportion with first-trimester body mass index ≥30 kg/m^2 in women with SLE versus without SLE. The annual number of deliveries per 1,000 women with SLE aged 15 to 49 years in Sweden substantially increased from 21 in 2003 to 36 in 2022 (Figure 2), whereas it remained relatively stable at around 51 deliveries per 1,000 women in the overall Swedish population.

Table 1. Maternal characteristics and APOs in pregnancies with and without SLE matched on delivery year, maternal delivery age, and parity, Sweden, 2003 to 2022*

Maternal characteristics and APOs	SLE pregnancies (N = 1,417), n (%)	Non-SLE pregnancies (N = 14,133), n (%)
Age at delivery, mean (±SD), y	32.2 (±4.7)	32.2 (±4.5)
Parity group		
Nulliparous	621 (43.8)	6,174 (43.7)
Parous	796 (56.2)	7,959 (56.3)
Nordic country of birth	1,185 (83.6)	11 735 (83.0)
First-trimester smoking	62 (4.4)	606 (4.3)
First-trimester BMI ≥ 30 kg/m^2	152 (10.7)	1,842 (13.0)
≥13 years of education	826 (58.3)	7,830 (55.4)
APO		
Any APO[a]	354 (25.0)	1,582 (11.2)
Preeclampsia	129 (9.1)	503 (3.6)
Gestational hypertension	35 (2.5)	308 (2.2)
Placental abruption	7 (0.5)	48 (0.3)
Preterm delivery	209 (14.7)	662 (4.7)
Spontaneous onset	84 (5.9)	428 (3.0)
Iatrogenic	125 (8.8)	234 (1.7)
SGA birth	98 (6.9)	321 (2.3)
Cesarean delivery	435 (30.7)	2,476 (17.5)
Elective	265 (18.7)	1,351 (9.6)
Emergency	170 (12.0)	1,125 (8.0)

* APO, adverse pregnancy outcome; BMI, body mass index; SGA, small for gestational age; SLE, systemic lupus erythematosus.
[a] APOs include preeclampsia, preterm delivery, SGA birth, gestational hypertension, and placental abruption.

APOs during 2003 to 2022. The overall proportion of SLE pregnancies with any APOs during 2003 to 2022 was 25.0%, preeclampsia 9.1%, preterm delivery 14.7%, SGA birth 6.9%, gestational hypertension 2.5%, placental abruption 0.5%, and Cesarean delivery 30.7%. All were higher than those in non-SLE pregnancies (Table 1). Overall, APO proportions in SLE pregnancies decreased during 2003 to 2022 (Figure 3; Supplementary Table S2). Preeclampsia proportion decreased from 14.1% in 2003-2004 to 9.6% in 2021-2022 (*P* trend 0.41, mean annual reduction 0.11 pp). Preterm delivery decreased from 25.9% to 11.2% over the same period (*P* trend <0.001, mean annual reduction 0.63 pp), mainly driven by iatrogenic preterm delivery (declined 0.49 pp annually vs 0.14 pp for spontaneous preterm delivery; Supplementary Figure S1). SGA birth proportions decreased by 0.22 pp annually, from 10.6% to 7.0% (*P* trend 0.047). The proportion with any APO also decreased by 0.29 pp per year (*P* trend 0.15). Cesarean delivery decreased by 0.34 pp annually, from 34.1% to 27.3% (*P* trend 0.13). The majority of this reduction was attributed to elective Cesarean (Supplementary Table S2; Supplementary Figure S2). We did not perform trend

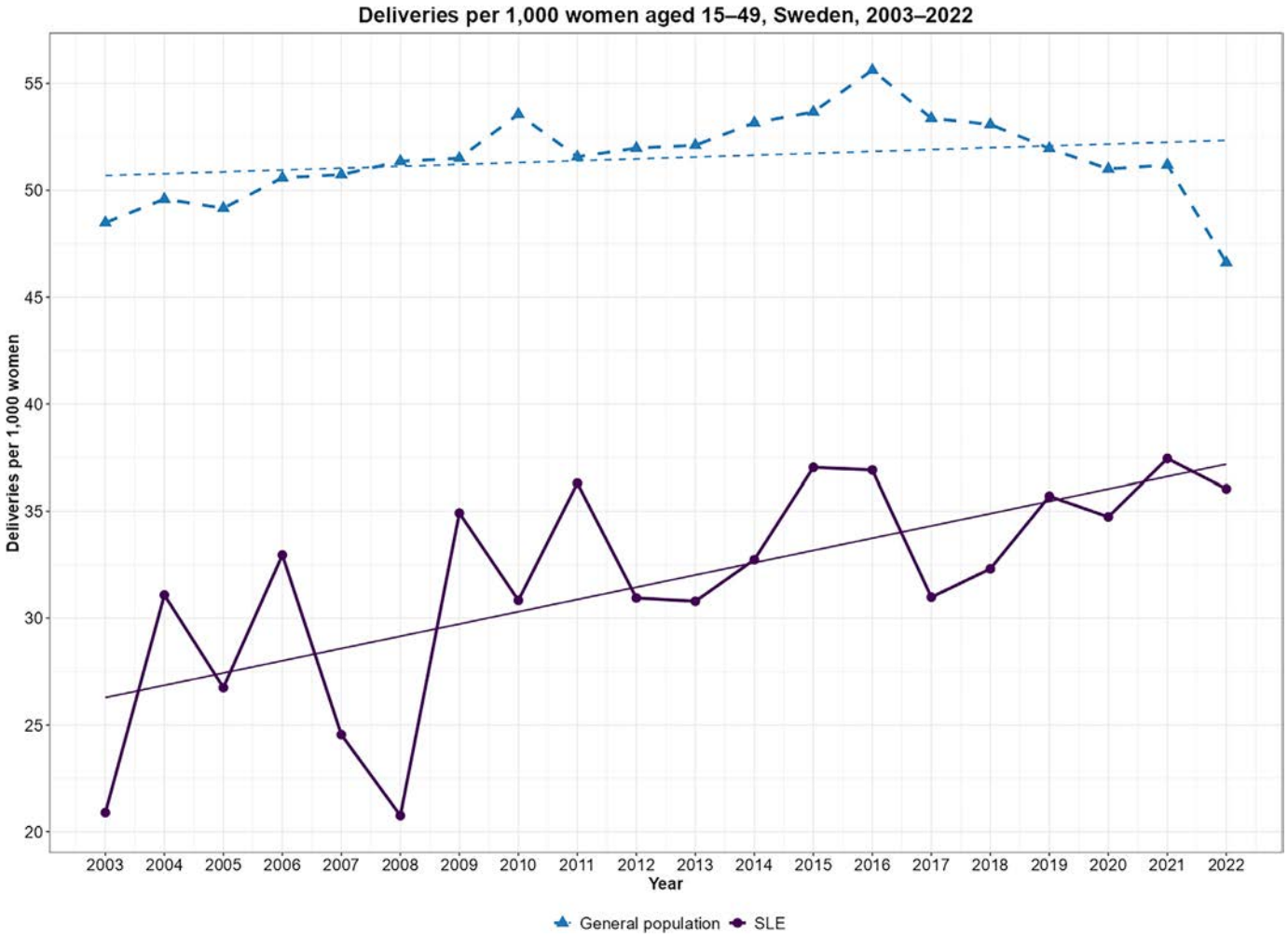

Figure 2. Number of deliveries per 1,000 women aged 15 to 49 years in Sweden from 2003 to 2022. SLE, systemic lupus erythematosus. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/art.70018/abstract.

analysis for gestational hypertension and placental abruption due to very few events per calendar period. In the matched non-SLE pregnancies, annual APO proportions remained relatively stable during the period (Figure 3), except for Cesarean delivery, which increased over time. Trend analysis when the data were grouped into four-year intervals showed similar results (Supplementary Figure S3). The decreasing trends of APOs in SLE pregnancies were significantly different from those in non-SLE pregnancies for any APOs (P = 0.005), preterm delivery (P = 0.004), and Cesarean delivery (P = 0.04; Supplementary Table S3).

In SLE, APOs were more common in nulliparous versus parous groups overall as well as across calendar periods. The decreasing trends of APOs were also more noticeable in nulliparous pregnancies (Supplementary Tables S4 and S5; Supplementary Figure S4). The mean annual pp reduction of APO proportion and P trend in nulliparous SLE pregnancies were as follows: preeclampsia 0.22 pp (P trend 0.39), preterm delivery 1.12 pp (P trend < 0.001), SGA birth 0.59 pp (P trend 0.002), and Cesarean delivery 1.01 pp (P trend 0.004). However, APOs in parous SLE pregnancies fluctuated over time, but overall, there were no clear trends.

APOs occurred more frequently in SLE+APS pregnancies (N = 360) versus SLE without APS (N = 864; preeclampsia 11.7% versus 7.4%; preterm delivery 19.2% vs 11.6%). In SLE +APS pregnancies, any APO, preeclampsia, preterm delivery, and Cesarean delivery, but not SGA birth, declined over three periods, 2007 to 2012, 2013 to 2017, and 2017 to 2022, but the trends were not statistically significant (Figure 4; Supplementary Table S6). In lupus nephritis pregnancies (N = 173), preeclampsia, preterm delivery, and Cesarean delivery were more prevalent than in the overall SLE pregnancies and also decreased over four periods: 2003 to 2007, 2008 to 2012, 2013 to 2017, and 2018 to 2022 (Supplementary Table S7; Supplementary Figure S5). The number of SGA births was few in each period (n < 5).

SLE treatments during 2007 to 2022. The overall proportions of SLE pregnancies with an antimalarial dispensation six

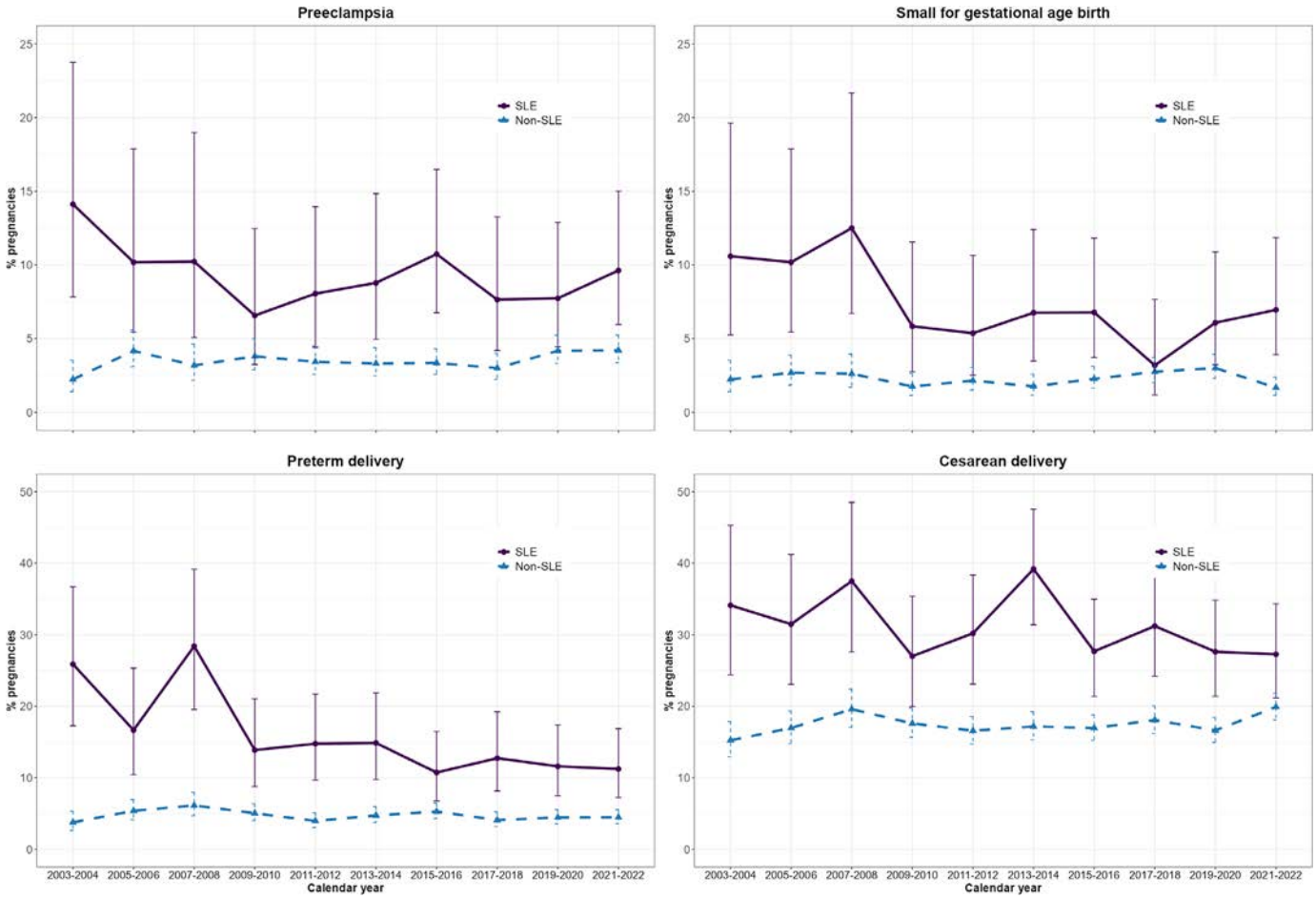

Figure 3. Proportions of systemic lupus erythematosus (SLE) pregnancies (N = 1,417) and non-SLE pregnancies (N = 14,133) with (top left) preeclampsia, (top right) small for gestational age birth, (bottom left) preterm delivery, and (bottom right) Cesarean delivery in Sweden over time, 2003 to 2022. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/art.70018/abstract.

months before and during pregnancy during 2007 to 2022 were 52.9% (51.2% HCQ) and 58.1% (56.5% HCQ), respectively. Antimalarial use substantially increased over the study period. The mean annual increase was 2.7 pp for use before pregnancy (from 31.8% in 2007–2008 to 69.0% in 2021–2022; *P* trend < 0.001) and 3.3 pp for use during pregnancy (from 23.9% to 76.5%; *P* trend < 0.001; Figure 5; Supplementary Table S8). Glucocorticoid use slightly decreased over time, with an average annual reduction of 0.4 pp (from 42.0% to 36.4%, *P* trend 0.18) for use before pregnancy and 0.7 pp (from 43.2% to 40.1%, *P* trend 0.04) for use during pregnancy. The proportion of pregnancies with glucocorticoid use before and during pregnancy remained around 40% to 50% over the study period. Low-dose aspirin use during pregnancy rose significantly from 39.8% in 2007 through 2008 to 85.6% in 2021 through 2022 (*P* trend < 0.001, mean annual increase 3.7 pp). Low-dose aspirin use before pregnancy also increased, but to a lesser extent, from 9.1% to 16.0% (*P* trend 0.028, mean annual increase 0.5 pp). Azathioprine, heparin, and LMWH use before and during pregnancy modestly increased. Similar trends were observed in SLE+APS pregnancies (Supplementary Figure S6).

DISCUSSION

In this nationwide descriptive analysis of over 1,400 SLE pregnancies, APOs (preeclampsia, preterm delivery, and SGA birth) and Cesarean delivery have decreased over the last two decades in Sweden. The decrease was primarily driven by nulliparous pregnancies, whereas APOs in parous pregnancies fluctuated but overall remained relatively stable. Among SLE+APS pregnancies, the decreasing trends of APOs were less noticeable, underscoring the need for continued efforts. The temporal trends of any APO, preterm delivery, and Cesarean delivery were significantly different between SLE versus non-SLE pregnancies. Concerning SLE treatments, antimalarial use (before and during pregnancy) and low-dose aspirin use (during pregnancy) substantially increased, whereas glucocorticoid use slightly declined during 2007 to 2022.

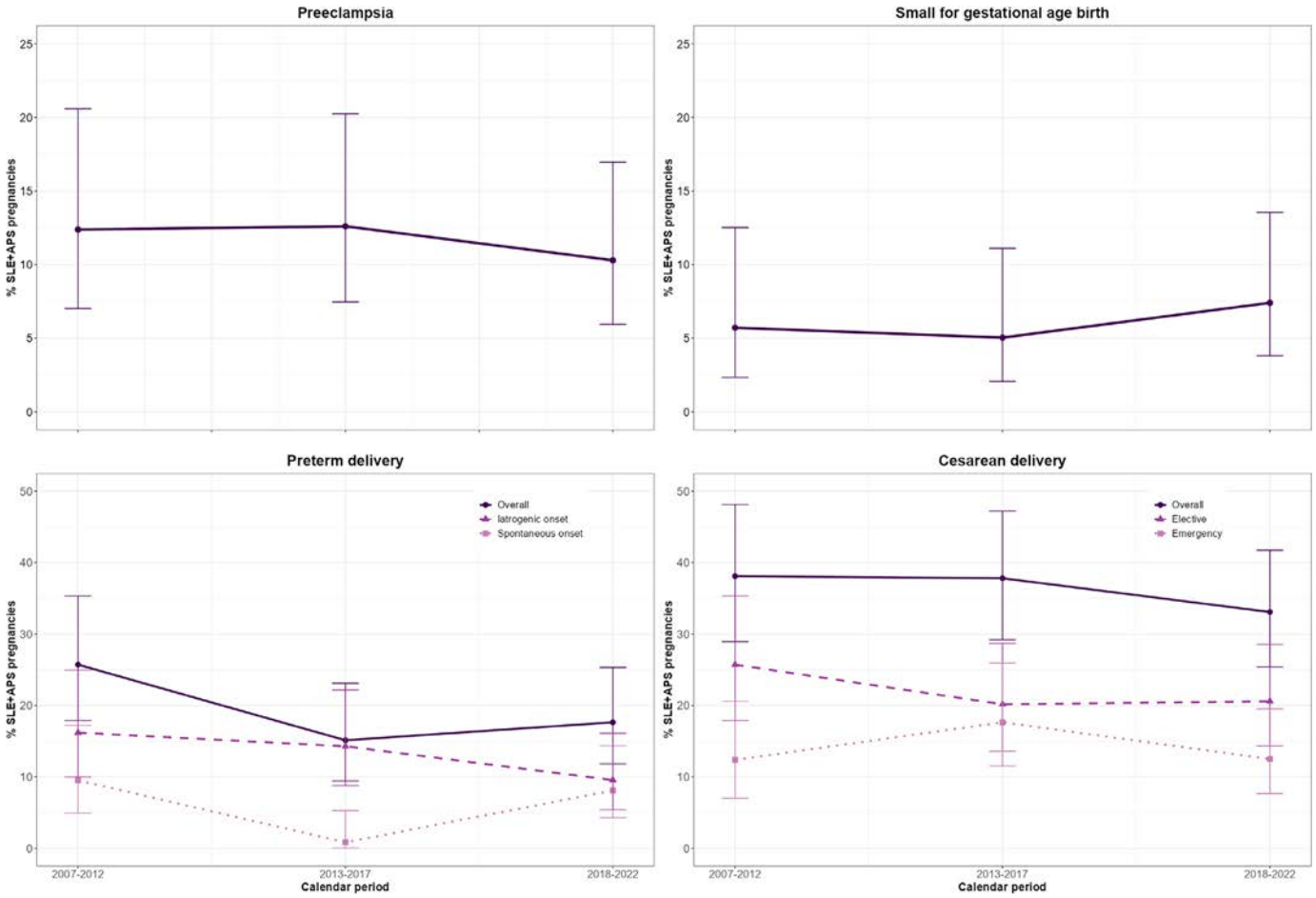

Figure 4. Proportions of systemic lupus erythematosus pregnancies complicated by antiphospholipid syndrome (SLE+APS pregnancies; N = 360) with (top left) preeclampsia, (top right) small for gestational age birth, (bottom left) preterm delivery, and (bottom right) Cesarean delivery in Sweden over time, 2007 to 2022. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/art.70018/abstract.

Our study also observed an increasing delivery rate among patients with SLE over the last 20 years, from 21 per 1,000 patients in 2003 to 36 per 1,000 in 2022. Similar results were also reported in the United States and Korea, with an increasing number of pregnancies and deliveries in patients with SLE.[5,6,18] These findings likely reflect greater awareness and acceptance of the possibility of successfully pursuing pregnancy for patients with SLE, as well as improved disease control, leading to more women being able to pursue pregnancy.

Women with SLE have a significantly increased risk of APOs, but little has previously been known about whether these outcomes have decreased over the years as guidelines and practices have evolved.[1,4,13,14] One analysis in the United States, using a nationwide sample of SLE pregnancies during 1998 to 2015, reported a marked reduction in in-hospital maternal mortality (from 442 to 140 per 100,000 admissions) but only a modest decrease in preeclampsia (9.5%–9.1%), although this trend was statistically different from that of non-SLE pregnancies.[5] In our study, the decline in preeclampsia in SLE was also modest and smaller than that of preterm delivery and SGA birth and did not reach statistical significance. A small study in Denmark also showed a reduced proportion of preterm delivery but not preeclampsia in SLE pregnancies comparing periods 2010 through 2020 (N = 66 pregnancies) to 2000 through 2010 (N = 84).[29] Furthermore, a single-center analysis of 178 SLE pregnancies in the United States reported a stable trend in preeclampsia and preterm delivery between 1989 and 2020.[30] These discrepancies could stem from the fact that these studies had low power to study temporal trends and were based on a single referral care center, which likely had health care providers who were better aware of SLE pregnancy and likely included patients with severe disease and, thereby, severe outcomes, whereas our analysis included all patients in Sweden regardless of severity. Furthermore, the definition of preeclampsia has become more inclusive since 2019 in Sweden, leading to an increased proportion since then. Nevertheless, the modest reduction in preeclampsia in SLE suggests that preeclampsia remains a challenge, and general prevention strategies might have been inadequate over the years, particularly because preeclampsia in non-SLE pregnancies actually slightly increased over the years in our study.

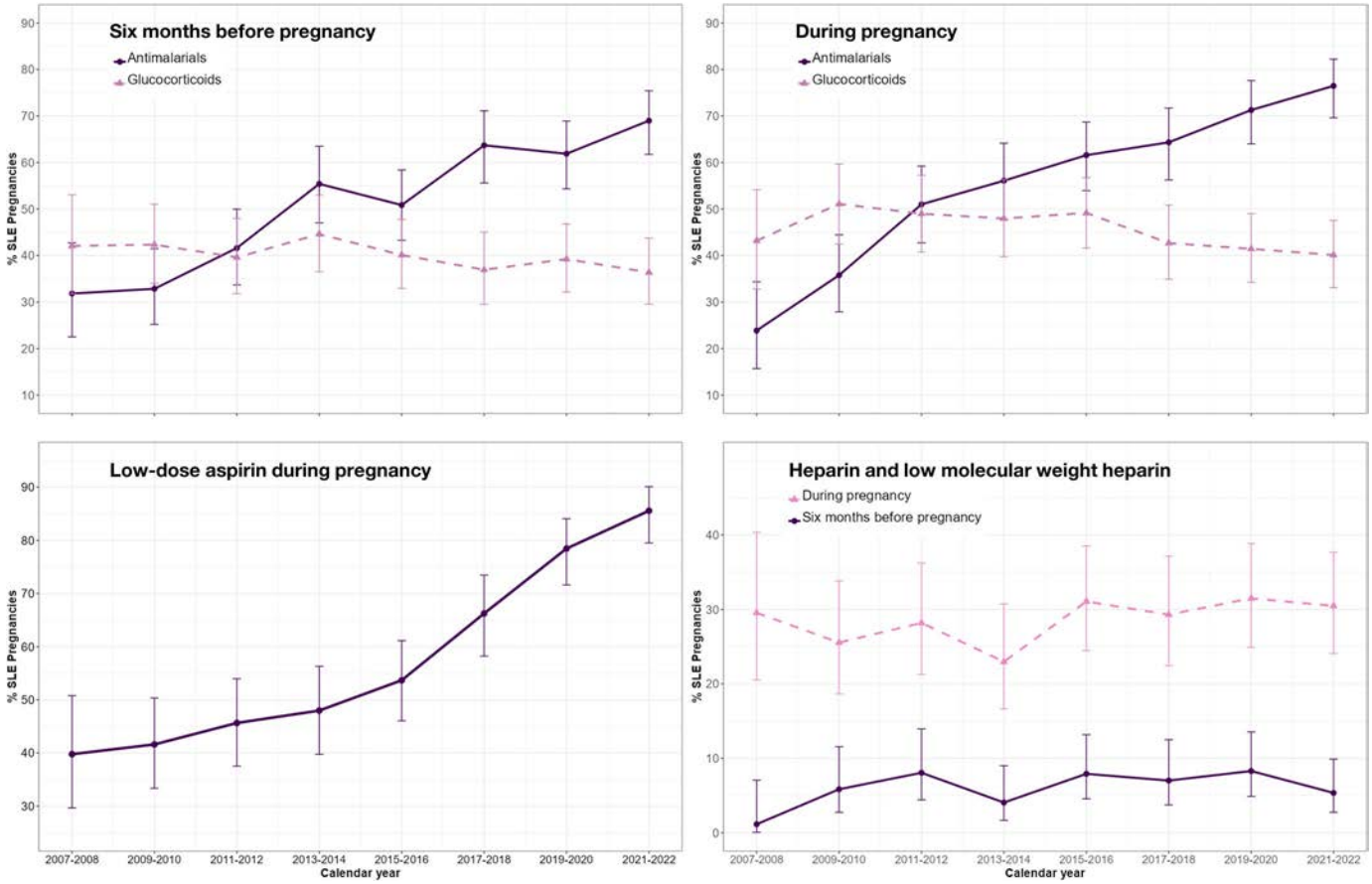

Figure 5. Proportions of systemic lupus erythematosus (SLE) pregnancies (N = 1,224) in Sweden, 2007 to 2022, with (top left) antimalarials and glucocorticoids before pregnancy, (top right) antimalarials and glucocorticoids during pregnancy, (bottom left) low-dose aspirin during pregnancy, and (bottom right) heparin and low-MW heparin before and during pregnancy. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/art.70018/abstract.

Our findings also revealed that APOs in SLE+APS pregnancies were more common than in SLE pregnancies without APS, but some modest improvements were observed over the last 16 years (2007–2022), though not significant. Although this may represent improved care and treatment for APS around pregnancy, continued commitment to advancing care for this high-risk pregnancy population is needed. Despite persistently higher APO proportions in SLE versus non-SLE pregnancies, the decreasing trends in APOs for SLE in our study and others highlight the positive impacts that efforts from health care professionals, policymakers, and patients have made on SLE pregnancy care over the years. Several factors could contribute to these improvements. Enhanced diagnostic capabilities for milder SLE, better prepregnancy counseling (ie, effectively managing risk factors and achieving low disease activity before attempting pregnancy), improved multidisciplinary care (ie, collaborations between rheumatologists and obstetricians), updated management guidelines for SLE and related complications, and conventional advances in obstetric care might have all played a role. Additionally, the promotion of initiation and continuation of HCQ throughout pregnancy and the increasing use of low-dose aspirin prophylaxis and LMWH likely contribute to better outcomes.

There has been a substantial rise in the use of antimalarials (primarily HCQ) and low-dose aspirin in SLE pregnancies over the years in Sweden, with around 80% of SLE pregnancies on antimalarials in recent years versus only around 30% during 2007 to 2008. Increased use of HCQ was also reported in cohorts with SLE pregnancy in the United States.[17,30] These findings reassure the implementation of management guidelines in clinical practice, which may contribute to the observed decrease in APOs reported above.[7–12] However, 30% of SLE pregnancies were still not treated with HCQ, and 25% were not treated with low-dose aspirin in 2022, which is suboptimal because these treatments are recommended for all. Contraindications or intolerant adverse drug reactions are expected to be rare; hence, this suboptimal use may suggest that clinicians are not prescribing the treatments and/or the patients are not filling the prescribed medications (primary medication nonadherence). Future studies should look into this topic. Although not officially recommended to prevent APOs, preconception use of low-dose aspirin also

increased, which could be due to other indications (ie, cardiovascular disease prevention). It could be relevant to assess whether or not preconceptional low-dose aspirin use improves pregnancy outcomes in future studies. Glucocorticoid use both before and during pregnancy in SLE slightly declined, which may reflect that more women with SLE achieved low disease activity before pregnancy, contributing to better outcomes. However, this could also result from clinicians' tendency to avoid glucocorticoids due to safety concerns and prescribe pregnancy-compatible immunosuppressants instead.[31] Correspondingly, we observed a small increase in azathioprine and ciclosporin use for SLE pregnancies. LMWH before and during pregnancy also increased modestly. Despite these trends, 40% to 50% of SLE pregnancies still had glucocorticoid treatment. The exact daily dose of glucocorticoids was not available because we had information on the total number of pills dispensed but not the intended duration or regimen. However, even if all were low dose, this level of glucocorticoid use represents a considerable gap between current practice and guideline recommendations.[8,10] Reported estimates of glucocorticoid use during SLE pregnancy from previous studies vary widely, ranging from 59.1% in a UK specialist clinic (2007–2012) to 19.7% in a Canadian cohort (2002–2012).[32,33]

Our study has several limitations. We did not have information on some clinical factors that influence APOs and treatment choices, such as disease activity before and during pregnancy, and antiphospholipid or anti-Ro/SSA antibodies. We defined APS by combining ICD codes and relevant medication use, which might be subject to some misclassification (ie, undiagnosed/undocumented APS in the group without APS, misclassified APS in the group with APS because warfarin or LMWH could be prescribed for other indications). Identifying pregnancies with lupus nephritis using ICD codes could be subject to misclassification because the validity of ICD codes for this condition remains unknown in Swedish registers. Exact categorization of glucocorticoid use into low dose or high dose was not possible, which prevented us from discussing in-depth how the management guidelines were implemented because both the indication and the dose matter for glucocorticoids. In addition, we could not assess miscarriage or pregnancy termination (<20 weeks of gestation) due to data unavailability.

Our study is among the first to examine temporal trends over two decades of several APOs and medication therapies in SLE pregnancies, with comparison to the general population. We used national registers with excellent coverage, thereby ensuring the representativeness of the Swedish SLE population and generalizability to similar health care settings. Also, we examined SLE pregnancies stratified by important factors such as APS and parity, which has not been done before, providing insights for multiple clinical scenarios.

In summary, we observed a declining trend in APOs, especially preterm delivery, in SLE pregnancies in Sweden over the past two decades, whereas the trend has been stable in non-SLE pregnancies. However, the proportion of APOs remained higher in SLE versus non-SLE pregnancies. Notably, HCQ and low-dose aspirin use in SLE pregnancies increased significantly, aligning with changes in guidelines over time and potentially contributing to the observed decrease in APOs. Our study provides robust nationwide evidence, not only highlighting the impacts of clinical efforts over the years but also suggesting that continued advancements in care for SLE pregnancy are needed.

AUTHOR CONTRIBUTIONS

All authors contributed to at least one of the following manuscript preparation roles: conceptualization AND/OR methodology, software, investigation, formal analysis, data curation, visualization, and validation AND drafting or reviewing/editing the final draft. As corresponding author, Ngoc V. Nguyen confirms that all authors have provided the final approval of the version to be published and takes responsibility for the affirmations regarding article submission (eg, not under consideration by another journal), the integrity of the data presented, and the statements regarding compliance with institutional review board/Declaration of Helsinki requirements.

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Prediction of Relapse and Glucocorticoid Dependence in Eosinophilic Granulomatosis With Polyangiitis: Findings From a Large European Cohort

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Objective. Eosinophilic granulomatosis with polyangiitis (EGPA) is a small vessel vasculitis characterized by eosinophilia, asthma, and ear, nose, and throat (ENT) involvement. Although glucocorticoids (GCs) are effective in controlling symptoms, relapses and GC dependence are common. The aim of this study was to develop predictive models for vasculitis relapse and GC-dependent asthma and/or ENT symptoms.

Methods. This multicenter European retrospective cohort study included patients with EGPA fulfilling the 2022 American College of Rheumatology/EULAR criteria. Using Fine-Gray and logistic regression, we developed two multivariable prediction models, one for vasculitis relapse and another for GC-dependent asthma and/or ENT symptoms at 2 Internal validation was performed using bootstrapping.

Results. A total of 809 patients were observed for a median of 72 months (interquartile range 37–115). Vasculitis relapse occurred in 228 patients with a 12-year cumulative incidence of 41.2% (95% confidence interval 36.3–46.8). GC-dependent asthma and/or ENT symptoms were observed in 66.4% at two years. Predictors of vasculitis relapse included age (nonlinear), GC-dependent asthma before EGPA diagnosis (hazard ratio [HR] 1.57), arthralgia (HR 1.27), myocarditis (HR 1.74), peripheral neuropathy (HR 1.39), myeloperoxidase–antineutrophil cytoplasmic antibody (HR 1.56), and baseline eosinophil count (nonlinear). Predictors of GC-dependent asthma and/or ENT symptoms included older age (odds ratio [OR] 0.98 per year), GC-dependent asthma at diagnosis (OR 1.50), chronic sinusitis (OR 1.78), and baseline eosinophil count (OR 0.70 per 10^9/L).

Conclusion. Using a large cohort with EGPA, we developed predictive models for vasculitis relapse and GC-dependent asthma and/or ENT symptoms. These tools may help guide treatment decisions. Prospective external validation in the current therapeutic era is warranted.

INTRODUCTION

Eosinophilic granulomatosis with polyangiitis (EGPA) is a rare systemic vasculitis characterized by eosinophil-rich necrotizing granulomatous inflammation of small- to medium-sized vessels, asthma, and eosinophilia.[1] The 2012 Revised International Chapel Hill Consensus Conference defined EGPA within the antineutrophil cytoplasmic antibody (ANCA)-associated

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vasculitides.[1] However, ANCAs are detected in fewer than 40% of patients with EGPA,[2–4] with the majority directed against myeloperoxidase (MPO).[4,5]

ANCA status has an influence on disease phenotype with patients with ANCA positivity more likely to present with renal involvement, peripheral neuropathy, and alveolar hemorrhage, whereas patients with ANCA negativity are more likely to present with cardiac manifestations and pulmonary infiltrates.[2–4] These differences have led to evolving concepts that distinguish manifestations related to eosinophilia, such as asthma and ear, nose, and throat (ENT) involvement, from those driven by vasculitis.[6,7]

EGPA treatment has long relied mainly on glucocorticoids (GCs). In patients without poor prognostic factors (1996 Five-Factor Score [FFS] = 0),[8,9] GCs monotherapy achieved a five-year overall survival of 92%, although complete remission was achieved in only 50% of patients.[10] In patients with poor prognostic factors (FFS ≥ 1), GCs plus cyclophosphamide induction therapy resulted in remission rates of 88% and overall survival of 97%, but relapse rates exceeded 70% (after a median follow-up of 42.5 months).[11] Long-term follow-up studies (mean 81 months) reported a relapse rate of 41%, with 57% of relapses occurring when GCs were tapered below 10 mg/day.[12] Despite a seven-year overall survival rate of 90%, sequelae such as chronic asthma, peripheral neuropathy, and persistent ENT symptoms were common, with a mean daily prednisone dose of 10 mg at last follow-up.[12] A prospective study on patients with nonsevere EGPA had shown that at five years, the respective vasculitis relapse and isolated asthma/rhinosinusitis exacerbation rates were 48% and 56%, respectively.[13] Recent advances, including the use of mepolizumab, an anti-interleukin-5 (anti-IL-5) monoclonal antibody,[14] and benralizumab, an anti-IL-5 receptor alpha monoclonal antibody,[15] have demonstrated efficacy in controlling the disease and sparing GCs, but long-term outcomes remain to be elucidated.

EGPA appears to follow distinct phenotypic trajectories: some patients develop GC-dependent asthma and/or ENT symptom manifestations, whereas others are prone to vasculitis relapse. This study, conducted before the availability of anti-IL-5 therapies, aimed to develop predictive models to assess at baseline the risk of vasculitis relapse and GC-dependent asthma and/or ENT symptom manifestations during follow-up.

METHODS

Study design and population. We conducted a retrospective, multicenter cohort study of 809 patients diagnosed with EGPA between January 1995 and November 2018, a period that preceded the availability of anti-IL-5 therapies. Patients were recruited from 16 tertiary academic medical centers in France, Italy, Germany, and the United Kingdom. The diagnosis of EGPA was made by expert physicians in the field of vasculitis, and all patients met American College of Rheumatology (ACR)/EULAR classification criteria[16] (Supplementary Table 1).

Ethics and regulation. This study was conducted in compliance with the Good Clinical Practice protocol and the principles of the Declaration of Helsinki. The Ethics Committee of Cochin University Hospital approved this study (Comité d'Ethique Local pour les Publications decision AAA-2024-10020). Patients were informed verbally and in writing of their full right to request the deletion of their data.

Baseline data collection. Data were extracted from medical records, including demographic characteristics, clinical features, laboratory findings (eg, eosinophil count, C-reactive protein [CRP] levels, and ANCA status), radiologic and histologic findings, and treatment regimens. Disease activity was assessed

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using the Birmingham Vasculitis Activity Score (BVAS) 2003,[17,18] whereas prognosis was assessed using the 1996 FFS.[8]

Induction and maintenance therapies were recorded. Data were collected throughout the follow-up period. Daily prednisone dose was recorded at 3 ± 1, 6 ± 1, 12 ± 1, 24 ± 3, 36 ± 3, 48 ± 3, 60 ± 3 months and at last follow-up. Eosinophils counts were assessed at 3 ± 1, 6 ± 1, 24 ± 3 and 60 ± 3 months and at last follow-up. The Vasculitis Damage Index[19] was assessed at 24 ± 3 and 60 ± 3 months and at last follow-up.

Outcomes. Endpoints included (1) vasculitis relapse, defined as the recurrence or worsening of clinical manifestations attributable to active vasculitis (BVAS > 0) requiring treatment escalation, excluding isolated asthma or ENT exacerbations, and (2) GC-dependent asthma and/or ENT symptom manifestations, defined as symptoms requiring >7.5 mg/day of prednisone within 24 months after diagnosis. From the database, we selected characteristics that had a possible influence on the relapse prognosis in the population.

Statistical analysis. A risk prediction model for relapse (up to 12 years after diagnosis) was developed using a Fine-Gray model. Given the study sample size, follow-up person-years, and event rates, we computed that a maximum number of model

Table 1. Characteristics of 809 patients with EGPA at baseline and comparison between patients with ANCA positivity and patients with ANCA negativity*

Characteristics	N	All patients, mean (±SD)	ANCA positivity, mean (±SD)	ANCA negativity, mean (±SD)	*P* value
Patients	–	809	274	519	–
Age, y	809	52 (±14.8)	55.2 (±14.1)	50.3 (±14.8)	<0.0001
Female	809	440 (±54.4)	133 (±48.5)	297 (±57.2)	0.02
Asthma before EGPA diagnosis	794	716 (±90.2)	235 (±86.1)	469 (±92.1)	0.40
Chronic sinusitis before EGPA	732	483 (±66.0)	159 (±65.2)	315 (±66.3)	0.008
Manifestations at EGPA diagnosis					
Constitutional symptoms	798	512 (±64.2)	191 (±70.2)	313 (±61.0)	0.012
Fever > 38°C	762	238 (±31.2)	105 (±39.2)	129 (±26.7)	0.0005
Myalgia	766	221 (±28.9)	81 (±30.0)	137 (±28.2)	0.62
Arthralgia	766	231 (±30.2)	99 (±36.8)	128 (±26.3)	0.003
Cutaneous manifestations	805	288 (±35.8)	107 (±39.2)	175 (±33.8)	0.14
Purpura	804	146 (±18.2)	62 (±22.7)	81 (±15.7)	0.019
Urticaria	802	75 (±9.4)	17 (±6.2)	57 (±11.1)	0.029
ENT symptom manifestations	804	672 (±83.6)	229 (±83.9)	431 (±83.4)	0.92
Nasal crusts	728	65 (±8.9)	25 (±10.0)	40 (±8.6)	0.59
Sinusitis	804	617 (±76.7)	207 (±75.8)	398 (±77.0)	0.72
Otitis	759	50 (±6.6)	19 (±7.1)	31 (±6.4)	0.76
Pulmonary manifestations	805	782 (±97.1)	266 (±97.1)	503 (±97.3)	0.82
Asthma	806	735 (±91.2)	244 (±89.1)	478 (±92.3)	0.15
Infiltrates	802	414 (±51.6)	111 (±40.7)	299 (±58.1)	<0.0001
Pleuritis	772	77 (±10.0)	14 (±5.2)	62 (±12.6)	0.0009
Cardiac manifestations	805	233 (±28.9)	57 (±20.8)	171 (±33.1)	0.0003
Pericarditis	798	147 (±18.5)	29 (±10.6)	115 (±22.6)	<0.0001
Myocarditis	753	108 (±14.3)	23 (±9.2)	82 (±16.8)	0.005
Cardiomyopathy	799	78 (±9.8)	16 (±5.9)	60 (±11.7)	0.008
Gastrointestinal manifestations	804	125 (±15.5)	43 (±15.8)	82 (±15.9)	>0.99
Renal manifestations	803	96 (±12.0)	69 (±25.3)	26 (±5.0)	<0.0001
Proteinuria > 1 g/24 h	800	63 (±7.9)	47 (±17.3)	15 (±2.9)	<0.0001
Hematuria	802	71 (±8.9)	56 (±20.5)	14 (±2.7)	<0.0001
Biopsy-proven GN	750	39 (±5.2)	34 (±13.8)	5 (±1.0)	<0.0001
Neurologic manifestations	802	462 (±57.6)	201 (±73.6)	253 (±48.9)	<0.0001
Mononeuritis multiplex	786	288 (±36.6)	136 (±50.2)	148 (±29.3)	<0.0001
Polyneuropathy	795	193 (±24.3)	72 (±26.5)	117 (±22.9)	0.29
Biologic parameters					
Positive ANCA	793	274 (±34.6)	274 (±100)	–	–
MPO-ANCA	761	216 (±28.4)	216 (±83.4)	–	–
PR3-ANCA	747	19 (±2.5)	19 (±7.8)	–	–
CRP, median (IQR), mg/L	547	30 (7–75)	59 (23–100)	17.8 (5–57.2)	<0.0001
Eosinophils count, median (IQR), 1,000/mm^3	658	3,836 (1,400–8,260)	5,300 (2,060–10,060)	3,050 (1,268–7,370)	<0.0001
BVAS, median (IQR)	788	14 (9–19)	16 (12–22)	13 (8–18)	<0.0001

* Data are indicated as number (percentage) unless indicated differently. N is the number of nonmissing observations. ANCA, antineutrophil cytoplasmic antibody; BVAS, Birmingham Vasculitis Activity Score; CRP, C-reactive protein; EGPA, eosinophilic granulomatosis with polyangiitis; ENT, ear, nose, and throat; GN, glomerulonephritis; IQR, interquartile range; MPO, myeloperoxidase; PR3, proteinase 3.

parameters of 28 would allow for developing a model with small overfitting (expected shrinkage by 10% or less and a 0.05 acceptable difference between apparent and adjusted R-squared) and sufficient precision of predictions (0.05 margin of error in estimating overall risk at 12 years), assuming a model with concordance *c*-index of 0.85.[20] Missing baseline data were handled with multiple imputations with the Multivariate Imputation by Chained Equations algorithm (50 imputations). All predictors considered in the model development were used in the imputation model. Convergence of the multiple imputation algorithms was assessed by visual inspection of the mean and variance of the imputation streams.

To account for a potential nonlinear effect of continuous predictors in the model, fractional polynomials were used, leading to a polynomial of degree 3 for age, a logarithmic transformation for CRP, and a cubic effect for eosinophil count (the latter being capped at 15,000/mm^3). We used a backward selection procedure based on Wald tests for the pooled regression coefficients to select a subset of predictors, with *P* value cutoffs mimicking the use of Akaike information criterion. Two-by-two interactions among each of the selected variables were then examined using Wald tests for the pooled regression coefficients. Model performance was evaluated using the *c*-index for discrimination and calibration curves. The latter displayed observed versus predicted values for equal-sized groups of participants. A smoothed calibration curve was additionally estimated using loess. In addition, the calibration was assessed in terms of integrated calibration index, which is the average of the absolute difference between observed and predicted probabilities, as well as the related E50 and E90, which represent the median and 90th percentile of those absolute differences.[21,22]

Given the study sample size, we considered that sample splitting would be an inefficient strategy for model development and validation and resorted to bootstrapping for internal model validation.[23–25] The model development strategy was therefore replicated on 500 bootstrap samples, the performance of the models estimated in each bootstrap sample was evaluated in the original sample, and the differences between the bootstrap and the original sample performance were taken as measures of the overoptimism of the selected model. These measures were used to obtain an optimism-adjusted *c*-index and to shrink the regression coefficients of the selected model by the corrected calibration slope. A similar modeling approach was adopted to develop a risk prediction model for GC-dependent asthma and/or ENT symptom manifestations at two years, although it was based on logistic regression. The association of the predicted risk of relapse and the predicted risk of GC-dependent asthma was assessed using Spearman's rank correlation and visually by displaying predictions with a smoothed lined estimate by loess.

Categorical variables were presented as counts and percentages, whereas continuous variables were summarized as means (±SD) or medians (interquartile range [IQR]). Analyses were conducted using R software (version 3.6.3). Nomograms were used to display the risk prediction models and allow computing predicted probabilities obtained by the rms R package. A two-sided *P* value ≤0.05 was considered statistically significant unless stated otherwise.

RESULTS

Baseline characteristics of patients with EGPA and comparison by ANCA status. Baseline characteristics of the 809 patients enrolled are summarized in Table 1. The mean age at diagnosis was 52 ± 14.8 years, with a female to male ratio of 1.2. Before EGPA diagnosis, 90.2% of patients reported asthma and 66.0% reported chronic sinusitis.

At diagnosis, 97.1% of patients had pulmonary involvement, including active asthma (91.2%), pulmonary infiltrates (51.6%), and alveolar hemorrhage (2.5%), 83.6% had ENT symptom manifestations, 64.2% of patients had constitutional symptoms, and 35.8% had skin involvement. Neurologic, cardiac, and renal involvement occurred in 57.6%, 28.9%, and 12.0% of patients, respectively. ANCA was detected in 34.6% of patients, predominantly MPO-ANCA (28.4%). The median CRP level was 30.0 mg/L (IQR 7–75), and the median eosinophil count was 3836/mm^3 (IQR 1,400–8,260).

Comparisons by ANCA status revealed significant differences. Patients with ANCA positivity were older ($P < 0.0001$) and more likely to present with fever ($P = 0.0005$), arthralgia ($P = 0.003$), purpura ($P = 0.019$), renal involvement ($P < 0.0001$), and neurologic manifestations ($P < 0.0001$). In contrast, patients with ANCA negativity were more likely to have urticaria ($P = 0.029$), pulmonary infiltrates ($P < 0.0001$), and cardiac involvement ($P = 0.0003$). Patients with ANCA positivity also had higher CRP levels ($P < 0.0001$) and eosinophil counts ($P < 0.0001$).

Vasculitis relapse prediction model. During a median follow-up of 72 months (IQR 37–115), 228 patients experienced at least one vasculitis relapse, with a 12-year cumulative incidence of 41% (95% confidence interval [CI] 36–47; Figure 1). The prediction model for vasculitis relapse included the following variables (Table 2): age at EGPA diagnosis, GC-dependent asthma before EGPA diagnosis (hazard ratio [HR] 1.57, 95% CI 1.24–1.99), arthralgia (HR 1.27, 95% CI 1.01–1.61), myocarditis (HR 1.74, 95% CI 1.13–2.69), peripheral neuropathy (HR 0.52, 95% CI 0.28–0.99), MPO-ANCA positivity (HR 1.56, 95% CI 1.21–2.01), and baseline eosinophil count. The model showed good calibration, with predicted vasculitis relapse probabilities closely matching observed risks at both 5 and 12 years (Supplementary Figures 1 and 2). A nomogram was developed to estimate the risk of relapse over time (Figure 2).

GC-dependent asthma and/or ENT symptom manifestations risk prediction model. For GC-dependent asthma and/or ENT symptom manifestations, because the exact time is more difficult to define than for relapse, we are developing a risk prediction model for GC-dependent asthma and/or ENT

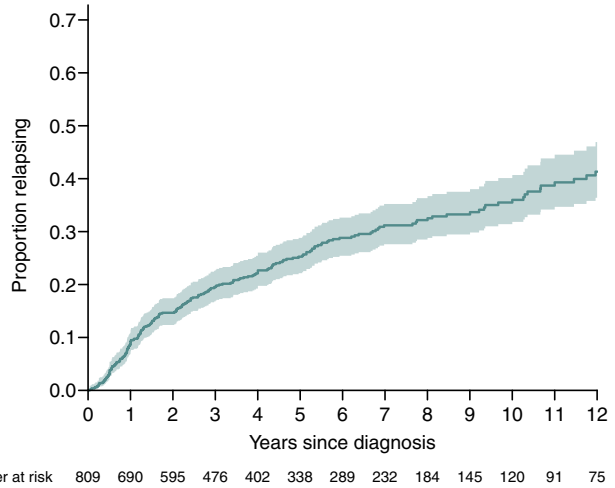

Figure 1. Cumulative incidence of vasculitis relapse over 12 years. Death without relapse (n = 31) was considered as a competing event. The shaded region represents the pointwise 95% confidence interval of the curve.

symptom manifestations at two years. After two years of follow-up, 66.4% of patients had GC-dependent asthma and/or ENT symptom manifestations. The prediction model for this outcome included the following variables (Table 3): age at EGPA diagnosis (per 10 years more; odds ratio [OR] 0.84, 95% CI 0.75–0.94), history of chronic sinusitis before EGPA diagnosis (OR 1.780, 95% CI 1.27–2.48), GC-treated asthma at diagnosis (OR 1.50, 95% CI 1.02–2.20), and baseline eosinophil count (per 1,000/mm^3; OR 0.97, 95% CI 0.93–1.00). This model was used to generate a nomogram to estimate the risk of GC-dependent asthma and/or ENT symptom manifestations at two years (Figure 3).

Correlation between vasculitis relapse and GC-dependent asthma/ENT symptom manifestations. The interaction between vasculitis relapse and GC-dependent asthma/ENT symptom manifestations was analyzed. Patients with higher GC dependency showed a trend toward reduced relapse-free survival, although the association was not statistically significant. Detailed stratified analyses are presented in Supplementary Figures 3 and 4, showing different trajectories for patients with primarily vasculitis-driven disease versus those dominated by asthma and/or ENT symptoms.

Table 2. HRs of predictors in the model for vasculitis relapse risk*

Factor	HR	95% CI
Age at diagnosis, y	–[a]	–
Eosinophil counts, per 1,000/mm^3	–[a]	–
Asthma treated by glucocorticoids	1.57	1.24–1.99
Arthralgia	1.27	1.01–1.61
Anti-MPO positivity	1.56	1.21–2.01
Peripheral neuropathy	1.39	1.09–1.78
Myocarditis	1.74	1.13–2.69
Peripheral neuropathy × myocarditis (interaction)	0.52	0.28–0.99

* HR is the measure of how often a particular event (ie, vasculitis relapse) happens in one group compared to another over time. HR = 1 indicates that relapse is the same in both groups; HR > 1 suggests an increased event rate in the group of interest (eg, group with asthma treated by glucocorticoids) compared to the reference group; HR < 1 suggests a decreased event rate in the group of interest. CI, confidence interval; HR, hazard ratio; MPO, myeloperoxidase.
[a] This is a nonlinear relationship; please see nomogram on Figure 2.

DISCUSSION

This multicenter European study includes the largest cohort of patients with EGPA reported to date and provides valuable insights into long-term disease. Consistent with previous literature,[12] our findings confirm that EGPA predominantly evolves into GC-dependent asthma and/or ENT symptom manifestations. However, we also highlight an ongoing risk of vasculitis relapse, particularly during the first two years after diagnosis but that persists many years later. This underscores the chronic and relapsing nature of the disease, which requires long-term vigilance in disease management.

The difficulty in comparing relapse rates with previous studies stems from the evolving definitions of relapse in EGPA, with recent distinctions between vasculitis-related manifestations and those associated with asthma and ENT involvement.[6,7] This distinction is becoming increasingly important in light of therapeutic advances in EGPA and other ANCA-associated vasculitides (AAVs). Current concepts suggest that EGPA encompasses two distinct clinical profiles: one characterized by eosinophilic-driven asthma and ENT symptom manifestations and another dominated by vasculitis-related organ damage. This dichotomy provides a framework for personalized therapeutic strategies.

Advances in biologics have revolutionized the treatment landscape for AAVs. B cell–targeting therapies such as rituximab are now standard of care in GPA and microscopic polyangiitis,[26] diseases with higher rates of ANCA positivity (70%–90%) compared to EGPA.[27,28] Several studies in EGPA suggest that rituximab may be effective in patients with ANCA positivity with a better relapse-free survival compared to the conventional strategy.[29–32] Similarly, anti-IL-5/IL-5R therapies such as mepolizumab and benralizumab have shown efficacy in controlling eosinophilic manifestations and reducing GC dependence,[14,15,] although data on ANCA-specific vasculitis outcomes are limited. Additionally, although rare, the presence of patients with PR3-ANCA positivity in our cohort reflects the heterogeneity of EGPA and has been previously reported. All patients fulfilled the 2022 ACR/EULAR classification criteria for EGPA, and this subgroup may represent atypical forms with prominent vasculitic or granulomatous features. Further studies are needed to better understand the clinical course and therapeutic response of this rare phenotype.

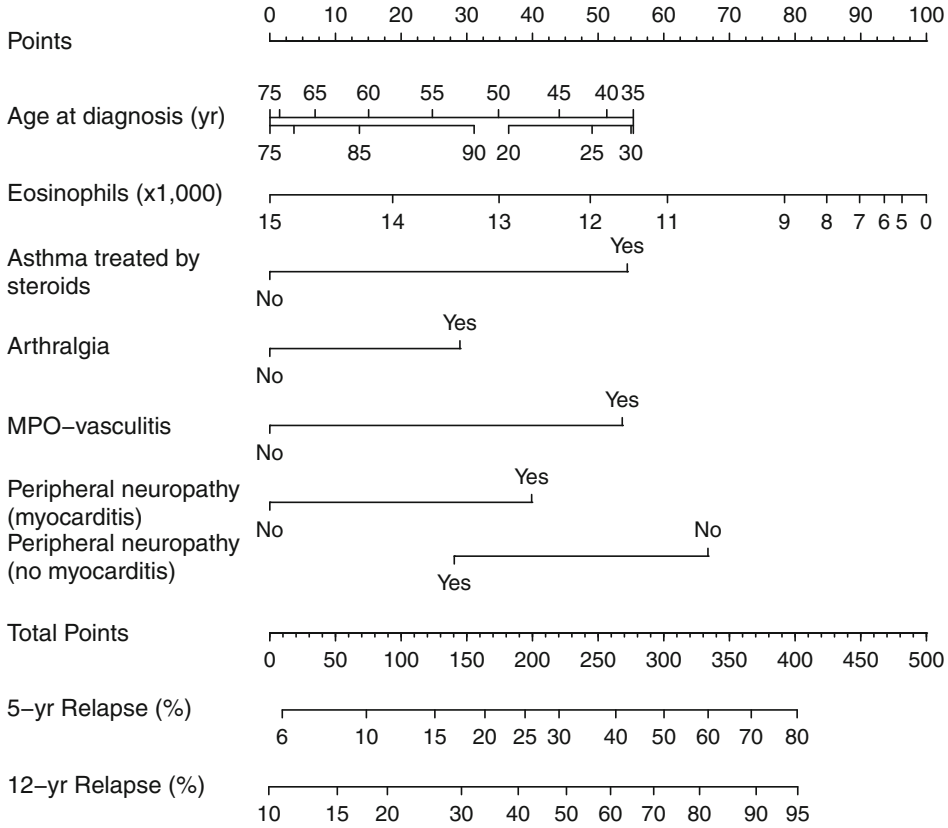

Figure 2. Nomogram for the vasculitis relapse risk at 5- and 12-yr follow-up. For example, consider a 55-yr-old male patient (25 points) presenting at baseline with an eosinophil count of 7 g/L (90 points), pre-existing asthma already treated with glucocorticoids (55 points), no arthralgia (0 points), absence of MPO-ANCA (0 points), no peripheral neuropathy, and a history of myocarditis (0 points). The total score is therefore 170 points, corresponding to an estimated vasculitis relapse risk of 21% at 5 yrs and 36% at 12 yrs. ANCA, antineutrophil cytoplasmic antibody; MPO, myeloperoxidase; yr, year.

Our study addresses a pressing clinical need by proposing two predictive models: one for vasculitis relapse risk and another for GC-dependent asthma and/or ENT symptom manifestations. These models represent a step toward personalized medicine in EGPA by identifying distinct developmental trajectories that may benefit from targeted therapeutic interventions. Early identification of patients at high risk of vasculitis relapse could guide the use of immunosuppressive therapies such as rituximab, whereas patients with a predominantly eosinophilic profile may benefit from early initiation and prolonged continuation of anti-IL-5/IL-5R therapies such as mepolizumab and benralizumab. Risk factors associated with vasculitis relapse previously identified in the literature were, at diagnosis, a lower eosinophil count, presence of anti-MPO antibodies, and presence of ENT involvement, which are supported by our results.[4,12] Both age at diagnosis and baseline eosinophil count emerged as independent predictors in our multivariable models, each contributing unique prognostic information. Although prior GC use, particularly for asthma, may influence eosinophil levels, the low doses typically used in this context are unlikely to fully suppress active vasculitis or account for the elevated eosinophil counts observed at diagnosis. The persistence of both variables in the final models, along with their nonlinear associations, especially for age, underscores the complex pathophysiology of EGPA and supports the need to consider these variables separately when stratifying patients' risk profiles.

This study has several strengths. First, the large sample size from a multicenter European cohort allows for robust statistical analyses and increases the generalizability of the findings. Second, the study provides novel insights by distinguishing among

Table 3. ORs of predictors in the model for GC-dependent asthma and/or ENT symptom manifestations risk at two years of follow-up*

Factor	OR	95% CI
Age at diagnosis, per 10 years	0.84	0.75–0.94
Eosinophil counts, per 1,000/mm^3	0.97	0.93–1.00
Asthma treated GCs	1.50	1.02–2.20
History of sinusitis	1.78	1.27–2.48

* OR quantifies how the odds of the outcome occurring (ie, asthma or ENT symptom manifestations) change with a one-unit increase in the predictor variable (eg, age at diagnosis plus one year). OR = 1 indicates no association; OR > 1 indicates higher odds of the outcome with the exposure, suggesting a risk factor; OR < 1 indicates lower odds, suggesting a protective factor. CI, confidence interval; ENT, ear, nose, and throat; GC, glucocorticoid; OR, odds ratio.

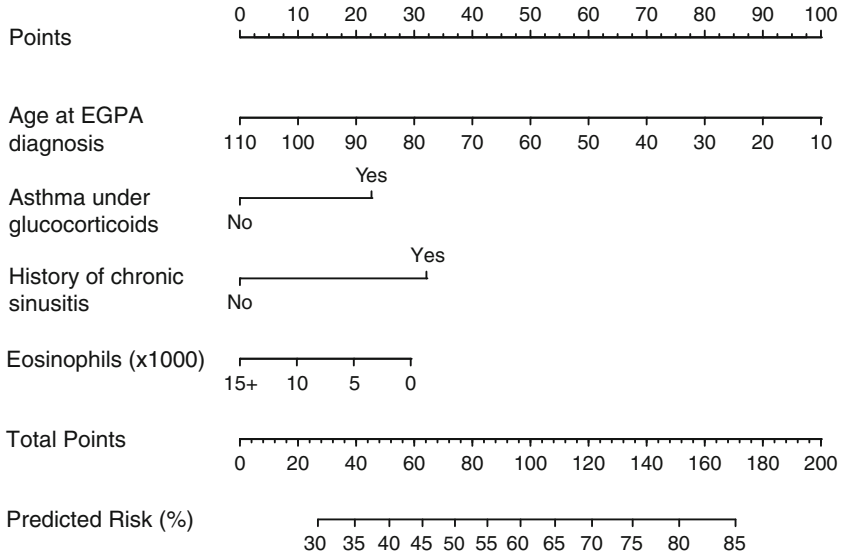

Figure 3. Nomogram for glucocorticoid-dependent asthma and/or ear, nose, and throat (ENT) symptom manifestation risk at two-year follow-up. For example, consider a 55-year-old male patient (55 points) with baseline asthma already treated with glucocorticoids (22.5 points), a history of chronic sinusitis (32.5 points), and an eosinophil count of 7 g/L (15 points). The total score is 125 points, corresponding to a predicted two-year risk of glucocorticoid-dependent asthma and/or ENT symptom manifestations of 72%. EGPA, eosinophilic granulomatosis with polyangiitis.

the risks of relapse depending on whether it is a vasculitis relapse or a relapse of GC-dependent asthma and/or ENT symptom manifestations, reflecting evolving concepts in EGPA management. However, several limitations must be acknowledged. The retrospective design inherently limits the ability to control for all confounding factors. In particular, data on treatment regimens, including specific agents, dosages, tapering schedules, and modifications over time, were inconsistently reported across centers, preventing robust adjustment for therapeutic exposure in our models. This limitation highlights the need for standardized treatment documentation in future prospective studies. Although the predictive models were rigorously developed and internally validated using bootstrap resampling, prospective external validation is needed to confirm their applicability in clinical practice. In addition, the study focused primarily on clinical and biologic variables and did not evaluate patient-reported outcomes such as quality of life or treatment satisfaction. Finally, the inclusion of patients treated over a wide time span (1995–2018) may introduce variability in treatment practices and outcome, all the more so because this period preceded the era of anti-IL5 therapies, which are likely to impact long-term outcomes. It is worth noting that the absence of anti-IL-5 therapies during the study period likely enhanced our ability to identify patients with true GC-dependent asthma and ENT involvement, a phenotype that may be less discernible in contemporary cohorts for whom eosinophilic inflammation is often masked by biologic therapy.

In conclusion, this study provides the largest evidence base to date for understanding the long-term evolution of EGPA. By identifying risk profiles for vasculitis relapse and GC-dependent asthma and/or ENT symptom manifestations, we lay the groundwork for personalized therapeutic approaches in EGPA. Future prospective validation of these models is essential, but their clinical implementation has the potential to optimize treatment strategies, reduce GC dependence, and improve patient outcomes. This work represents a significant step forward in the quest for tailored treatment of EGPA despite the limitations inherent to historical data predating the era of biologics, addressing a critical need in this rare and heterogeneous disease.

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AUTHOR CONTRIBUTIONS

All authors contributed to at least one of the following manuscript preparation roles: conceptualization AND/OR methodology, software, investigation, formal analysis, data curation, visualization, and validation AND drafting or reviewing/editing the final draft. As corresponding author, Dr Terrier confirms that all authors have provided the final approval of the version to be published, and takes responsibility for the affirmations regarding article submission (eg, not under consideration by another journal), the integrity of the data presented, and the statements regarding compliance with institutional review board/Declaration of Helsinki requirements.

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Interstitial Lung Disease in Antineutrophil Cytoplasmic Antibody–Associated Vasculitis: A European Multicenter Study

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Objective. Interstitial lung disease (ILD) can occur in association with antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis (AAV-ILD) or as an isolated entity with positive ANCA (ANCA-ILD). However, data on the epidemiology and outcomes of these conditions remain limited.

Methods. A European multicenter retrospective study encompassed patients with AAV-ILD or ANCA-ILD. Baseline and subsequent chest computed tomography studies were centrally reviewed. Primary outcomes included forced vital capacity % (FVC%) decline, respiratory failure, and mortality.

Results. Of 162 patients (myeloperoxidase [MPO]–ANCA 85%), 123 (76%) had AAV-ILD and 39 (24%) ANCA-ILD. At baseline, usual interstitial pneumonia (UIP) was the most frequent radiologic pattern (57%), whereas half had a radiologic fibrosis grade >10%. Kidney involvement was present in 73%, most commonly Berden focal class. UIP and nonspecific interstitial pneumonia (NSIP) patterns showed greater annual FVC% decline than other patterns (UIP −1.99%, NSIP −3.76% [P = 0.35], others +0.36%). An adjusted mixed-effects model indicated that rituximab was associated with mean FVC% improvement at 12 months (+6.02%; P = 0.07). Radiologic progression occurred in ∼50%, mainly in younger patients with a higher fibrosis severity grade. Respiratory failure (19%) was associated with fibrosis severity (grade 4 hazard ratio [HR] 4.7, P = 0.029) and baseline FVC% (HR 0.95, P = 0.002). Over a median 4.2-year follow-up, 48% died. Age (HR 1.08, P = 0.04) and baseline FVC% (HR 0.97, P = 0.05) were independent predictors of mortality.

Conclusion. At baseline, higher fibrosis severity, UIP, and lower FVC% were associated with worse outcomes. Immunosuppressives, such as rituximab, may help preserve lung function. The need for early identification and individualized treatment in ILD associated with AAV or ANCA is underscored.

INTRODUCTION

Antineutrophil cytoplasmic antibody (ANCA)–associated vasculitides (AAV)—including microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA), and eosinophilic GPA (EGPA)—are small-vessel necrotizing diseases marked by myeloperoxidase (MPO)/proteinase 3 (PR3)–ANCA autoantibodies and neutrophil-predominant inflammation. AAV frequently involves the lungs and kidneys, with pulmonary manifestations ranging from alveolar hemorrhage and granulomatous nodules to

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Drs Kotnik and Sadler contributed equally to this work.

interstitial lung disease (ILD).[1] ILD is particularly common in MPO-ANCA–positive patients and may occur independently of vasculitis.[2] Prevalence varies due to heterogeneity in study designs and patient cohorts.

The pathogenesis of ILD remains unclear, though hypotheses include neutrophil- and macrophage-driven inflammation in association with MPO-ANCA and release of neutrophil extracellular traps.[3,4] Genetic factors, such as the MUC5B variant (rs35705950T), suggest overlap with other fibrotic lung diseases.[5,6] ILD in AAV is associated with poor outcomes, influenced by AAV subtype and radiologic pattern, yet treatment guidance remains limited.[7,8] The immunosuppressants routinely used for remission induction in AAV, cyclophosphamide (CYC) and rituximab (RTX), have been used to slow ILD progression with mixed results.[9] Antifibrotic agents (pirfenidone, nintedanib) remain understudied in AAV, with most clinical trials excluding this population.[10] This underscores the need for targeted research and evidence-based treatment strategies.

METHODS

Patients. This multicenter retrospective study included patients from six centers across four European countries (Cambridge University Hospitals, Norfolk and Norwich University Hospitals, General Hospital of Athens Hippokration, University Hospital of Heraklion, Skåne University Hospital, Lund University, Fondazione IRCCS Policlinico San Matteo) with ILD associated with AAV (AAV-ILD) or ILD with MPO/PR3–ANCA positivity without vasculitis (ANCA-ILD). All patients had at least six months of follow-up and a baseline chest computed tomography (CT) scan. Patients with other vasculitis diagnoses, other autoimmune diseases, or alternative ILD causes were excluded. Patient inclusion was completed up to December 2023.

Ethics. The study complied with Good Clinical Practice and the Declaration of Helsinki. It was approved by Health Research Association and Health and Care Research Wales (IRAS ID: 33655, REC ref: 24/PR/1370) and sponsored by Cambridge University Hospitals. Local ethics approval was obtained at each country before data collection.

Data collection. We collected demographic and clinical data from medical records, including age at diagnosis, sex, clinical phenotype, ANCA serotype, respiratory symptoms, organ involvement, immunosuppressive treatments, and estimated glomerular filtration rate (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration 2021 formula. Treatment decisions followed standardized protocols or were determined through multidisciplinary team meetings across the participating centers. ILD diagnosis date was defined by the first pathologic chest CT scan (baseline), and total follow-up was calculated from time of AAV or ANCA-ILD diagnosis to last visit until December 2023 or death. Histopathologic features on the lung biopsy sample were included if available.

Lung function tests recorded at baseline and follow-up included forced vital capacity (FVC%), diffusing capacity for carbon monoxide corrected (DL_{CO_c}%), forced expiratory volume in 1 second (FEV_1%), and total lung capacity (TLC%). FVC% decline was assessed by absolute changes. Treatment effects were evaluated by comparing FVC% from pretreatment (±3 months) to 12 months post treatment for CYC, RTX, or mycophenolate mofetil (MMF). Changes in FVC% were categorized as follows: major progression (>10% decline), moderate progression (5%–10% decline), stable (<5% change), or improvement (≥5% increase). Respiratory failure was defined as long-term oxygen dependence of more than three months.

Chest CT studies. The majority of the chest CT studies from diagnosis and follow-up were centrally reviewed by specialist thoracic radiologists at Cambridge University Hospitals, who reached consensus on each study, independent of clinical data. Radiologists with a specialist interest in thoracic imaging classified the pattern of ILD according to established radiologic criteria for these diseases[11,12]: (1) usual interstitial pneumonia (UIP), including definite and probable; (2) nonspecific interstitial pneumonia (NSIP); (3) other patterns, including organizing pneumonia (OP), interstitial lung abnormality (ILA), and postinflammatory scarring; and (4) overlap of the previous three. The definition of ILA followed the criteria established by the Fleischner Society.[13] Fibrosis severity was graded using a five-point grade based on the percentage of total bilateral lung volume involved, modified from previously published semiquantitative visual scoring systems that derive overall fibrosis extent by averaging percentage-based assessments across defined lung areas.[14–16] The fibrosis severity was graded as follows: grade 0 (no fibrosis), grade 1 (<5%), grade 2 (5%–10%), grade 3 (10%–25%), and grade 4 (>25%). Radiologic progression was assessed by comparing the first and last CT studies for unequivocal change in the fibrosis severity grade and pattern.

Statistical analysis. Continuous variables, presented as means ± SDs for normally distributed data and as medians (interquartile ranges [IQRs]) for nonparametric distributions, were compared using the *t*-test or the Mann–Whitney test, where

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appropriate. Categorical variables, presented as n (percentage), were compared with the chi-square test. Longitudinal associations between FVC% and baseline exposures were examined using linear mixed-effects models with random intercepts and slopes. A separate mixed-effects model was used to compare pre- and posttreatment FVC%, adjusting for age, sex, and treatment naivety. Time-to-event analyses for overall and respiratory survival employed Kaplan–Meier curves and Cox proportional hazards models, with right-censoring for patients lost to follow-up or event free at the end of observation. Model selection used likelihood ratio tests and the Akaike information criterion. Radiologic progression was assessed with logistic regression. Analyses were performed in R (v4.4.2) using the lme4 package.

RESULTS

Clinical characteristics total cohort. A total of 162 patients with ILD were included in the study (Supplemental Figure S1). Of these, 123 (76%) had AAV-ILD and 39 (24%) had ANCA-ILD. The majority patients with AAV (n = 90, 61%) were classified as having MPA, followed by GPA (n = 23, 14%), and EGPA (n = 1, 1%). The median age at diagnosis was 72 years (IQR 65–79 years), and 57% (n = 93) of the patients were male. MPO-ANCA was present in 85% (n = 137), and PR3-ANCA was present in 15% (n = 25). Common symptoms at ILD diagnosis were cough and dyspnea; pulmonary hemorrhage occurred in 15%, whereas 15% were asymptomatic, with ILD detected incidentally (Table 1).

Radiologic and Histopathologic findings. On the baseline chest CT scan, UIP was the most common pattern, seen in 57 patients (56%), followed by NSIP in 17 (17%) and other patterns (OP, ILA, postinflammatory scarring) reported in 28 (27%) (Table 1, Supplemental Table S1). Fibrosis severity was assessed using a five-point grade: 8% of patients were categorized as having grade 0; 27%, grade 1; 35%, grade 2; 24%, grade 3; and 11%, grade 4. During a median follow-up of 2.8 years (IQR 1–6 years), 53% (55 of 103) showed radiologic progression, marked by increased UIP prevalence (66%) and worsening fibrosis. The fibrosis severity increased in 38% of patients, and 32% had a change in CT pattern (Figure 1, Supplemental Table S1). Notably, all patients with definite UIP at baseline maintained this pattern over time. Among those with probable UIP, 54% progressed to definite UIP, whereas 29% of NSIP cases and 27% of other baseline patterns also evolved into a UIP pattern. Lung biopsies (n = 8) showed predominantly lymphocytic inflammation, occasional macrophages, neutrophils, giant cells, and necrosis in one case. Fibrosis was the main histopathologic feature (Supplemental Table S2).

Kidney involvement in AAV-ILD. Among 123 patients with AAV-ILD, kidney involvement was the most common extrapulmonary manifestation, affecting 86 (73%) patients (Supplemental Table S3). The median age was 75 (IQR 72–79) years. At baseline, the most common radiologic pattern was UIP (49%), and the fibrosis severity was as follows: 4%, grade 0; 33%, grade 1; 31%, grade 2; 22%, grade 3; and 8%, grade 4. The median eGFR was 29 mL/min per 1.73 m^2 (IQR 13–49 mL/min per 1.73 m^2), with 25 patients (29%) having an eGFR <15 mL/min per 1.73 m^2. Albuminuria, measured as a urine albumin-to-creatinine ratio of >300 mg/g, was seen in 63% of patients, and 87% had hematuria. Kidney biopsy was performed in 64 patients; the most common Berden class was focal (47%), followed by mixed (31%), crescentic (17%), and sclerotic (5%). The median percentage of normal glomeruli in each biopsy was 50% (IQR 23–72), cellular crescents 9% (IQR 0–29), and global sclerosis 12% (IQR 2–28). The majority of the patients showed absent or mild tubulointerstitial fibrosis in the kidney biopsy (72%). Over a median follow-up period of 5 years (IQR 2–9 years), 13 progressed to end-stage kidney disease, whereas half had radiologic progression of ILD.

ANCA-ILD vs AAV-ILD. Demographics were similar between the groups (Table 1). Patients with ANCA-ILD had lower MPO and PR3 levels (P = 0.029 and P = 0.014, respectively), despite similar serotype distribution. At baseline, respiratory symptoms, particularly cough and dyspnea, were more common in ANCA-ILD (P = 0.026, P = 0.002). At baseline, FVC% was comparable, but TLC was lower in ANCA-ILD (P = 0.006). ANCA-ILD more frequently showed a UIP pattern (69% vs 51%; P = 0.019) and higher fibrosis grades (P = 0.031). Immunosuppressive treatment, particularly glucocorticoids and induction regimens, was used more commonly in AAV-ILD (P < 0.001). Mortality, respiratory failure, and radiologic progression were similar across both groups. During the follow-up period, no patient with ANCA-ILD progressed to AAV-ILD.

MPO-ANCA vs PR3-ANCA. Of the total cohort (N = 162), 137 had MPO-ANCA and 25 had PR3-ANCA. Demographics were similar between the groups (Supplemental Table S4). MPO-ANCA was associated with MPA, whereas PR3-ANCA was linked to GPA, with more ear, nose, and throat and skin involvement (P = 0.023, P = 0.008, P = 0.004). Regarding the respiratory symptoms at diagnosis, patients with PR3-ANCA were more symptomatic compared to patients with MPO-ANCA (100% vs 82%; P = 0.043). FVC% was similar, though patients with PR3-ANCA had lower FEV_1% and higher TLC% (P = 0.012, P = 0.029). UIP was more common in patients with MPO-ANCA (61% vs 40%; P = 0.006), with a trend toward greater fibrosis severity. Treatment regimens and outcomes were comparable.

Pulmonary function decline. Sequential FVC% data were available for 116 patients (72%) over a median follow-up of 4.2 years (IQR 2–8 years). Baseline FVC% did not differ between

Table 1. Clinical characteristics of the total cohort*

Characteristics	Total cohort (N = 162)	AAV-ILD (n = 123)	ANCA-ILD (n = 39)	*P* value
Demographics				
Sex, % (n)				
Female	43 (69)	41 (44)	46 (18)	0.711
Male	57 (93)	59 (72)	54 (21)	–
Age at AAV diagnosis, median (IQR), y	72 (65–79)	72 (63–79)	72 (66–78)	0.903
Smoking history[a]				
Ex-/current smoker, % (n)	57 (92)	63 (70)	56 (22)	0.567
BMI, median (IQR)[b]	29 (23–32)	28 (23–31)	31 (27–34)	0.064
Serologic phenotype, % (n)				1.00
MPO-ANCA	85 (137)	84 (104)	85 (33)	
PR3-ANCA	15 (25)	16 (19)	15 (6)	
ANCA levels at diagnosis, mean ± SD[c]				
MPO-ANCA (0.0–3.4 IU/mL)	89 ± 199	103 ± 227	49 ± 50	**0.029**
PR3-ANCA (0.0–1.9 IU/mL)	101 ± 168	134 ± 185	10 ± 5	**0.014**
Clinical phenotype, % (n)				
MPA	61 (99)	61 (99)	–	–
GPA	14 (23)	14 (23)	–	–
EGPA	1 (1)	1 (1)	–	–
Organ involvement, % (n)[d]				
Kidney	73 (86)	73 (86)	–	–
ENT	21 (25)	21 (25)	–	–
Eyes	13 (15)	13 (15)	–	–
Skin	15 (18)	15 (18)	–	–
Heart	2 (2)	2 (2)	–	–
GI	2 (2)	2 (2)	–	–
PNS	18 (21)	18 (21)	–	–
Respiratory symptoms at diagnosis, % (n)[e]				
None	15 (21)	17 (19)	7 (2)	0.368
Cough	62 (85)	57 (63)	81 (22)	**0.026**
Dyspnea	54 (75)	48 (53)	81 (22)	**0.002**
Pleuritic pain	1 (2)	2 (2)	0 (0)	1.000
Asthma	2 (3)	3 (3)	0 (0)	1.000
Diffuse alveolar hemorrhage	15 (20)	18 (20)	0 (0)	**0.013**
Lung function test at baseline, median (IQR)				
FVC%[f]	88 (71–102)	91 (74–105)	85 (66–101)	0.079
TLCOc%[g]	60 (45–74)	59 (48–73)	62 (39–77)	0.852
FEV_1%[h]	102 (95–109)	100 (94–109)	105 (101–109)	0.185
TLC%[i]	85 (68–94)	90 (75–93)	63 (56–80)	**0.006**
Radiologic pattern at baseline, % (n)[j]				**0.019**
UIP	56 (57)	51 (39)	69 (18)	
NSIP	17 (17)	14 (11)	23 (6)	
Others	27 (28)	34 (26)	8 (2)	
Fibrosis severity grade at baseline, % (n)[k]				**0.031**
0: no fibrosis	8 (8)	9 (7)	4 (1)	
1: <5% fibrosis	27 (28)	30 (24)	14 (4)	
2: 5%–10% fibrosis	35 (36)	35 (28)	31 (8)	
3: 10%–25% fibrosis	24 (24)	19 (15)	35 (9)	
4: >25% fibrosis	11 (11)	9 (7)	15 (4)	
Immunosuppressive treatment, % (n)[l]				
Induction treatment				**<0.001**
Cyclophosphamide	51 (82)	60 (70)	31 (12)	
Rituximab	16 (26)	21 (24)	5 (2)	
Rituximab + cyclophosphamide	10 (17)	14 (16)	3 (1)	
MMF	10 (16)	5 (6)	26 (10)	
GCs	86 (140)	100 (117)	59 (23)	
No treatment	9 (14)	0 (0)	36 (14)	
Maintenance treatment				
Rituximab	41 (50)	45 (50)	–	
MMF/AZA/MTX	49 (60)	55 (60)	–	
Switch treatment				**0.002**
Cyclophosphamide	3 (5)	7 (2)	38 (3)	
Rituximab	74 (28)	87 (26)	25 (2)	

(Continued)

Table 1. (*Cont'd*)

Characteristics	Total cohort (N = 162)	AAV-ILD (n = 123)	ANCA-ILD (n = 39)	*P* value
Other (MMF, AZA)	3 (5)	7 (2)	38 (3)	
Antifibrotic agent	2 (4)	3 (3)	3 (1)	1.00
Follow-up, median (IQR), y	4.2 (2–8)	4.7 (2–9)	3 (2–5)	**<0.001**
End-stage kidney disease, % (n)	9 (14)	11 (14)	0	**0.023**
Respiratory failure, % (n)	19 (31)	17 (21)	26 (10)	0.242
Mortality, % (n)	48 (78)	50 (62)	56 (22)	0.583
Radiologic progression, % (n)[m]	53 (55)	55 (42)	50 (13)	0.821

* Bold *P* values indicate <0.05. AAV, ANCA-associated vasculitis; ANCA, antineutrophil cytoplasmic antibody; AZA, azathioprine; BMI, body mass index; EGPA, eosinophilic granulomatosis with polyangiitis; ENT, ear, nose, throat; FEV_1, forced expiratory volume in 1 second; FVC%, forced vital capacity %; GCs, glucocorticoids; GI, gastrointestinal; GPA, granulomatosis with polyangiitis; ILD, interstitial lung disease; IQR, interquartile range; MMF, mycophenolate mofetil; MPA, microscopic polyangiitis; MPO, myeloperoxidase; MTX, methotrexate; NSIP, nonspecific interstitial pneumonia pattern; PNS, peripheral nervous system; PR3, proteinase 3; TLC, total lung capacity; TLCOc, carbon monoxide transfer factor corrected for hemoglobin; UIP, usual interstitial lung disease.
[a] Twelve missing values.
[b] Fifty-two missing values.
[c] Seven missing values.
[d] Five missing values.
[e] Twenty-four missing values.
[f] Forty-six missing values.
[g] Sixty-four missing values.
[h] Ninety-six missing values.
[i] One hundred twenty-five missing values.
[j] One hundred two available values.
[k] One hundred two available values.
[l] Thirteen missing values.
[m] One hundred two available values.

the radiologic patterns (Table 1, Figure 2). Changes in FVC% from baseline over time for the three radiologic categories (UIP, NSIP, other patterns) are shown in Figure 2.

Annual FVC% changes by radiologic pattern were as follows: UIP, −1.99% (95% confidence interval [CI] −2.9 to −1.0, $P < 0.001$); NSIP, −3.76% (95% CI −6.1 to −1.4, $P = 0.002$); other, +0.36% (95% CI −1.0 to 1.7, $P = 0.62$). Both UIP and NSIP showed greater FVC% decline compared to other patterns (UIP −2.35%, $P = 0.02$; NSIP −4.12%, $P = 0.01$), with no difference between UIP and NSIP ($P = 0.35$).

Within group comparisons assessed whether radiologic pattern was associated with FVC% decline over time. In the UIP pattern, we observed declines from baseline at year 4 (adjusted difference −8.34%, 95% CI −14 to −3, $P = 0.01$) and year 5 (adjusted difference −9.18%, 95% CI −15 to −3, $P = 0.02$). In contrast, no within-group FVC% changes were observed in the NSIP or other patterns groups.

Between-group comparisons evaluated whether the FVC% decline differed between radiologic subtypes. Compared to patients with other patterns, those with UIP demonstrated greater FVC% decline as early as year 1 (adjusted difference −16.6%, 95% CI −28 to −6, $P = 0.009$), which persisted through year 5 (adjusted difference −22.8%, 95% CI −37 to −9, $P = 0.005$). Similarly, NSIP was associated with a greater decline than other patterns by year 5 (adjusted difference −32.1%, 95% CI −56 to −8, $P = 0.02$).

Radiologic progression. Radiologic progression was observed in 53% of the cohort (55 of 103) (Supplemental Table S5). Patients with radiologic progression were younger ($P = 0.014$). Radiologic progressors tended to present more often with a UIP pattern (64% vs 48%; $P = 0.069$) and were less likely to have the lowest fibrosis severity grade at baseline (29% vs 40%; $P = 0.004$). Although radiologic progressors and nonprogressors had similar overall FVC% decline by year 5 (−8.88% vs −8.97%; $P = 0.931$), progressors presented a more consistent and sustained trajectory of functional deterioration (Supplemental Figure S2).

Immunosuppressive treatment. In the total cohort, 96% of the patients received immunosuppressive treatment. In the ANCA-ILD group, 59% received glucocorticoids, 31% received CYC, 5% received RTX, 3% received combination therapy (CYC + RTX), 26% received other agents (MMF, azathioprine, methotrexate, leflunomide), and 38% received no immunosuppression. All patients with AAV-ILD received glucocorticoids; 60% received CYC, 21% received RTX, 14% received combination therapy (CYC + RTX), and 5% received MMF as induction therapy, with RTX (46%) and MMF/azathioprine (54%) for maintenance (Table 1).

Using an adjusted mixed-effects model, mean FVC% change at 12 months post induction was as follows: CYC, −1.39% (95% CI −4.18 to 1.41, $P = 0.33$); RTX, +6.02% (95% CI −0.44 to 12.48, $P = 0.07$); combination therapy (CYC + RTX), +0.35% (95% CI −8.79 to 9.49, $P = 0.94$); and MMF, −3.57% (95% CI −16.49 to 9.35, $P = 0.59$) (Figure 3). Baseline lung function and CT patterns were similar across treatment groups (Supplemental Table S6). In the total cohort, RTX showed the

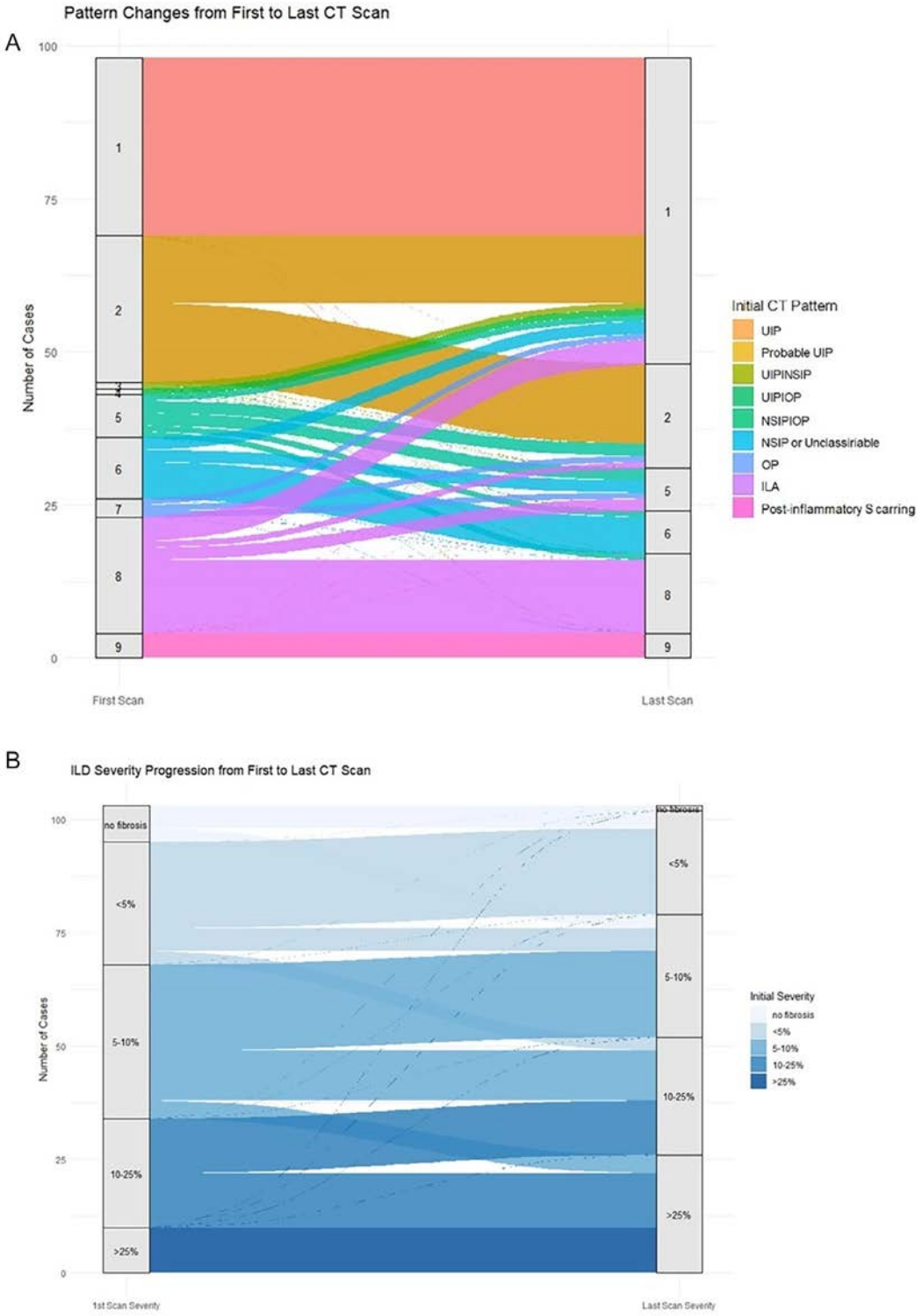

Figure 1. (A) Sankey diagram illustrating CT pattern changes between the first and last chest CT study. The y-axis represents the number of cases, whereas the x-axis tracks the transition from the first to the last CT study. The width of each bar is proportional to the number of patients with each pattern transition. Bar 1, UIP; bar 2, probable UIP; bar 3 UIP/NSIP; bar 4, UIP/OP; bar 5, NSIP/OP; bar 6, NSIP or unclassifiable; bar 7, OP; bar 8, ILA; bar 9, postinflammatory scarring. 32% of the study population had a change in radiologic pattern. (B) Sankey diagram illustrating fibrosis percent changes from the first to the last chest CT study. The y-axis represents the number of cases, whereas the x-axis tracks the transition from the first to the last CT study. The width of each bar is proportional to the number of patients with each severity grade transition. 38% of the patients progressed to a higher fibrosis severity grade. CT, computed tomography; ILA, interstitial lung abnormality; NSIP, nonspecific interstitial pneumonia; OP, organized pneumonia; UIP, usual interstitial pneumonia.

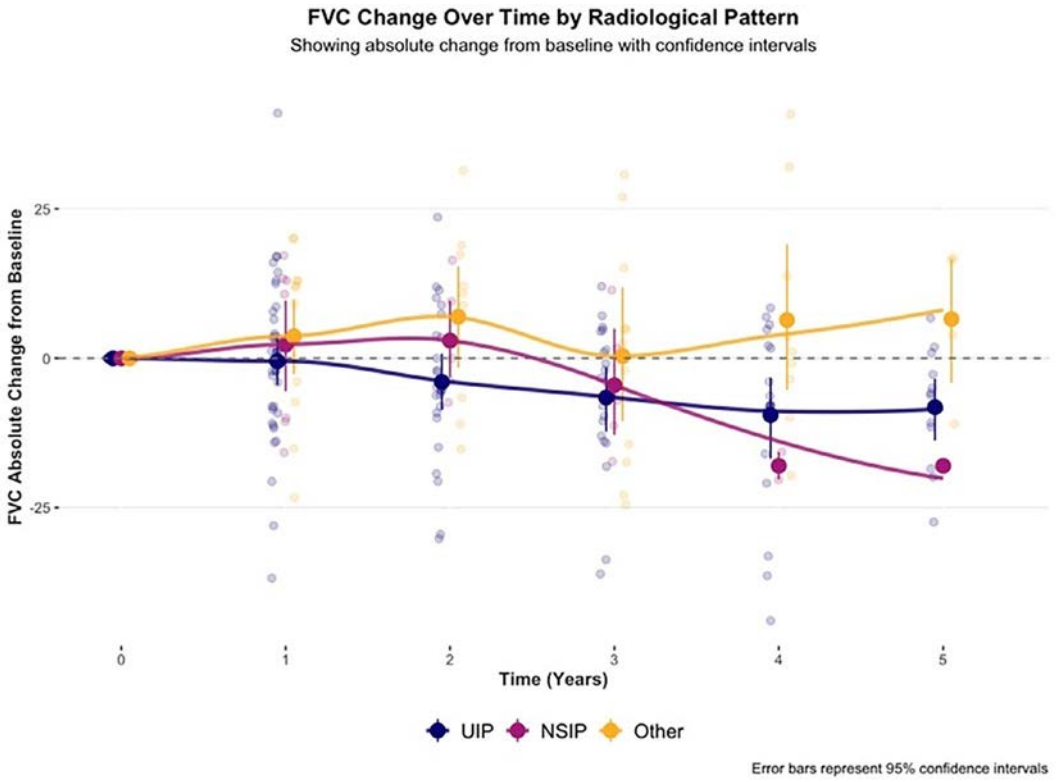

Figure 2. FVC% absolute change from baseline value over time, stratified by radiologic pattern. Longitudinal analysis of absolute FVC% change over a five-year period. Points represent marginal mean values, as estimated by a mixed-effects model, at each time point, and vertical bars represent 95% confidence intervals. Individual patient data are shown as background dots. The UIP and NSIP groups exhibited a declining trend, whereas other patterns demonstrated relatively stable or improved FVC% values over time. FVC%, forced vital capacity %; NSIP, nonspecific interstitial pneumonia; UIP, usual interstitial pneumonia.

greatest annual FVC% gain: +3.07% per year (95% CI 0.67–5.47) (Supplemental Table S7). Notably, in the subgroup analysis of patients with a UIP pattern (n = 51), those who received RTX (n = 17) showed a greater increase in FVC% (+13.8; P = 0.013) (Supplemental Figure S3). Among patients with NSIP (n = 12) or other patterns (n = 17), RTX appeared to help stabilize lung function, though without significant differences (Supplemental Figure S4). In additional subgroup analysis, RTX also showed a consistent trend toward improved annual FVC% in both ANCA-ILD (n = 20) and AAV-ILD (n = 71) (Supplemental Figure S4).

Antifibrotic treatment. Four patients (3%; three men, one woman) received antifibrotics (one received pirfenidone, three received nintedanib). All were MPO-ANCA positive: three with AAV-ILD and one with ANCA-ILD. AAV-ILD cases showed renal involvement (eGFR 41 mL/min/1.73 m^2), diffuse alveolar hemorrhage, cutaneous, or peripheral nervous system manifestations. All received CYC plus glucocorticoids. Baseline CT showed UIP in 75% of patients (fibrosis severity grade 4 in 75%, grade 3 in 25%); one had NSIP/OP. The median FVC% was 72 (range 44–72). At one year, half declined 5% to 10% in FVC% and half were stable. Over 2.3 years (range 2–5 years), two died and two developed respiratory failure.

Clinical outcomes and poor risk factors. *FVC% and radiologic progression.* After one year of treatment, FVC% progression was observed as followed: major progression (FVC% decline >10%) in 21% of patients (18 of 85), moderate progression (FVC% decline 5%–10%) in 8% of patients (7 of 85), stable or minimal improvement (<5% change in FVC%) in 38% of patients (32 of 85), and improvement (FVC% increase >5%) in 33% of patients (28 of 85). Logistic regression identified kidney involvement as the only predictor of major FVC% decline, with an odds ratio (OR) of 3.08 (95% CI 1.03–10.1) (Supplemental Table S8).

Fifty-three percent of the cohort (55 of 103) showed radiologic progression. Younger age (OR 0.94, 95% CI 0.89–0.98, P = 0.015) and greater baseline fibrosis severity (grade 4: OR 0.04, 95% CI 0.00–0.35, P = 0.012) were associated with a higher likelihood of progression (Supplemental Table S9).

Respiratory failure. Over a median follow-up of 4.2 years (IQR 2–8 years), 31 patients (19%) developed respiratory failure, defined as long-term oxygen dependence. Median respiratory failure–free survival time was 18.2 years (95% CI 11.6–20), with 5- and 10-year survival rates of 82.1% and 74.3%, respectively. Respiratory failure occurred earlier in the ANCA-ILD group compared to the AAV-ILD group (log-rank P = 0.003; Figure 4A).

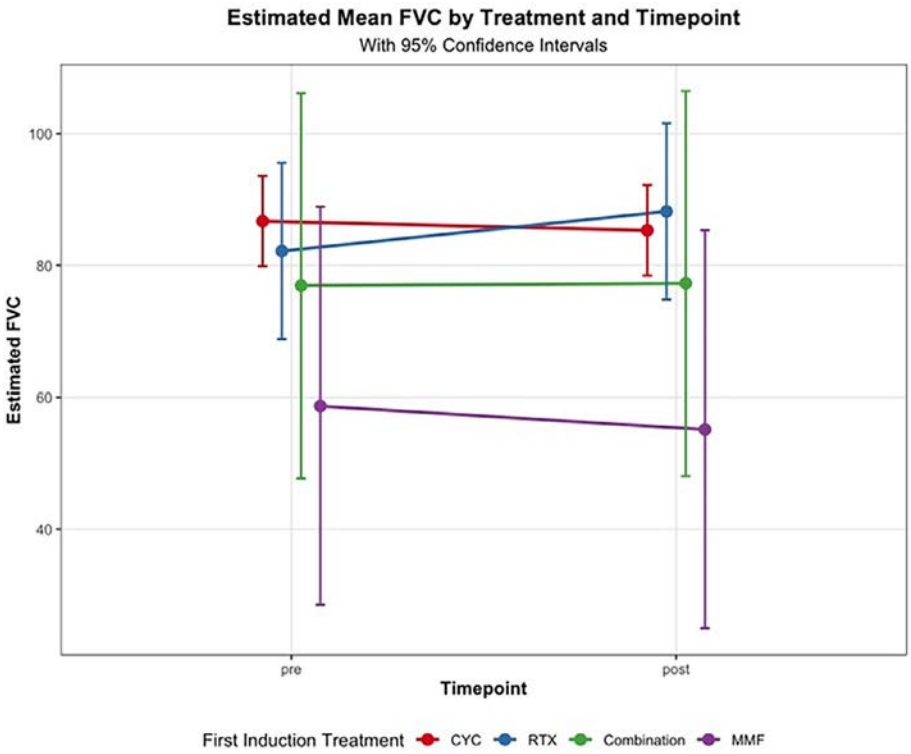

Figure 3. Estimated mean FVC% changes before and 12 months after treatment initiation. Dots represent the marginal mean values, as estimated by a mixed-effects model adjusted for age, sex, and treatment naivety, with vertical lines representing 95% confidence intervals, for patients who received different therapies. combination, CYC + RTX; CYC, cyclophosphamide; FVC%, forced vital capacity %; MMF, mycophenolate mofetil; RTX, rituximab.

Although radiologic patterns showed no differences, higher baseline fibrosis grades were associated with worse respiratory outcomes ($P < 0.001$; Figure 4B, Supplemental Table S10). In univariate analysis, predictors included fibrosis severity, ILD subtype, induction or antifibrotic treatment, and baseline FVC% and TLC (Supplemental Table S11). Multivariable analysis identified two independent risk factors: baseline FVC% (hazard ratio [HR] 0.95, 95% CI 0.92–0.98, $P = 0.002$) and grade 4 fibrosis (HR 4.7, 95% CI 1.17–19.1, $P = 0.029$; Table 2).

Mortality. Over a median follow-up of 4.2 years (IQR 2–8 years), 48% (n = 78) of patients died. Median survival was 8.1 years (95% CI 5.8–11.9), with 5- and 10-year survival rates of 61.9% and 40.6% respectively. Survival did not differ between the AAV-ILD and ANCA-ILD groups (log-rank $P = 0.13$; Figure 4A). The UIP pattern was associated with worse survival than NSIP or other patterns ($P = 0.022$; Figure 4C), and higher baseline fibrosis grades predicted poorer outcomes ($P = 0.001$; Figure 4B). A fibrosis grade 4 was associated with a nearly six-fold increase in mortality risk (HR 5.8, 95% CI 2.1–15.7, Supplemental Table S10). Lung disease progression—due to infection or ILD exacerbation—was the leading cause of death. Other infections were rare; two deaths were attributed to lung cancer (Supplemental Table S12). Univariate Cox analysis identified several mortality predictors: age, respiratory failure, radiologic pattern, induction treatment, ANCA levels, and baseline FVC%, DL_{CO_C}%, and TLC (Supplemental Table S11). On multivariate analysis, age at diagnosis (HR 1.08, 95% CI 1.03–1.14, $P = 0.004$) and baseline FVC% (HR 0.97, 95% CI 0.95–0.99, $P = 0.005$) were independent predictors of mortality (Table 2).

DISCUSSION

In this European multicenter cohort of patients with AAV-ILD and ANCA-ILD, we identified meaningful clinical, radiologic, and prognostic features that help define this underrecognized disease spectrum. The majority of patients were MPO-ANCA positive and presented with a UIP pattern. Rates of radiologic progression and functional decline were substantial, especially in patients with UIP and in those with severe fibrosis. Baseline pulmonary function, particularly FVC%, and the severity of radiologic fibrosis emerged as independent predictors of both mortality, which was high, with lung disease progression as a leading cause of death, and respiratory failure. Although immunosuppressive treatments were widely used, RTX showed a trend toward improved lung function. Importantly, kidney involvement was common but did not impact overall survival, highlighting respiratory decline as the primary driver of mortality in this population. Given the limited data from previous retrospective studies and the absence of standardized treatment approaches, our study offers real-world insights that may inform clinical practice and future research directions.

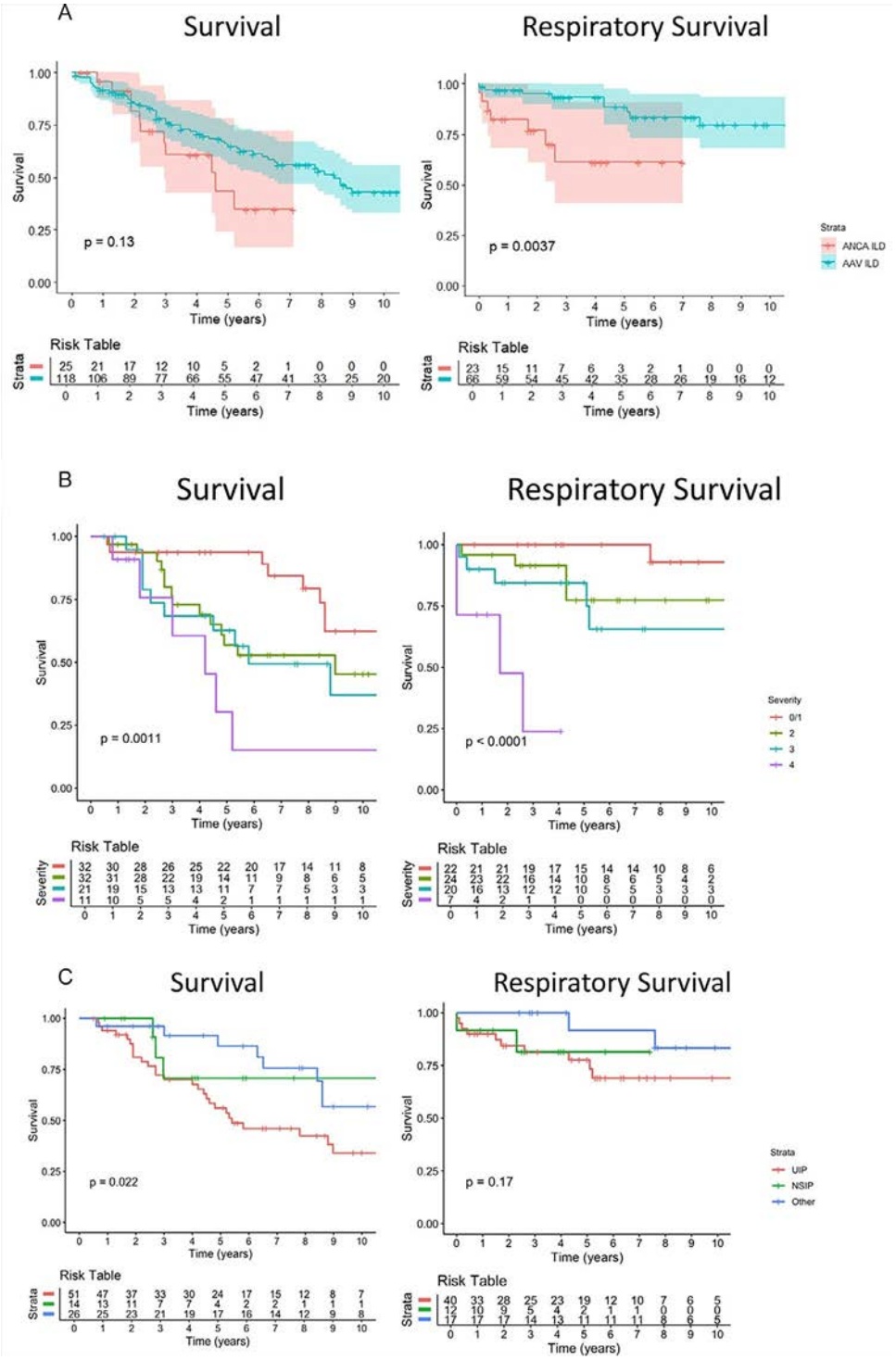

Figure 4. Overall and respiratory survival analyses. (A) Kaplan–Meier survival curves comparing the overall (left) and respiratory (right) survival of patients with ANCA-ILD (red) and AAV-ILD (blue). Shade areas represent estimated 95% confidence intervals. *P* values represent the respective log-rank test. Overall survival did not differ between the two groups; patients with ANCA-ILD demonstrated worse respiratory survival ($P < 0.01$). (B) Kaplan–Meier survival curves comparing overall (left) and respiratory (right) survival across different fibrosis severity groups. *P* values represent the respective log-rank test. Fibrosis severity was associated with lower overall ($P < 0.01$) and respiratory ($P < 0.0001$) survival, with a grade of 4 exhibiting the worse outcomes. (C) Kaplan–Meier survival curves comparing overall (left) and respiratory (right) survival of patients with UIP (red), NSIP (green), or other (blue) radiologic ILD patterns. *P* values represent the respective log-rank test. Overall survival was lower in the UIP group ($P < 0.05$). Respiratory survival did not differ ($P = 0.17$). AAV, ANCA-associated vasculitis; ANCA, antineutrophil cytoplasmic antibody; ILD, interstitial lung disease; NSIP, nonspecific interstitial pneumonia; UIP, usual interstitial pneumonia.

Table 2. Multivariable Cox regression analysis of factors associated with overall survival and respiratory survival*

Variables	Survival			Respiratory survival		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Age at AAV diagnosis	1.08	1.03 to 1.14	**0.004**	1.02	0.96 to 1.09	0.43
Sex						
Male (ref)	–	–	–	–	–	–
Female	0.64	0.28 to 1.46	0.29	1.49	0.45 to 5.00	0.51
ANCA type						
MPO (ref)	–	–	–	–	–	–
PR3	1.78	0.49 to 6.54	0.38	0.00	0.00 to inf	>0.99
ILD group						
ANCA-ILD (ref)	–	–	–	–	–	–
AAV-ILD	0.43	0.15 to 1.26	0.12	0.53	0.15 to 1.82	0.31
Radiologic pattern						
UIP (ref)	–	–	–	–	–	–
NSIP	0.54	0.12 to 2.47	0.43	–	–	–
Others	0.47	0.07 to 3.30	0.45	–	–	–
Fibrosis severity grade						
1 (ref)	–	–	–	–	–	–
2	1.91	0.32 to 11.4	0.48	1.69	0.45 to 6.34	0.44
3	2.13	0.29 to 15.5	0.46	2.43	0.78 to 7.59	0.13
4	3.48	0.42 to 29	0.25	4.72	1.17 to 19.1	**0.029**
FVC% predicted baseline	0.97	0.95 to 0.99	**0.005**	0.95	0.92 to 0.98	**0.002**
Kidney involvement (no ref)	1.08	0.44 to 2.67	0.87	1.04	0.30 to 3.64	0.95

* Bold *P* values indicate <0.05. AAV, ANCA-associated vasculitis; ANCA, antineutrophil cytoplasmic antibody; CI, confidence interval; FVC%, forced vital capacity %; HR, hazard radio; ILD, interstitial lung disease; MPO, myeloperoxidase; NSIP, nonspecific interstitial pneumonia pattern; PR3, proteinase 3; UIP, usual interstitial pneumonia.

In our cohort, the majority (85%) of patients were MPO-ANCA positive, consistent with prior studies—particularly from Asia—highlighting the strong association between MPO-ANCA, MPA, and pulmonary fibrosis.[17,18] Although the underlying mechanisms are unclear, MPO-ANCA might contribute to alveolar injury and fibrosis via neutrophil or macrophage activation and oxidative stress. Furthermore, the distinct clinical phenotypes have been reported between ANCA-positive and ANCA-negative vasculitis, in which the latter typically presents with more renal-limited disease and less pulmonary involvement, suggesting a potential pathogenic role of ANCA antibodies in alveolar injury.[19] In our cohort, the UIP pattern was more common with MPO-ANCA than PR3-ANCA, with a trend toward greater fibrosis severity. Although FVC% was comparable between groups, PR3-ANCA showed lower FEV_1% and higher TLC%, consistent with a previous report.[20] Lung histopathologic studies in AAV-ILD are limited[20,21]; however, our findings support fibrosis as the dominant pathologic process. Histopathologic studies in both AAV-ILD and ANCA-ILD are warranted to better elucidate disease mechanisms and identify potential therapeutic targets.

Recurrent or subclinical lung injury may initiate a sustained proinflammatory response, contributing to both pulmonary fibrosis and vasculitis.[22,23] We identified UIP as the predominant radiologic pattern (57%), consistent with previous AAV-ILD reports.[7,18] Notably, over half of the patients had a radiologic fibrosis grade exceeding 10% at baseline—this being, to our knowledge, the first study to quantify radiologic fibrosis burden in AAV-ILD using a standardized scoring system. Both ANCA-ILD and AAV-ILD showed similar baseline pulmonary function, though fibrosis was more severe in ANCA-ILD, likely reflecting earlier ILD onset, consistent with previous report.[24] Despite these differences, long-term outcomes were comparable, supporting the rationale for a unified therapeutic strategy. Although up to 25% of patients with ANCA-ILD have been reported to progress to MPA,[24,25] no such progression was observed in our cohort. Conversely, 19% of patients with AAV-ILD had a history of ILD, in which the absence of earlier ANCA testing may represent a diagnostic pitfall. Nevertheless, the clinical utility and cost-effectiveness of routine ANCA testing in patients with suspected idiopathic pulmonary fibrosis remain uncertain and warrant further investigation.

Kidney involvement in AAV-ILD is well recognized, though data on its histopathologic features and long-term outcomes remain limited.[17] In our cohort, kidney involvement was common (73%) predominantly in patients with MPO-ANCA positivity and a concurrent UIP pattern. Kidney biopsies typically revealed pauci-immune glomerulonephritis, most often within the focal and mixed classes of the Berden classification, corresponding to a low risk of progression according to ANCA Kidney Risk Score criteria.[26] Although MPO-ANCA is strongly linked to glomerulonephritis and renal fibrosis,[27] we did not observe an association between ILD and kidney fibrosis. One plausible explanation is the earlier clinical recognition and treatment of renal disease due to more overt symptoms, whereas ILD can progress subclinically until advanced fibrosis occurs. Despite a generally favorable renal prognosis in our cohort, over half of the patients experienced radiologic progression of ILD, and overall mortality remained high. These findings suggest that respiratory complications are a

stronger predictor of mortality than renal involvement and progress independently of kidney disease and that the treatment responses of ILD and kidney vasculitis are quite different.

At baseline, the median FVC% was modestly reduced, with no differences across radiologic subtypes, consistent with a prior report.[18] Despite similar initial lung function, FVC% trajectories diverged over time; patients with a UIP pattern experienced the most pronounced and rapid decline, followed by those with NSIP, underscoring the prognostic value of radiologic subtype. A major FVC% decline (>10%) at one year was observed in 21% of patients—an established marker of poor prognosis in idiopathic pulmonary fibrosis[28]—slightly lower than previously reported in AAV-ILD.[29] Approximately half of the cohort remained stable radiologically and functionally, whereas the remainder—predominantly younger patients and greater baseline fibrosis severity—progressed. Although a higher progression rate (87.5%) has been reported, that finding was based on a small sample.[9] In our study, all patients with baseline UIP maintained this pattern, whereas approximately 30% of those initially diagnosed with NSIP or other patterns demonstrated progression to a UIP pattern, highlighting the dynamic and evolving nature of radiologic manifestations in ANCA-ILD. These findings highlight the urgent need for reliable biomarkers and clinical predictors of progression, as both radiologic pattern and fibrosis extent appear to offer practical prognostic value in guiding management and risk stratification in ANCA-ILD.

Most patients in our cohort received immunosuppressive therapy, primarily glucocorticoids combined with CYC or RTX. Although effective for inducing remission in vasculitis, the impact of these agents on ILD progression remains unclear.[30,31] RTX was associated with a trend toward improved FVC% at one year compared to CYC (alone or combined) or MMF, consistent with limited prior findings in AAV.[9] Although the sample size limited the power of subgroup analyses, the apparent benefit of RTX was consistent across both ANCA-ILD and AAV-ILD subgroups and appeared most pronounced in patients with a UIP pattern. Similarly, in other connective tissue disease–associated ILDs (CTD-ILDs), such as rheumatoid arthritis and scleroderma-related ILD, RTX has been shown to stabilize or even improve lung function across both UIP and non-UIP patterns, suggesting that the disease course and underlying pathogenesis in CTD-ILDs differ from those in idiopathic ILD.[32] However, the apparent benefit observed with RTX in our cohort may be influenced by treatment selection bias, with CYC preferentially used in more severe systemic disease. Whether the benefit of RTX persists with continued therapy, or whether specific antifibrotic treatment is required, remains unknown. Similarly, the effect of the complement C5a receptor inhibitor, avacopan, on ILD has not been studied; none of the patients in our cohort received avacopan, as it was not available during the study period. Mortality and respiratory failure remained high, particularly in patients with extensive baseline fibrosis, underscoring the limited impact of current treatments.[17] Antifibrotics (nintedanib or pirfenidone) were used in only 3% of cases, reflecting their exclusion from major trials and the absence of clear guidance in AAV-ILD. These findings highlight the urgent need for prospective studies evaluating antifibrotics, alone or with immunosuppression, in this population.

Survival in our cohort was poor, with a 5-year survival rate of 62% and median survival of 8.1 years, highlighting the severe prognosis associated with ILD. Our findings align with previously published cohort studies focusing specifically on AAV-ILD.[33,34] Respiratory progression emerged as the leading cause of death, emphasizing the need for early identification and aggressive management of lung disease. Baseline FVC%, UIP pattern, and fibrosis severity were independent predictors of mortality and respiratory failure, reinforcing the prognostic importance of early and accurate radiologic and functional assessment. Notably, no survival differences were observed between patients with AAV-ILD and those with ANCA-ILD, suggesting that fibrotic burden and radiologic pattern may carry greater prognostic weight than the presence of systemic vasculitis.

This study has several limitations. The retrospective, observational design introduces risks of selection bias, incomplete data, and variable follow-up. Heterogeneity in imaging protocols and pulmonary function testing across centers may have influenced radiologic and functional assessments, and treatment was nonrandomized, reflecting real-world clinical practice. Limited use of antifibrotic agents restricts conclusions on their efficacy, and the inclusion of patients from specialized ILD referral centers may limit generalizability. Nevertheless, this represents one of the largest European cohorts of patients with AAV-ILD and ANCA-ILD, with centralized CT re-evaluation enhancing diagnostic consistency and standardized fibrosis scoring. Longitudinal assessment of radiologic progression, alongside epidemiologic and functional data, provides novel insights into disease natural history and prognostic factors, highlighting the need for prospective trials in this underrecognized population.

ILD is an increasingly recognized manifestation of AAV, frequently presenting with a UIP pattern and substantial fibrotic burden. These features were associated with radiologic progression, functional decline, and increased mortality. Notably, baseline pulmonary function and the extent of radiologic fibrosis emerged as independent predictors of adverse outcomes, whereas renal involvement—despite being prevalent—did not impact overall survival. Immunosuppressive therapy demonstrated limited efficacy in halting respiratory progression, particularly RTX, and the use of antifibrotic agents was minimal, underscoring existing uncertainties regarding their role. These findings highlight the urgent need for early diagnosis, standardized radiologic evaluation, and a multidisciplinary strategy to optimize care and improve prognosis in this underrecognized, high-risk patient population. Future advances will rely on the integration of clinical, molecular, and imaging data to elucidate disease mechanisms and guide precision therapies in AAV-ILD. Prospective multicenter studies

exploring B cell–targeted and complement-targeted treatments, in combination with antifibrotic, are essential to translate these insights into improved patient care.

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AUTHOR CONTRIBUTIONS

All authors contributed to at least one of the following manuscript preparation roles: conceptualization AND/OR methodology, software, investigation, formal analysis, data curation, visualization, and validation AND drafting or reviewing/editing the final draft. As corresponding author, Dr Jayne confirms that all authors have provided the final approval of the version to be published and takes responsibility for the affirmations regarding article submission (eg, not under consideration by another journal), the integrity of the data presented, and the statements regarding compliance with institutional review board/Declaration of Helsinki requirements.

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Prescribing of Medication to Prevent Glucocorticoid Harms in Patients With Polymyalgia Rheumatica: A Cross-Sectional Study and Two Emulated Target Trials in the Clinical Practice Research Datalink Aurum

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Objective. Polymyalgia rheumatica (PMR) is a common indication for long-term glucocorticoid (GC) treatment. Bone-protective and gastroprotective medications are recommended for those at high risk of adverse events from GCs, but no trials have evaluated their effectiveness in PMR. We describe bone-protective and gastroprotective medicine prescribing in people with PMR and evaluate its impact on adverse GC outcomes using a target trial approach.

Methods. A sample of >40,000 individuals aged ≥50 years with a coded PMR diagnosis from January 2010 to March 2022 who were prescribed GCs within 21 days of the first PMR diagnosis code was constructed in the Clinical Practice Research Datalink Aurum. Prescriptions were defined as prevalent (pre-PMR diagnosis), incident (at diagnosis), or late (post diagnosis, still GC-treated), reported stratified by age, sex, and deprivation. A target trial approach assessed the effects of (1) bisphosphonates on fragility fractures and (2) proton-pump inhibitors/H_2 receptor antagonists (PPIs/H_2RAs) on gastrointestinal (GI) ulceration/bleeding. Treatment effect, adjusted for confounders, was modeled using targeted maximum likelihood estimation.

Results. 67.2% participants were coprescribed bisphosphonates and 78.6% were coprescribed PPIs/H_2RAs. Male patients and those in more deprived areas were less likely to receive bisphosphonates. 1.40% (95% confidence interval [CI] 1.10%–1.70%) of those prescribed bisphosphonates for 12 months versus 2.32% (95% CI 2.12%–2.52%) of those not prescribed bisphosphonates for 12 months experienced a fracture (risk difference 0.92% points [95% CI 0.56%–1.27%], number needed to treat 109). Prescribing gastroprotective medications was not associated with serious GI events.

Conclusion. Rates of prescribing to mitigate GC harms are higher than previously reported. Bisphosphonates are associated with approximately one less fragility fracture per year for every 100 people treated. Gastro-prophylaxis is not associated with reduced risk of GI ulceration/bleeding, suggesting potential to reduce prescribing for this indication.

INTRODUCTION

Polymyalgia rheumatica (PMR) is a common inflammatory musculoskeletal condition causing pain, stiffness, and disability in older adults.[1] Core treatment is with glucocorticoids (GCs) started in a moderately high dose and tapered down. Recent UK data[2] have shown that the median time to cessation of continuous GC treatment is 1.93 years but that 25% of patients receive more than 4 years of GC therapy. GCs have a known toxicity profile,[3] particularly in older adults, who are more likely to

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Data may be obtained from a third party and are not publicly available. The data were obtained from the Clinical Practice Research Datalink (CPRD). CPRD data governance does not allow us to distribute patient data to other parties. Researchers may apply for data access at http://www.CPRD.com/.

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experience multimorbidity and polypharmacy. Mitigating the harmful effects of GC treatment is a major challenge in managing PMR. Two potentially serious adverse outcomes associated with GC use are fragility fractures and gastrointestinal (GI) adverse effects (esophagitis, gastritis, GI ulceration, and bleeding).

PMR management guidelines[4] recommend prophylactic calcium and vitamin D supplements for all patients commencing GC treatment and bisphosphonates for those at high fracture risk (aged >65 years, prior fragility fracture, requiring higher initial GC dose). Consideration of prophylactic proton-pump inhibitors (PPIs) is advised for people at high risk of GI bleeding and dyspepsia (older adults, a history of GI ulceration/bleeding, taking nonsteroidal anti-inflammatory drugs [NSAIDs] or anticoagulants). Given that PMR affects older adults, many people with the condition will meet the criteria for consideration of bone and GI prophylaxis. However, prophylactic medications are not without their own risks and treatment burden. Oral bisphosphonates can cause upper GI side effects, including nausea and reflux symptoms, and are associated with the rare but significant adverse effects of osteonecrosis of the jaw and atypical femoral fractures.[5] Long-term use of PPIs is associated with adverse effects, including diarrhea, increased risk of respiratory infections, increased risk of fractures, and impaired absorption of nutrients.[6]

Previous studies have shown that rates of prescribing prophylaxis are low,[7,8] and it is unclear what proportion of those at highest risk from GCs receive prophylactic medications. Furthermore, there is no trial evidence of the risk reduction gained from taking bisphosphonates or gastroprotective medications in people with PMR. Because PMR affects older adults, who are more likely to have multimorbidity and therefore are more likely to be particularly prone to the risks of GC harms, it is crucial to ensure that care adheres to best practice recommendations. However, it is also vital to ensure that these recommendations are evidence based, with the lack of trial evidence in this population representing an important evidence gap. Placebo-controlled trials of such prophylaxis would be prohibitively complex, expensive, and ethically questionable, but emulated trials using observational data offer an opportunity to address this question.

In this article, we aim to describe current practice and variation in prescribing prophylactic medication in people treated with GCs for PMR in English primary care and evaluate the potential modification of risk associated with prescribing (1) bisphosphonates on fragility fractures and (2) gastroprotection on serious GI adverse events.

PATIENTS AND METHODS

Study design. We conducted a cross-sectional study followed by two emulated target trials in the Clinical Practice Research Datalink (CPRD) Aurum, linked to Hospital Episode Statistics Admitted Patient Care (HES APC) data, to optimize outcome ascertainment, and individual-level index of multiple deprivation (IMD) score. Study protocols are provided in the Supplementary Materials. CPRD Aurum contains anonymized, routinely collected data from >1,400 English general practices. It is representative of the English population by geographic spread, deprivation, age, and sex.[9] Read/Systematized Nomenclature of Medicine Clinical Terms (SNOMED CT) codes are used to record diagnoses. Further details about CPRD are available in the Supplementary Data. Code lists for this study were based on existing freely available lists[10–12] and modified through a consensus process. For code lists used, see https://researchdata.keele.ac.uk/117/.

Patient and public involvement. Ongoing work with members of the patient support charity PMRGCAuk has emphasized patient concerns about side effects of GCs and burden of multiple medications. Two meetings were held with people with PMR. The first shaped the synthesis of the descriptive work and informed the focus of the target trials; the second explored patient perspectives of the findings and refined our key messages. Participants were surprised by the small absolute risk reduction for fragility fracture conferred by bisphosphonates.

Cross-sectional study. *Study population.* Data were extracted from the CPRD Aurum May 2022 build.[13,14] Individuals (≥50 years) were included if they had a clinical code for PMR between January 1, 2010, and March 31, 2022, and had been registered with the practice for more than one year. Individuals were then excluded if they had a record of giant cell arteritis (GCA) diagnosed before their PMR or an end-of-life care code at any time.

To increase confidence in the diagnosis of PMR, individuals were required to have had a prescription for prednisolone (the only oral GC used in English primary care) within 21 days of either side of their first PMR code and a further prescription for prednisolone within 90 days. The date of the first prednisolone prescription was considered the index date. A continuous GC treatment period was defined as another prescription being issued within 90 days of the previous prescription. Individuals were included in the study if they were treated for a minimum of 90 days and their average daily dose of prednisolone over the first 90 days was at least 3 mg (for details, see Supplementary Table 1).

Medication usage. Continuous treatment periods for each medication type (calcium and vitamin D, oral bisphosphonates, PPIs or H_2 receptor antagonists [H_2RAs]) were calculated. A calculated break in treatment of >90 days was considered the end of that treatment period, and any further prescription after this date was considered a new treatment period.

Treatment periods were classified as prevalent (began ≥21 days before the index date, ending no earlier than the index date), incident (began 21 days on either side of the index date and ended on or after the index date), or late (began ≥21 days after the index date and before the last prednisolone prescription in the index treatment period). Individuals were classified as

prevalent users, incident users, late users, or nonusers of each type of medication.

High-risk groups. Based on current UK guidance,[4] comparisons in bisphosphonate prescription were made between those (1) aged <65 and ≥65 years, (2) with a mean daily dose of prednisolone of <7.5 mg and ≥7.5 mg in the first 90 days, and (3) with and without a previous fragility fracture at >40 years. Similarly, PPI and H_2RA prescriptions were compared between those (1) aged <75 and ≥75 years, (2) with and without previous GI adverse events, and (3) with and without prevalent or incident prescriptions for anticoagulants, aspirin, and NSAIDs.

Statistical analysis. Proportions of people in each medication use category were calculated overall and by age group, IMD quintile, sex, and geographic region. Simultaneous 95% confidence intervals (CIs) were calculated using the "MultinomialCI" R package (version 1.2).

Emulated target trials. *Study populations.* The population was defined by people in the CPRD Aurum December 2023 build[15,16] aged ≥50 years with a first code for PMR (index date) between January 1, 2010, and February 28, 2021, that was not in the first year of practice registration. For the study of fragility factures, people were excluded if they had been prescribed bisphosphonates within the five years before the index date (due to the long duration of effect of bisphosphonates even after ceasing therapy[17]), and for the study of GI adverse events, people were excluded if they had been prescribed a PPI/H_2RA within six months before the index date.

Outcomes. Fragility fractures (hip, humerus, wrist, vertebrae) and serious GI adverse events (bleeding, ulceration) were defined in CPRD Aurum and HES APC using relevant Read, SNOMED, international classification of diseases, tenth revision (ICD-10), and operation and procedure (OPS) codes (https://researchdata.keele.ac.uk/117/).

Time-periods. Individuals were observed for a maximum of five years from their "time zero" (equivalent to the point of randomization in a trial and here representing the first likely opportunity to consider prophylactic prescribing), which was the latter of their consultation date for PMR and the issue date of their first prednisolone prescription, which must have been within 21 days of each other. An individual's study end date was the earliest of the end of their index prednisolone period plus six months, death, registration end date, last collection date, time zero plus five years, or March 31, 2021, with the index prednisolone period being a continuous prescription period from time zero to the date of the last issue within that period. An illustration of the derivation of time in the study is given in Supplementary Figure 1 and a schematic overview of the two emulated trials is given in Supplementary Figure 2.

Analysis. Two counterfactuals were assessed, always treated and always untreated, estimated by modeling the treatment as time varying. The probability of having an outcome within 6, 12, and 18 months for each person in each counterfactual was estimated, and the average treatment effect (mean average of the difference in the probabilities for each person) was estimated, with 95% CIs for each, using targeted maximum likelihood estimation,[18,19] allowing for fixed and time-varying confounders (Figure 1). Further details of the modeling are provided in the Supplementary Materials.

Analysis software. Data preparation and analysis were performed using R (version 4.1.3 for cross-sectional study and version 4.3.0 for emulated trials) in RStudio (version 2022.02.0).

Approvals. The study was approved by the CPRD Research Data Governance Process (22_002246 and 23_003597).

RESULTS

Cross-sectional study. Table 1 shows the characteristics of the 43,091 people in the study. 43.6% were in the 70 to 79 years age group, and 61.6% were female. A majority were from IMD quintiles 1 and 2 (least deprived), with only 9.6% from the most deprived quintile.

Figure 2A shows the percentages of prevalent, incident, and late users for each medication type. The most frequent prevalent medications were PPIs/H_2RAs (34.6%, 95% CI 34.6%–34.8%). Incident prescribing of calcium and vitamin D, bisphosphonates, and gastroprotective medications occurred in 36.3% (95% CI 36.2%–36.4%), 35.8% (95% CI 35.7%–35.9%), and 29.9% (95% CI 29.8%–30.0%), respectively. Late prescribing occurred in a further 26.1% (95% CI 26.0%–26.2%), 25.5% (95% CI 25.5%–25.6%), and 14.0% (95% CI 13.9%–14.1%), respectively. Full results are in Supplementary Table 2.

There was variation in use of all medications by all sociodemographic factors (Figure 2B), but this differed by medication type. Higher rates of bisphosphonate prescribing were seen in female patients (70.0% vs 62.8% in male patients) and in the least deprived groups (68.1% in least deprived quintile vs 62.1% in most deprived quintile). Differences in rates of prescribing preventive medications between those who had a particular risk factor and those who did not were generally small (Figure 2C and D). The exception to this was the dose of prednisolone; 34.3% of those taking a dose equivalent to <7.5 mg daily for three months were prescribed a bisphosphonate (incident or late use), whereas 63.1% of those taking a dose equivalent to >7.5 mg daily for three months were prescribed a bisphosphonate. Of those at high risk in at least one relevant risk factor, 32.5% never received a bisphosphonate and 19.0% never received gastroprotection.

Emulated target trials. The inclusion/exclusion process for each trial is given in Supplementary Table 3. Because the exposure was time varying, each month was considered separately, and individuals could move between groups, it is not possible to specify population characteristics for each trial arm.

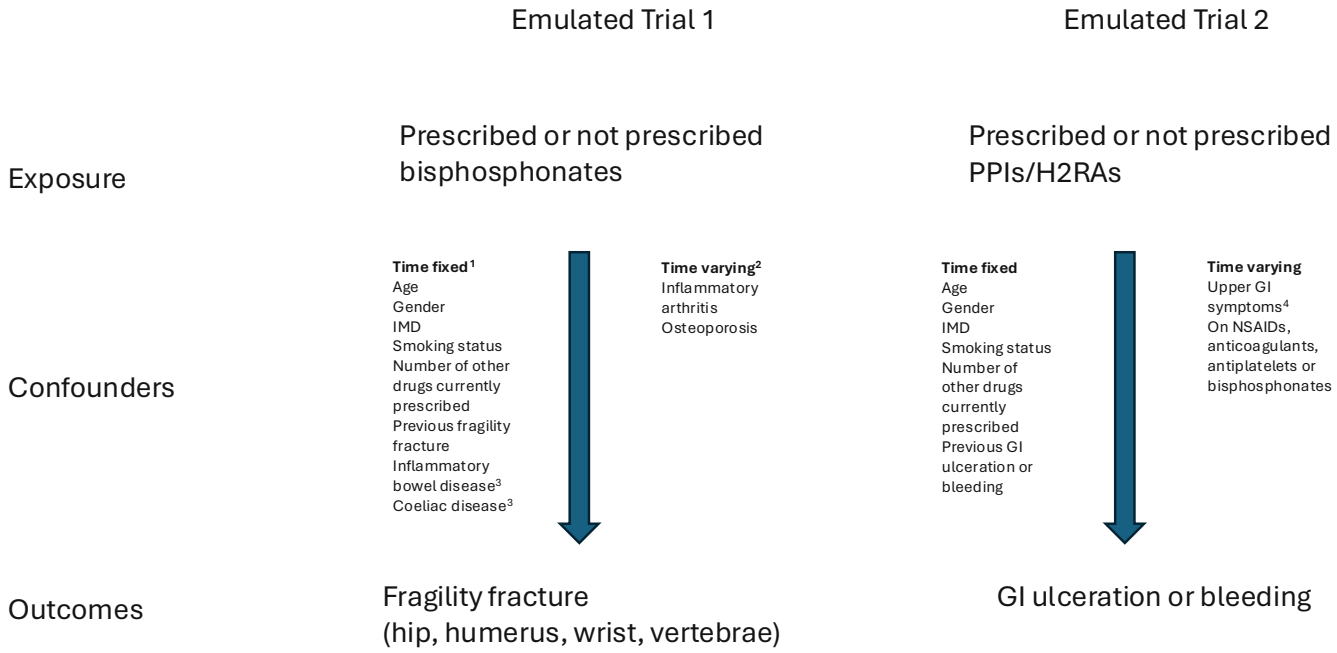

Figure 1. Exposures, confounders, and outcomes for each emulated target trial. [1]Assessed at time zero. [2]Assessed on the first day of each included month. [3]Intended to be assessed as time varying, but the numbers were too low to allow this. [4]Esophagitis, gastritis, gastroesophageal reflux disease, ulceration, or bleeding. GI, gastrointestinal; H2RA, H_2 receptor antagonists; IMD, index of multiple deprivation; NSAID, nonsteroidal anti-inflammatory drug; PPI, proton-pump inhibitor. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/art.70087/abstract.

Table 1. Descriptive statistics of population for cross-sectional study*

	n	%
Total in study	43,091	–
Age, y		
50–59	3,590	8.3
60–69	10,424	24.2
70–79	18,786	43.6
80+	10,291	23.9
IMD quintile		
1: least deprived	12,490	29.0
2	11,068	25.7
3	8,786	20.4
4	6,153	14.3
5: most deprived	4,131	9.6
NA	463	1.1
Sex		
Male	16,565	38.4
Female	26,526	61.6
Prednisolone dose >7.5 mg/day for 3 mos		
Yes	40,402	93.8
No	2,689	6.2
Previous fragility fracture		
Yes	3,816	8.9
No	39,275	91.1
Previous GI bleeding or ulceration		
Yes	323	0.7
No	42,768	99.3
Medication increasing GI bleeding risk (anticoagulants, aspirin, or NSAIDs)		
Yes	8,385	19.5
No	34,706	80.5

* GI, gastrointestinal; IMD, index of multiple deprivation; NA, not applicable; NSAID, nonsteroidal anti-inflammatory drug.

Bisphosphonates and fragility fractures. A total of 41,826 people were included. The mean age was 73.0 years (SD 9.0 years), and 59.7% were female.

The estimated proportions of people who would sustain a fragility fracture were 1.40% (95% CI 1.10%–1.70%) if everyone was treated with a bisphosphonate for 12 months and 2.32% (95% CI 2.12%–2.52%) if everyone was untreated over the same period (average treatment effect 0.92% points, 95% CI 0.56%–1.27%, $P < 0.001$). At six months, the proportions were 0.89% (95% CI 0.65%–1.13%) and 1.32% (95% CI 1.17%–1.46%), respectively, with an average treatment effect of 0.43% points (95% CI 0.16%–0.70%, $P = 0.002$). At 18 months, the proportions were 1.93% (95% CI 1.56%–2.30%) and 3.19% (95% CI 2.93%–3.45%), respectively, with an average treatment effect of 1.26% points (95% CI 0.83%–1.70%, $P < 0.001$; Figure 3 and Supplementary Figure 3). This means that the number needed to treat (NNT) to prevent one fragility fracture over 12 months in people with PMR who are taking prednisolone is 109 (Figure 4).

Gastroprotective medication and serious GI adverse events. A total of 22,526 people were included. The sample size here was considerably smaller due to the high number of people who were prescribed these medications within six months before their index date. The mean age was 73.1 years (SD 9.17 years), and 61.3% were female.

The estimated proportions of people who would have serious GI adverse events were 1.03% (95% CI 0.61%–1.45%) if everyone was treated with a PPI/H_2RA for 12 months and

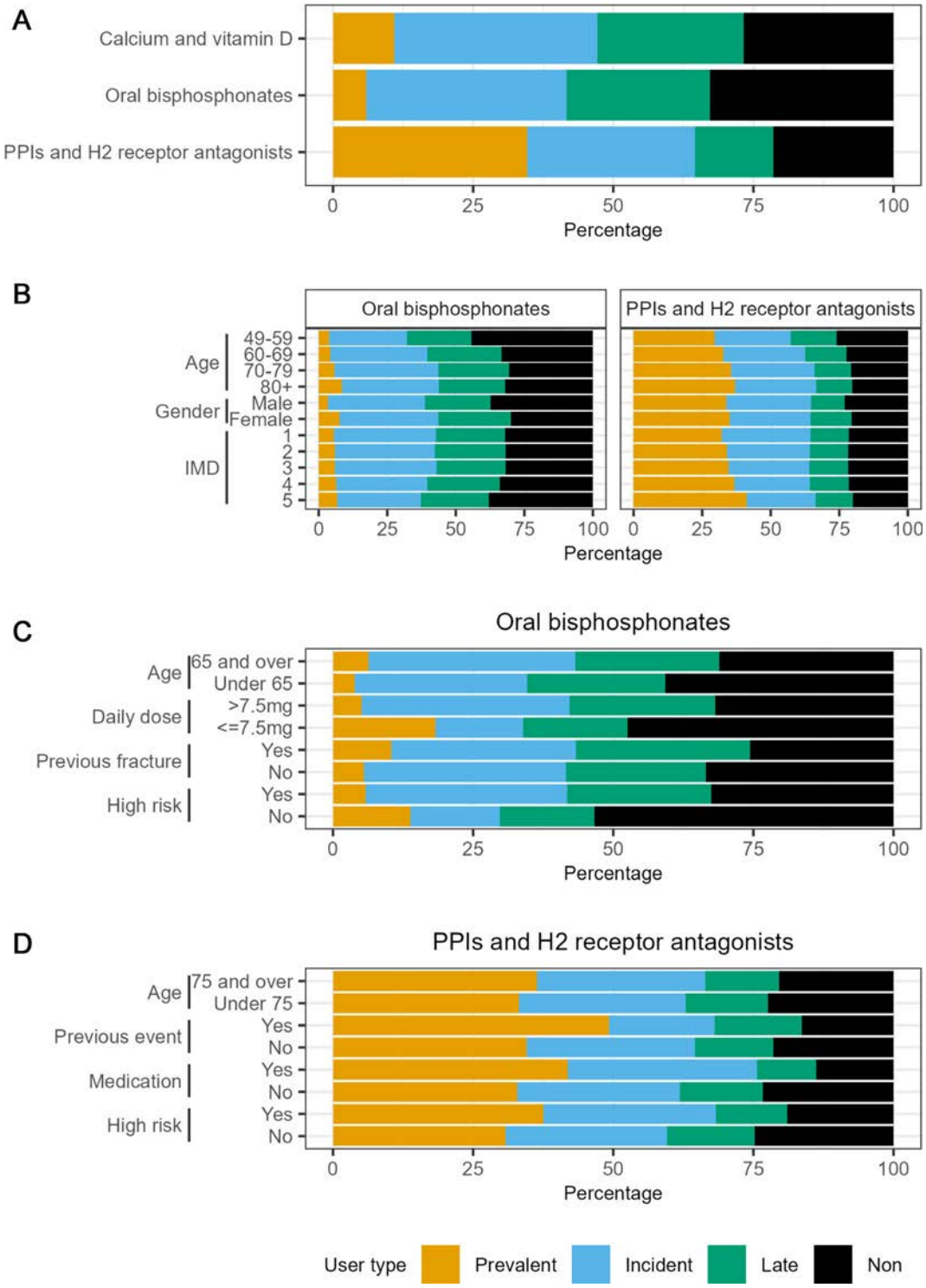

Figure 2. Percentage of prevalent users, incident users, late users, and nonusers for each medication type. (A) Overall. (B) Stratifed by age, gender and IMD. (C) Comparison by risk for fragility fracture (age, daily dose of prednisolone, previous fragility fracture, and being high risk in at least one risk factor). (D) Comparison by risk for GI adverse event (previous GI adverse event, medication increasing GI bleeding risk, and being high risk in at least one risk factor). GI, gastrointestinal; IMD, index of multiple deprivation; PPI, proton-pump inhibitor. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/art.70087/abstract.

0.78% (95% CI 0.61%–0.95%) if everyone was untreated over the same period (average treatment effect –0.25% points, 95% CI –0.71% to 0.21%, $P = 0.28$). At six months, the proportions were 0.71% (95% CI 0.38%–1.03%) and 0.46% (95% CI 0.34%–0.57%), respectively, with an average treatment effect of –0.25% points (95% CI –0.59% to 0.09%, $P = 0.15$). At 18 months, the proportions were 1.81% (95% CI 0.44%–3.18%) and 1.10% (95% CI 0.84%–1.36%) respectively, with an average

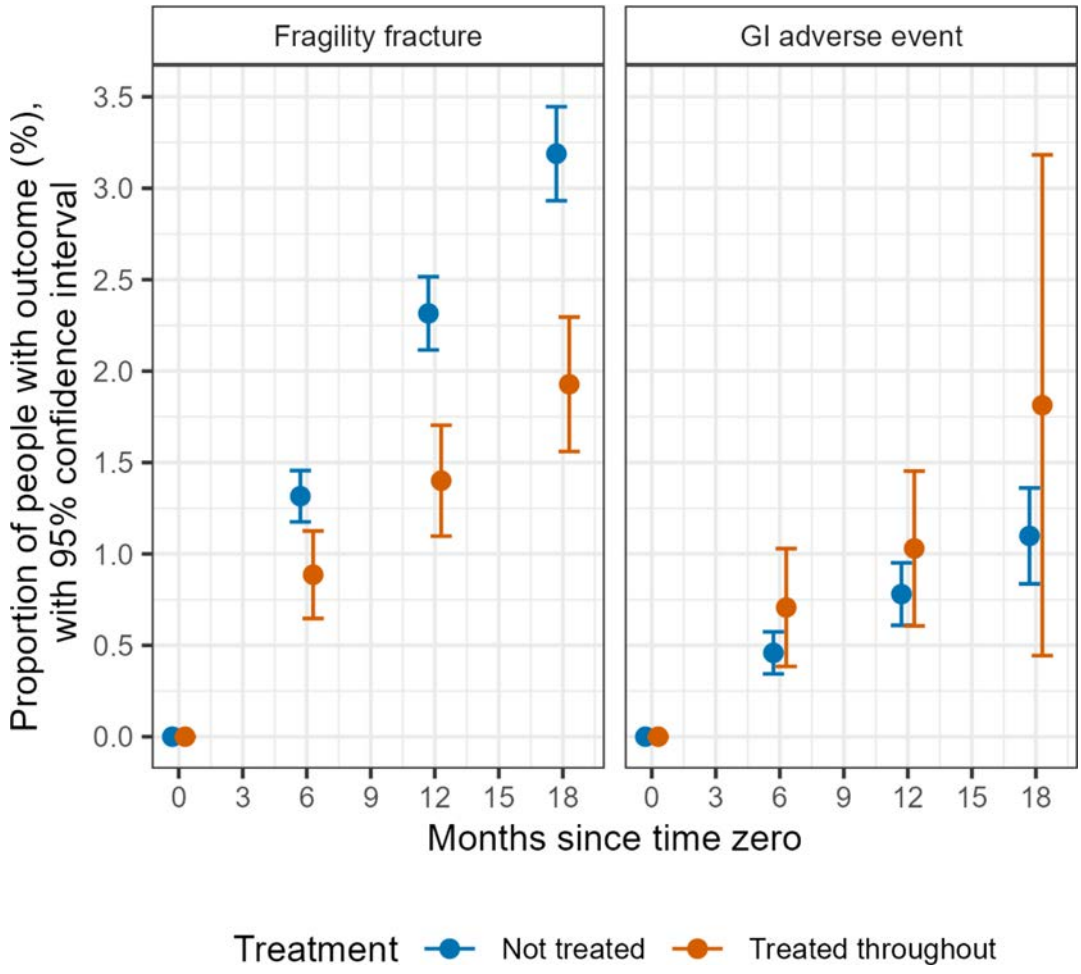

Figure 3. Estimates of the proportion of people who would sustain a fragility fracture and/or have a GI adverse event before 6 months, 12 months, and 18 months if everyone was treated and if no one was treated. GI, gastrointestinal. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/art.70087/abstract.

treatment effect of –0.72% points (95% CI –2.11% to 0.68%, $P = 0.31$; Figure 3).

DISCUSSION

This research has provided the first picture of national prescribing patterns for medications commonly used to mitigate risk of harm from GCs in people with PMR in English primary care. Furthermore, it involves the first emulated trials, using national linked primary and secondary care data to examine the impact of prophylactic prescribing on GC-related adverse events in PMR, a condition affecting older adults who may be particularly susceptible to risks of polypharmacy. We have shown a small but statistically significant reduction in fracture risk in people prescribed bisphosphonates but no statistically significant difference in serious GI events in people prescribed PPIs/H_2RAs. This has important implications for decisions around appropriate prophylactic medication use. Overall, 67.2% of people prescribed prednisolone for PMR were coprescribed bisphosphonates and 78.6% were coprescribed PPIs/H_2RAs. 61.3% of people were prescribed bisphosphonates on or after their first prednisolone prescription for PMR, suggesting this was the likely indication. Around a third of people were prescribed PPIs/H_2RAs before their PMR diagnosis, but a further 44% were prescribed PPIs/H_2RAs on or after commencement of prednisolone. There was variation in prescribing by age, sex, and level of deprivation, particularly for bisphosphonates. However, with the exception of the dose of prednisolone, existing risk factors for adverse events made little difference to prescribing rates.

Fracture risk associated with GCs, particularly risk of vertebral and hip fractures, is dose dependent and increases rapidly with GC commencement.[20] A previous study of fracture risk in individuals with PMR[10] found a 63% increased risk compared with matched controls. This risk was highest within the first year of diagnosis but remained elevated for more than five years. Previously reported rates of bisphosphonate prescribing in PMR were significantly lower than those in our study. A retrospective database study[10] of a cohort of people diagnosed with PMR between 1990 and 2004 found that among patients with PMR with at least two prescriptions for GCs, only 10.1% were prescribed

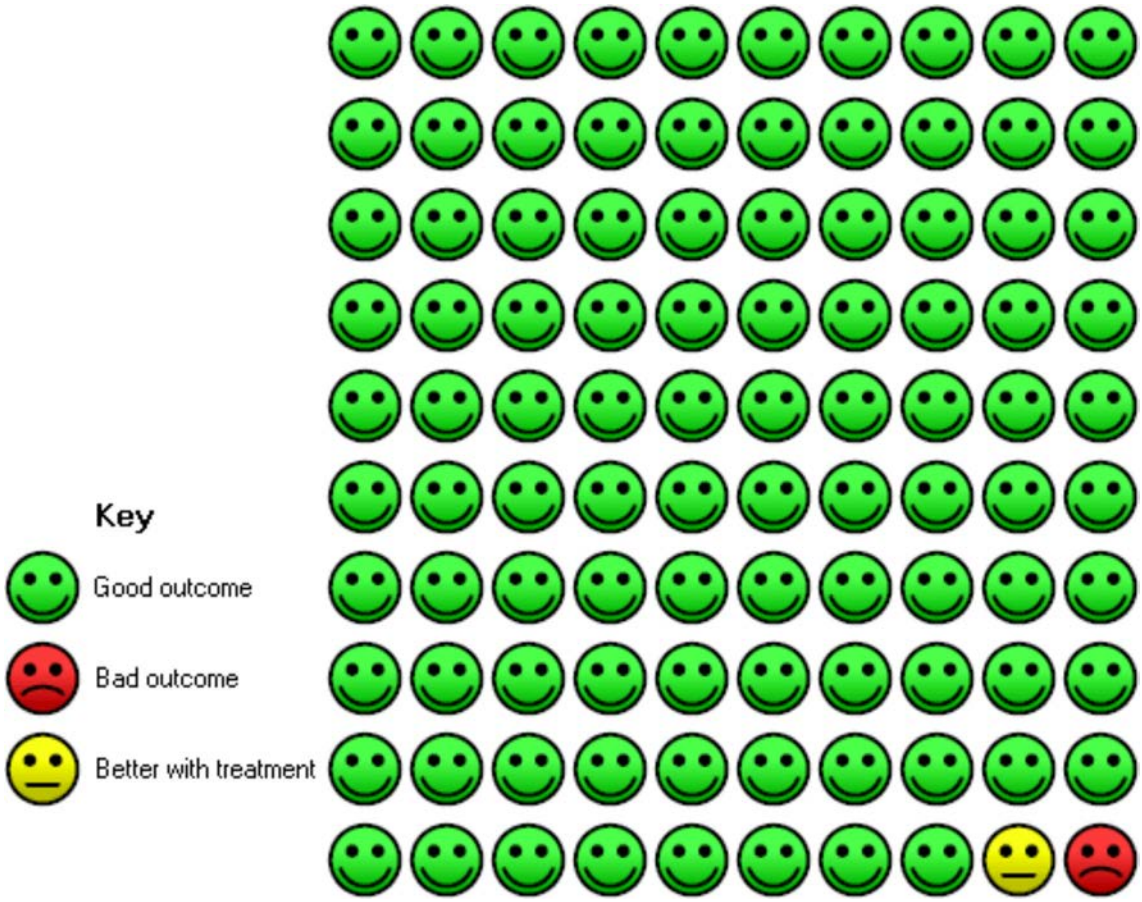

Figure 4. The effect of bisphosphonates on risk of fragility fracture in people treated with prednisolone for PMR. For every 100 people started on prednisolone for PMR, 2.3 people will have a fragility fracture in the next 12 months. For every 100 people started on prednisolone for PMR who also take a bisphosphonate for the full 12 months, 1.4 people will have a fragility fracture in the next 12 months. Cates plot based on data from this emulated target trial: control group risk 2.32% (95% CI 2.12%–2.52%), treatment group risk 1.40% (95% CI 1.10%–1.70%). CI, confidence interval; PMR, polymyalgia rheumatica. Created using Dr Chris Cates EBM website, Cates plot generator, https://www.nntonline.net/visualrx/.

bisphosphonates. In the UK PMR cohort study,[7] only 46.6% reported taking calcium/vitamin D, with only 26.1% taking other medication for osteoporosis. However, this cohort was recruited from 2012 to 2014. The higher prescribing rates in our current study may therefore reflect practice changing over time as awareness of the deleterious effect of GCs on bone health increases. In addition to guidelines on management of PMR, several other guidelines promote consideration of bone health for those taking GCs.[21,22] Most recently, guidance from the National Osteoporosis Guideline Group[22] on preventing fragility fractures in postmenopausal women and men over 50 years of age with a risk factor (of which GC treatment is one) includes recommendations to assess and address falls risk and conduct a comprehensive fracture risk assessment using a tool such as FRAX (https://www.fraxplus.org/). However, in people who are starting GC treatment of ≥7.5 mg/day of prednisolone equivalent and expected to continue this for three months or more, it is advised to start bone-protective treatment without waiting for a bone density scan. Our findings therefore suggest that prescribing bisphosphonates in UK primary care has moved closer to "best practice" over recent years, but we highlight possible unwarranted variation with factors such as male sex and higher levels of deprivation being associated with lower rates of prophylactic prescribing.

Previous research has shown similar findings in inequalities in bisphosphonate prescribing, although no studies have explored this issue specifically in relation to prophylactic treatment for those taking GCs. A practice-level prescribing data analysis in England[23] published in 2020 showed lower rates of bone-active medication prescribing in areas of greater income deprivation, and other CPRD studies reporting bisphosphonate prescribing over time[24,25] have shown consistently lower rates of prescribing in men compared to women and Black ethnic groups compared to other ethnic groups. Qualitative work[26,27] with clinicians has highlighted that bisphosphonate prescribing is not straightforward, requiring significant discussion and follow-up, and that competing priorities, time, and resource constraints affect prescribing. This may go some way to explaining the identified inequalities, but further research with patients and clinicians is required to fully explore and address this issue.

The evidence on the risk of GI adverse events associated with GC treatment is less clear than that on fragility fractures. Observational studies[28,29] have reported an increased risk of GI ulceration and bleeding, particularly when GCs are coprescribed with NSAIDs, but a meta-analysis of randomized controlled trials[30] found a significantly increased risk only in hospitalized patients prescribed GCs. In people with PMR, GI symptoms are commonly reported,[31] and an American population-based cohort reported that 7.3% of 124 patients with PMR prescribed GCs experienced an upper GI bleed.[3] However, the mean starting dose of prednisolone in this cohort was 27 mg, considerably higher than that recommended by current guidelines. Rates of PPI/H_2RA prescribing in our study are higher than those previously reported, with a study of people with PMR managed in UK primary care reporting that only 28% were prescribed a PPI.[8] This increase is in keeping with the overall trend in prescribing these medications in the UK population.[32]

In addition to describing current prescribing, this research aimed to provide evidence to inform decision-making around the use of bone-protective and gastroprotective medications in this population. The results have shown that bisphosphonates are associated with reduced risk of fragility fracture in people prescribed GC treatment for PMR, and the magnitude of the benefit increased with longer durations of bisphosphonate treatment. However, reduction in absolute risk is small (around 1% point in the first 12 months, equating to an NNT of 109). A 2016 Cochrane systematic review of bisphosphonates for prevention or treatment of steroid-induced osteoporosis[33] found high-certainty evidence of reduction in vertebral fracture risk, with an absolute increased benefit of 2% fewer people sustaining fractures with bisphosphonates (risk difference –0.02, 95% CI –0.05 to 0.01). The risk reduction for nonvertebral fractures was smaller, with lower certainty of the estimate. Included studies considered a range of different GC-treated conditions, many of which tend to affect a younger demographic than PMR. We anticipated that benefits of bisphosphonates would be greater in people with PMR due to higher background risk of fragility fracture, but our findings are of a similar magnitude to those in the Cochrane review. However, in the Cochrane review, studies of incident vertebral fractures were only included if they used routine radiographic screening to identify fractures. The risk reduction found in our study may well have been lowered by underdiagnosis of vertebral fractures that did not present clinically, meaning that the benefit of bisphosphonates may have been underestimated.

With respect to gastroprotective medications, there was no reduction in serious GI adverse events in those prescribed versus not prescribed PPIs/H_2RAs. There are no previous studies of the benefits of gastroprotective medications in people taking oral GCs for PMR. Although PPIs are commonly prescribed to relieve upper GI symptoms, our study question was specifically about prophylactic prescribing and its relationship with serious GI adverse events. We therefore only considered prescriptions for PPIs started after initiation of GC treatment and adjusted for presence of GI symptoms in our analysis to account for those who were started on a PPI during their GC treatment in response to symptoms.

Our findings suggest that prescribing PPIs/H_2RAs prophylactically to people taking prednisolone for PMR will not reduce serious GI adverse events. Given the large proportion of people prescribed these medications at the time or after they are initially prescribed prednisolone for PMR, this raises the possibility that initiation of these medications could be reduced. This is important because these medications are not without associated harms and incur considerable cost for health services.

There are several limitations to our study linked to the use of observational data. First, PMR is a difficult diagnosis to make with no single diagnostic test, and there is therefore potential for misclassification. The approach we took was based on that used in previous studies of PMR that used electronic health care record data,[34] with a requirement for a prescription for prednisolone within 21 days of the first PMR code and a further prescription within 90 days of that, but it is still possible that there was some misclassification in our study population. Second, there is the possibility that fragility fractures were underrecorded, as vertebral fractures may be asymptomatic or undiagnosed, which may be an explanation for the smaller than expected fracture reduction observed. Third, we were unable to ascertain whether people were receiving intravenous bisphosphonates, taking other bone-active medications, or using nonprescribed analgesia, vitamin D, or low-dose PPIs, potentially resulting in some level of misclassification that could have biased our findings toward the null. Finally, our study used data from English primary care, and approaches to GC dosing and prophylactic prescribing may be different in other health care systems. However, the findings in relation to efficacy should be generalizable to other PMR populations with similar background fracture risk.

The trend observed in the results of the emulated trial on gastroprotective medication, which is toward those treated being at higher risk of significant GI adverse events (albeit not statistically significant), suggests residual confounding, the source of which we have not been able to identify. It is feasible that there is confounding by indication, stemming from polypharmacy or multimorbidity that we have been unable to fully model, especially if this is related to morbidities that do not present to health care or have not otherwise been entered into the medical record.

Strengths of this work include the large representative data set and careful development of code lists using a variety of inputs and a consensus process. Furthermore, the use of linked HES APC data allowed for as comprehensive ascertainment of outcomes as possible, and the rigorous application of a predefined and relatively novel approach (emulated target trials) allowed the question of efficacy of preventive medications to be addressed.

This study has found that medications to reduce the risk of harms from GCs are prescribed more frequently than previously

identified, representing better adherence to management guidelines. However, the findings also suggest unwarranted variation in care that needs to be addressed, with prescribing found to vary by sex and deprivation.

Prophylactic prescription of medications such as bisphosphonates and PPIs/H_2RAs has to be balanced against the risks of polypharmacy, particularly for the age group affected by PMR, who are more likely to have frailty and multimorbidity. Individualized risk discussions should be informed by reliable evidence of benefits and harms of treatment options. The findings from this study provide new evidence to support these shared decisions, quantifying the magnitude of benefit of bisphosphonates on risk of fragility fracture and suggesting that prophylactic prescription of PPIs/H_2RAs could be reduced for this population.

ACKNOWLEDGMENTS

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AUTHOR CONTRIBUTIONS

All authors contributed to at least one of the following manuscript preparation roles: conceptualization AND/OR methodology, software, investigation, formal analysis, data curation, visualization, and validation AND drafting or reviewing/editing the final draft. As corresponding author, Dr Twohig confirms that all authors have provided the final approval of the version to be published and takes responsibility for the affirmations regarding article submission (eg, not under consideration by another journal), the integrity of the data presented, and the statements regarding compliance with institutional review board/Declaration of Helsinki requirements.

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Correction to "A Randomized, Double-Blind, Placebo-Controlled Trial of Abatacept for the Treatment of Relapsing, Nonsevere Granulomatosis With Polyangiitis"

Langford, C.A., Khalidi, N., Springer, J., Friedman, M., Hellmich, B., Pagnoux, C., Dehghan, N., Gewurz-Singer, O., Koening, C.L., Lin, Y.C., Monach, P.A., Moreland, L.W., Fifi-Mah, A., Flossmann, O., Forbess, L.J., Lanyon, P., Molloy, E., Specks, U., Spiera, R., Yacyshyn, E., McAlear, C.A., Burroughs, C., Jones, R.B., Rhee, R.L., Hajj-Ali, R., Warrington, K.J., Cuthbertson, D., Krischer, J.P., Jayne, D., and Merkel, P.A., for the Vasculitis Clinical Research Consortium and the European Vasculitis Society (2025), A Randomized, Double-Blind, Placebo-Controlled Trial of Abatacept for the Treatment of Relapsing, Nonsevere Granulomatosis With Polyangiitis. Arthritis Rheumatol, 77: 1739-1748. https://doi.org/https://doi.org/10.1002/art.43272

In the Results section of the Abstract, the *P* value for the primary endpoint was incorrectly reported as $P = 0.853$. The correct value is $P = 0.255$.

We apologize for this error.

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Cystathionine γ-Lyase-Dependent S-Sulfhydration of Smad3: A Novel Target to Alleviate Fibrosis in Systemic Sclerosis

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Objective. The cystathionine γ-lyase (CSE)/hydrogen sulfide (H_2S) axis has emerged as a key regulator in tissue fibrogenesis. This study aimed to explore the role of the CSE/H_2S axis in systemic sclerosis (SSc) and to investigate its underlying mechanisms to identify promising therapeutic targets.

Methods. CSE/H_2S levels were assessed in serum samples from 25 patients with SSc and 28 healthy controls. Human dermal fibroblasts from patients with SSc and healthy controls were used for functional studies, including propargylglycine (CSE inhibitor) treatment, Gyy4137, a slow-releasing hydrogen sulfide donor, CSE silencing, and CSE overexpression, combined with liquid chromatography–tandem mass spectrometry (LC-MS/MS)–based S-sulfhydration proteomics. Molecular dynamics simulations were performed to study the effects of S-sulfhydration on protein structure, and an Smad3 C121S (cysteine [Cys] 121 mutated to Ser) mutant was generated to verify the function targets of S-sulfhydration. In vivo, bleomycin-induced mouse models of skin and lung fibrosis were constructed to evaluate the effects of CSE overexpression.

Results. In human samples, CSE/H_2S levels were reduced in SSc. CSE inhibition promoted extracellular matrix deposition. S-sulfhydration proteomics showed that S-sulfhydration levels were globally reduced in SSc compared to controls. CSE overexpression increased S-sulfhydration on Smad3, suppressed transforming growth factor β 1 (TGFβ1)/Smad3 signaling, mitigating skin fibrosis. Notably, Cys121 on Smad3, identified as a pivotal target for S-sulfhydration by proteomics, was shown to fine-tune its MH1 domain, with its mutation impairing the antifibrotic effects. In mice, CSE overexpression attenuated bleomycin-induced skin and lung fibrosis.

Conclusion. Smad3 S-sulfhydration mediates the antifibrotic effect of CSE in SSc, highlighting it as a critical mechanism and promising therapeutic target.

INTRODUCTION

Systemic sclerosis (SSc) is an autoimmune connective tissue disease characterized by vasculopathy, immune dysregulation, and progressive fibrosis of the skin and internal organs including lungs and heart.[1] Skin fibrosis, the defining hallmark of SSc, significantly impairs patients' quality of life and serves as a key indicator of disease severity.[2] Although relatively uncommon, SSc has high morbidity, disability, and mortality rates among rheumatic diseases, making it one of the most severe conditions in this category.[3] Despite extensive research, effective therapies to reverse fibrosis in SSc remain elusive, partly due to an incomplete understanding of its complex pathogenesis. Fibroblasts, influenced by genetic, environmental, and epigenetic factors, are key effector cells in SSc fibrosis, overproducing extracellular matrix (ECM) in response to proinflammatory and profibrotic cytokines.[4] However, the mechanisms driving fibroblast overactivation in SSc remain inadequately characterized, limiting the development of targeted therapeutic strategies.[5]

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Transforming growth factor β 1 (TGFβ1)/Smad3 signaling pathway is central to fibrosis in SSc, with overactivation observed in SSc fibroblasts.[6] In response to TGFβ1, Smad3 undergoes phosphorylation, translocates to the nucleus with coactivators, and initiates the transcription of fibrotic genes, such as *COL1A1* and *FN1*, thereby contributing to excessive ECM production and ultimately irreversible fibrosis.[7,8] Although the fibrotic role of TGFβ1/Smad3 signaling is well established, the mechanisms underlying its abnormal activation in SSc remain poorly defined. Although direct TGFβ-targeted therapies have shown promise, their clinical application is limited due to significant side effects.[9] Thus, precise modulation of TGFβ1/Smad3 signaling remains a key focus for developing effective antifibrotic therapies in SSc.

Cystathionine γ-lyase (CSE)/hydrogen sulfide (H_2S) axis has recently been suggested as a potential regulator of fibrosis. CSE, the primary enzyme for H_2S synthesis in peripheral tissues including the skin, generates H_2S during cysteine (Cys) metabolism.[10] The CSE/H_2S axis is known to modulate vascular tone, oxidative stress, and inflammation.[11] Preliminary studies suggest that physiologic levels of CSE/H_2S may have antifibrotic effects: reduced CSE expression and H_2S levels are associated with fibrosis progression in hepatic models,[12] whereas exogenous H_2S administration has shown promise in attenuating fibrosis.[13] Additionally, down-regulation of CSE has been implicated in the myofibroblast transformation, contributing to renal fibrosis.[14] Despite these insights, the precise mechanisms underlying CSE/H_2S pathway in fibrosis remain unclear, and there are no studies on its specific role in SSc fibrosis, highlighting a significant research gap.

A central mechanism of CSE/H_2S signaling involves protein S-sulfhydration, a newly discovered posttranslational modification (PTM) in which H_2S modifies Cys residues, converting thiols (-SH) to persulfides (-SSH).[15] Indeed, this modification, widely observed in eukaryotic cells, is particularly prevalent under oxidative stress, in which it fine-tunes cellular signaling by inducing conformational changes in key proteins. Studies increasingly support the crucial role of S-sulfhydration in antioxidation, anti-inflammation, antiaging, and other physiologic processes.[16] For instance, H_2S-mediated S-sulfhydration of Keap1 at Cys151 promotes Nrf2 release, thereby alleviating oxidative stress,[17] whereas S-sulfhydration of protein disulfide isomerase enhances its activity and improves vascular function in acute aortic dissection models.[18] Despite these important regulatory roles, research on S-sulfhydration remains in its early stages. It has been reported that the H_2S/TGFβ1/Smad3 axis contributes to fibrosis in bleomycin (BLM)-induced models.[19] However, its impact on fibrosis in SSc, particularly with respect to protein S-sulfhydration, has yet to be investigated.

Notably, the elevated plasma homocysteine levels in patients with SSc suggest potential abnormalities in the endogenous CSE/H_2S axis.[20,21] Given that the stability of Smad3's DNA-binding domain—a region essential for its activity—relies on Cys residues that are susceptible to redox modification,[22] we hypothesized that CSE-mediated S-sulfhydration of Smad3 may modulate fibrosis in SSc through effects on TGFβ1/Smad3 signaling. This study aims to clarify the role of the CSE/H_2S pathway in SSc fibrosis, focusing on its potential regulation of Smad3 through S-sulfhydration. To test this hypothesis, we performed a proteomic analysis of S-sulfhydration in fibroblasts using liquid chromatography (LC)–mass spectrometry (MS)/MS, established SSc mouse models, and explored the interplay among the CSE/H_2S pathway, TGFβ1/Smad3 signaling, and SSc fibrosis. We propose that CSE-driven S-sulfhydration of Smad3 may represent a novel and promising therapeutic target for SSc, and we seek to elucidate the underlying molecular mechanisms.

MATERIALS AND METHODS

Patients and samples. Skin lesions, dermal fibroblasts, and serum were obtained from patients diagnosed with SSc at the Department of Dermatology, Second Xiangya Hospital. All included patients had not received systemic immunosuppressive therapy for at least three months. The diagnosis followed the 2013 American College of Rheumatology/EULAR classification criteria[23], and modified Rodnan skin thickness score (mRSS) was employed to evaluate dermal thickening. Skin biopsies from healthy individuals undergoing minor plastic surgery served as normal controls. A total of 25 patients with diffuse cutaneous SSc and 28 age- and sex-matched healthy controls were enrolled (Supplementary Tables S1 and S2). All participants signed the informed consent, and the study was approved by the Central South University Ethics Review Committee. The data supporting the findings of this study are included in the article and its supplementary materials. Further information is available from the corresponding author upon reasonable request.

S-sulfhydration assay. S-sulfhydration of Smad3 was measured using a modified biotin-switch analysis based on previous reports.[18,24] Details of procedure are available in the Supplementary Materials.

Generation of Smad3-knockdown fibroblasts and subsequent introduction of the Smad3 C121S mutant. Dermal fibroblasts were first infected with lentivirus-delivered Smad3 short hairpin RNA (shRNA) tagged with green fluroescent protein (GFP) at a multiplicity of infection (MOI) of 15. Three independent lentiviral Smad3 shRNAs (sequences in Supplementary Table S3) were initially screened for knockdown efficiency by Western blot. Among them, shRNA-2, which produced the most robust reduction of endogenous Smad3, was selected and used for subsequent experiments (Supplementary Figure S1). After 72 hours of infection, cells were briefly selected with puromycin (1.5 μg/mL). Next, these enriched, transiently Smad3-knockdown fibroblasts were subsequently

infected with lentivirus expressing the Smad3 C121S mutant with an mCherry tag (Cys121→Ser; Supplementary Figure S2A) at an MOI of 10. Neomycin (2 μg/mL) was briefly applied to enrich successfully transduced cells. The Smad3-C121S construct carried synonymous A→G substitutions within the shRNA-targeted region, rendering the exogenous transcript resistant to Smad3 shRNA (Supplementary Figure S3). Cells transduced twice with empty lentiviral vectors were used as negative controls to account for potential nonspecific effects.

BLM-induced fibrosis mice models. As previously described,[25,26] eight-week-old BALB/c female mice (for dermal fibrosis) and C57BL/6 male mice (for lung fibrosis) were housed in the specific pathogen-free (SPF) Animal Laboratory of Central South University and randomly assigned to groups (n = 6). All animal experiments were conducted in strict accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals and were approved by the Animal Ethical Review Committee of Central South University (application 20231278). Blinding procedures were strictly followed throughout the study.

To overexpress CSE, mice were administered a purified adeno-associated virus serotype 9 (AAV9) vector carrying the *CSE* gene (AAV-CSE, vector GV388, titer 10^{13} vg/mL; Genechem; Supplementary Figure S2B). AAV-empty vector served as the negative control. In the dermal fibrosis model, mice received subcutaneous AAV-CSE injections (2.5×10^{11} vg in 100 μL phosphate buffered saline [PBS]) into the dorsal skin (four sites, 25 μL per site).[27] In the pulmonary fibrosis model, mice received intratracheal instillation of AAV-CSE (2.5×10^{11} vg in 50 μL PBS) via the oral cavity.[28]

Four weeks after AAV-CSE administration, fibrosis was induced by BLM. For dermal fibrosis, BLM (1 mg/kg in 100 μL PBS) was injected subcutaneously into the back daily for four weeks. Additionally, propargylglycine (PAG) was administered subcutaneously (1 mg/kg in 100 μL PBS) daily starting one week after BLM treatment. For pulmonary fibrosis, mice received a single intratracheal instillation of BLM (4 mg/kg in 50 μL PBS) and were monitored for three weeks. At the experimental endpoint, skin and lung samples were collected for histologic analysis and fibrotic marker assessment. Skin fibrosis was assessed by skin thickness and collagen deposition. Pulmonary fibrosis was evaluated using the modified Ashcroft score.[29]

Statistical analysis. Statistical analysis was performed using GraphPad Prism version 10.1.1. All measurements were shown as the mean ± SD. Data were tested for normality (Shapiro–Wilk normality test) and homogeneity of variance (Brown–Forsythe test). Student's *t*-test or Mann–Whitney U test was applied for two-group comparisons. For comparisons among three or more groups, one-way analysis of variance (or Kruskal–Wallis test, if nonparametric) followed by Dunn's post hoc test was used. Each experiment was repeated at least in triplicate, and $P < 0.05$ was considered statistically significant. Expanded methods are provided in the Supplementary Materials, including the LC-MS/MS-based S-sulfhydration proteomics workflow (Supplementary Figure S4).

RESULT

Reduced serum H_2S levels and dermal CSE expression in patients with SSc. This study first aimed to evaluate serum H_2S levels in patients with SSc and healthy controls. Serum samples were collected from 25 patients with SSc and 28 healthy controls. Serum H_2S levels were significantly lower in patients with SSc compared with healthy controls ($P < 0.01$; Figure 1A). mRSSs in patients with SSc were inversely correlated with serum H_2S levels ($P < 0.01$; Figure 1B). The major enzymes responsible for endogenous H_2S production are CSE, cystathionine-β-synthase (CBS), and 3-mercaptopyruvate sulfurtransferase (3-MST). Among these, CSE is the primary H_2S-producing enzyme in the skin, whereas CBS and 3-MST are predominantly expressed in the brain and liver or mitochondrion, with minimal cutaneous expression.[30] CBS and 3-MST expression in dermal fibroblasts showed no significant differences between SSc and controls (Supplementary Figure S5). Notably, CSE expression was reduced in SSc skin lesions compared to normal controls (Figure 1C). This down-regulation was evident at both the messenger RNA (mRNA) and protein levels in dermal fibroblasts (Figure 1D and E).

CSE suppression in dermal fibroblasts promotes ECM deposition. To investigate the role of CSE in skin fibrosis, dermal fibroblasts from healthy controls were treated with varying concentrations of DL-propargylglycine (PAG), a recognized inhibitor of CSE, for 48 hours. CCK-8 assay confirmed that PAG (≤10 mM) did not affect fibroblast viability (Supplementary Figure S6A). Cell lysates and culture supernatants were then collected. PAG treatment dose-dependently increased COL1A1 and FN1 expression (key ECM components) while reducing MMP1 expression (a critical ECM-degrading enzyme). These effects were observed at the mRNA, protein, and secreted protein levels (Supplementary Figure S6B–D), consistent with excessive ECM deposition in SSc. Consistently, CSE knockdown via small interfering RNA yielded similar results (Supplementary Figure S6E–H).

CSE/H_2S axis inhibits overactivation of SSc dermal fibroblasts. Given its positive role in regulating ECM deposition, we explored whether CSE could mitigate dermal fibrosis in SSc. SSc dermal fibroblasts are overactive, characterized by elevated α-smooth muscle actin (α-SMA) expression, enhanced migration, and excessive ECM production. Immunofluorescence assays demonstrated that CSE overexpression reduced α-SMA

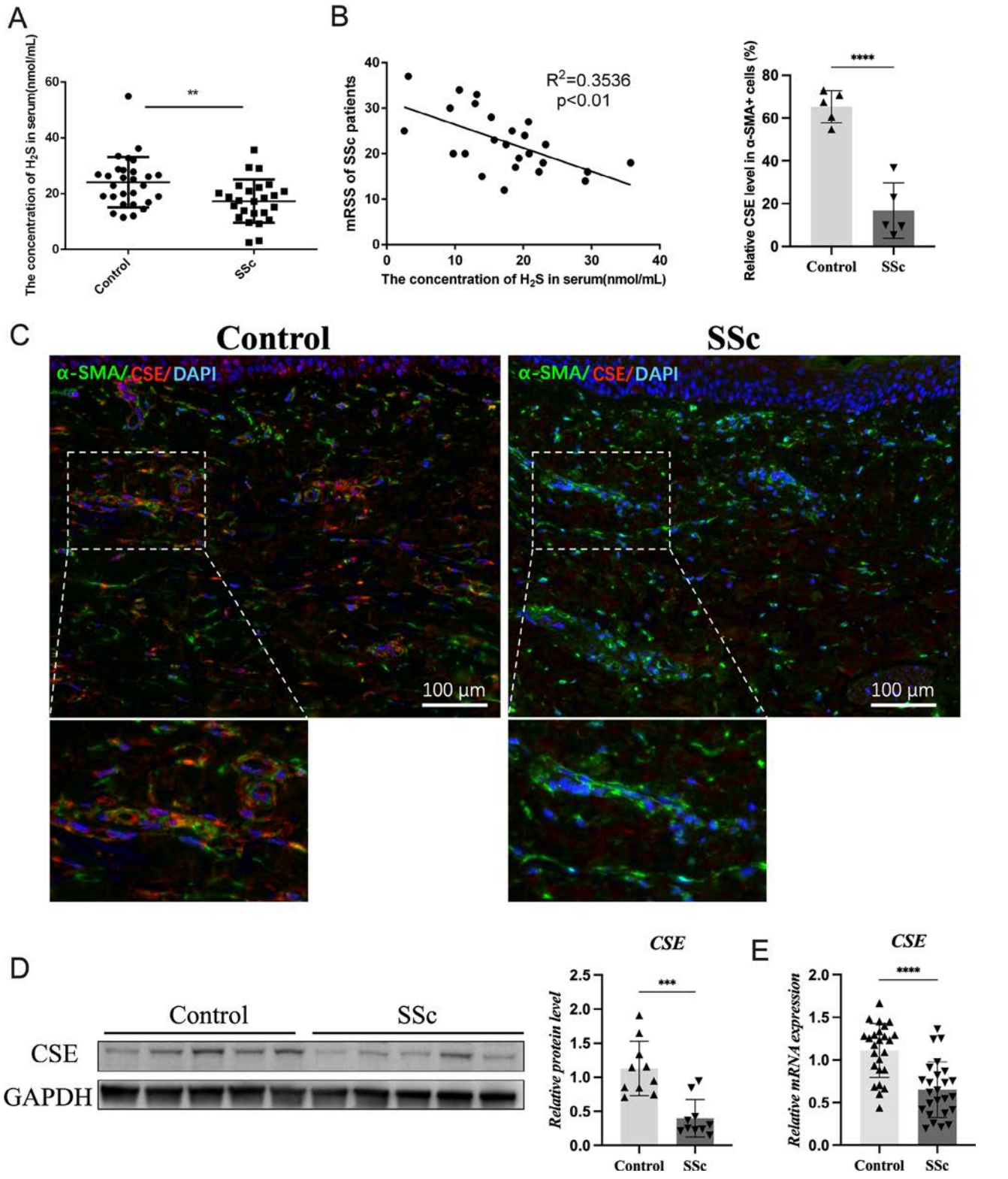

Figure 1. Reduced serum hydrogen sulfide (H_2S) levels and dermal cystathionine γ-lyase (CSE) expression in patients with systemic sclerosis (SSc). (A) Serum H_2S levels were significantly reduced in patients with SSc compared with healthy controls (n = 28 vs 25). $^{**}P < 0.01$ versus control. (B) A negative correlation between serum H_2S concentration and modified Rodnan skin thickness score (mRSS) in patients with SSc (n = 25) based on linear regression analysis ($R^2 = 0.3536$, $P < 0.01$). $^{****}P < 0.0001$ versus control. (C) Immunofluorescence analysis showed reduced CSE expression in SSc skin lesions, with DAPI staining in blue, CSE staining in red, and α-smooth muscle actin (α-SMA) staining in green (n = 5). (D and E) Both protein (n = 10) and messenger RNA (mRNA; n = 25) levels of CSE were down-regulated in fibroblasts derived from SSc skin lesions. $^{***}P < 0.001$; $^{****}P < 0.0001$ versus control.

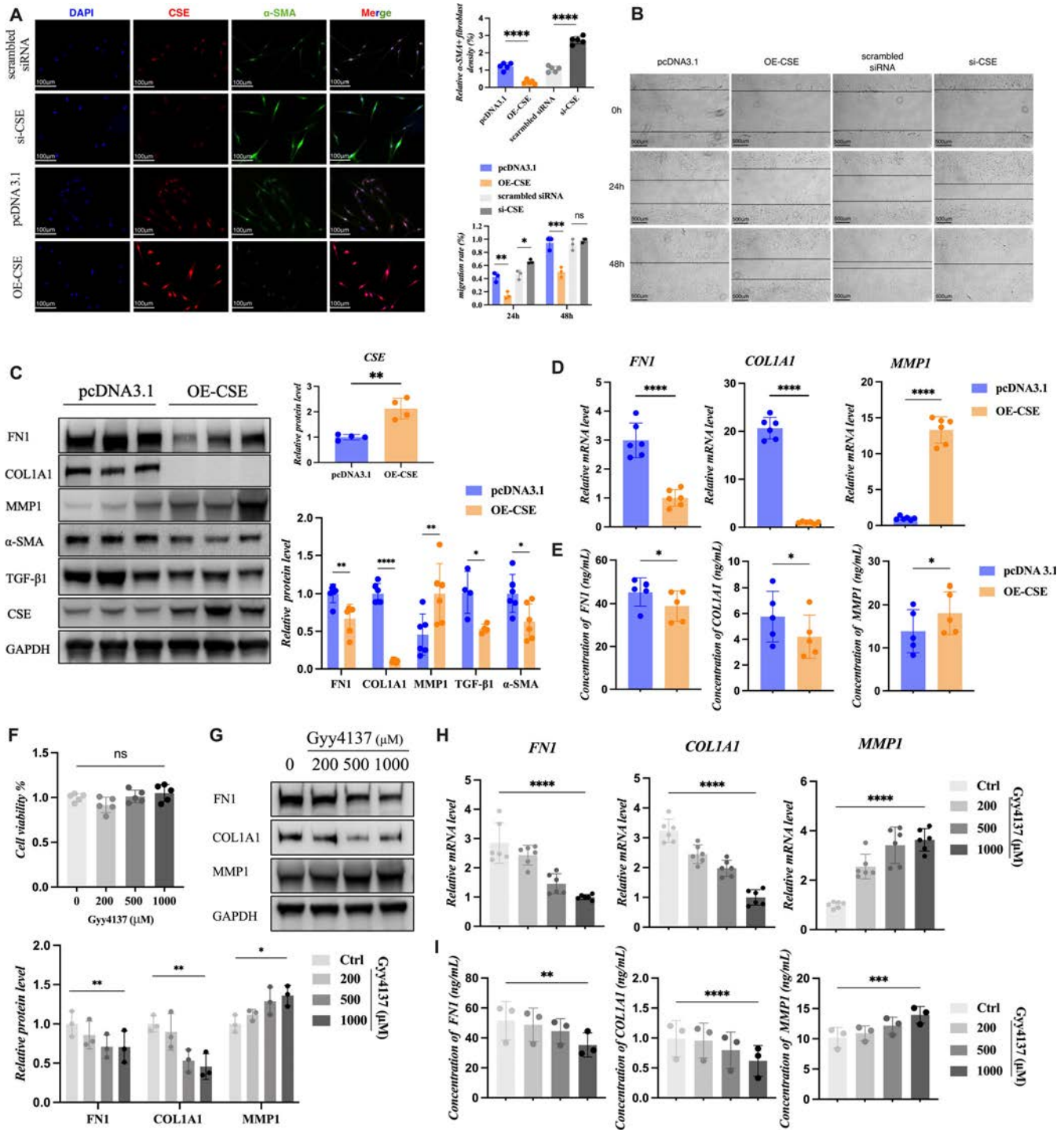

Figure 2. Cystathionine γ-lyase (CSE)/hydrogen sulfide (H_2S) axis inhibits overactivation of systemic sclerosis dermal fibroblasts. Fibroblasts were transfected with CSE-pcDNA3.1-3xFlag-C tag (CSE overexpression [OE-CSE], Ctrl [control]: pcDNA3.1, empty vector) or small interfering RNA targeting CSE (si-CSE; Ctrl: scrambled small interfering RNA [siRNA]) for 48 hours (h) to overexpress or knock down CSE. (A) Immunofluorescence of α-smooth muscle actin (α-SMA; DAPI, blue; CSE, red; and α-SMA, green; scale bar, 100 μm), quantified by ImageJ (n = 5). $P > 0.05$ is nonsignificant (ns); $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$; $^{****}P < 0.0001$ versus Ctrl. (B) The scratch assay measuring wound closure to assess cell migration (n = 3). (C–E) Fibroblasts transfected with OE-CSE (Ctrl: pcDNA3.1) were analyzed for fibrotic marker expression at (C) protein, (D) messenger RNA (mRNA), and (E) secreted protein levels by Western blotting, reverse transcriptase–quantitative polymerase chain reaction, and enzyme-linked immunosorbent assay (n = 4–6); for transforming growth factor β 1 (TGFβ1) in (C), n = 4 due to exclusion of two poor-signal samples. $^{*}P < 0.05$; $^{**}P < 0.01$; $^{****}P < 0.0001$ versus Ctrl. (F–I) Fibroblasts treated with Gyy4137 (a slow-releasing H_2S donor) at concentrations of 200 to 1,000 μM for 48 h were analyzed for (F) cell viability by CCK-8 and fibrotic marker expression at (G) protein, (H) mRNA, and (I) secreted protein levels (n = 3–6). $P > 0.05$ is ns; $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$; $^{****}P < 0.0001$ versus Ctrl. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/art.70085/abstract.

expression, whereas CSE knockdown increased α-SMA levels (Figure 2A). Scratch assays suggested that CSE negatively regulated fibroblast migration (Figure 2B). Fibrosis-related markers were assessed at the protein, mRNA, and secreted protein levels. The results showed that CSE overexpression decreased COL1A1, FN1, α-SMA, and TGFβ1 while increasing MMP1 (Figure 2C–E，Primers for rt-qPCR and antibodies for western blot in Supplementary Table S4–S5). To further investigate the effects of exogenous H_2S on dermal fibrosis, we treated SSc fibroblasts with Gyy4137, a widely used slow-releasing and long-lasting H_2S donor.[31] CCK-8 assay confirmed that Gyy4137 (≤1,000 μM) did not affect cell viability (Figure 2F). The effects of Gyy4137 on these ECM-related markers were consistent with those of CSE overexpression, further supporting the antifibrotic function of the CSE-H_2S axis in SSc (Figure 2G–I).

CSE inhibits TGFβ1/Smad3 signaling in SSc dermal fibroblasts. TGFβ1/Smad3 signaling is a key pathway in the pathogenesis of fibrosis in SSc.[32] We next investigated the effect of CSE on this pathway. Smad3 transduces TGFβ1 signaling primarily through phosphorylation, nuclear translocation, and binding to target genes.[7,33] SSc dermal fibroblasts with or without CSE overexpression were treated with TGFβ1 (10 ng/mL) in a time-dependent manner to assess phosphorylated Smad3 (p-Smad3) levels. The results revealed that p-Smad3 levels, markedly elevated by transient TGFβ1 stimulation, were suppressed in the CSE-overexpressing groups, particularly after 60 minutes of TGFβ1 stimulation (Figure 3A). To assess the effect of CSE on p-Smad3 nuclear translocation, nuclear and cytoplasmic proteins were extracted separately. We found that the majority of p-Smad3 translocated into the nucleus upon TGFβ1 stimulation. This process was inhibited by CSE overexpression but promoted by CSE knockdown (Figure 3B and C). Immunofluorescence assays further supported these observations (Figure 3D). Once inside the nucleus, Smad3 functions as a transcriptional activator, primarily by binding to Smad3-binding elements (SBEs) on target gene promoters. To assess Smad3 transcriptional activity, an SBE-luciferase reporter was employed. The results showed that TGFβ1 stimulation significantly increased SBE-luciferase activity, which was reduced by CSE overexpression but enhanced by CSE knockdown (Figure 3E). These findings suggested that CSE negatively regulates TGFβ1/Smad3 signaling.

S-sulfhydration is involved in CSE-mediated antifibrotic effects in SSc. S-sulfhydration is increasingly recognized as a key mechanism underlying the CSE/H_2S axis. To investigate whether S-sulfhydration mediates the antifibrotic effects of CSE in SSc, we performed LC-MS/MS–based S-sulfhydration proteomics in SSc dermal fibroblasts and healthy controls (Supplementary Table S6). S-sulfhydration levels were globally reduced in SSc compared to controls, consistent with low CSE levels in SSc (Figure 4A). For example, S-sulfhydration of the ECM-related proteins FBLN1 and COL16A1 were significantly reduced in SSc (Figure 4B). Gene Ontology (Figure 4C) and KEGG (Kyoto Encyclopedia of Genes and Genomes, Figure 4D) enrichment analyses revealed that differentially persulfidated proteins were significantly enriched in fibrosis-related processes, including ECM remodeling, cell adhesion, and hypoxia adaptation. Notably, the enrichment of I-SMAD binding suggests its involvement in Smad-mediated signaling. These findings further support the critical role of S-sulfhydration in fibrosis. Furthermore, we pretreated fibroblasts with dithiothreitol (DTT) to create a reducing environment that prevents sulfhydryl groups from forming S-sulfhydration. DTT (≤1 mM) showed no significant cytotoxic effects on fibroblasts (Supplementary Figure S7A) and partly abrogated the inhibitory effects of CSE overexpression on ECM deposition, as evidenced by increased COL1A1 and FN1 and decreased MMP1 (Supplementary Figure S7B). Additionally, the role of S-sulfhydration in TGFβ1/Smad3 signaling was evaluated. We found that p-Smad3 levels induced by transient TGFβ1 stimulation were markedly attenuated upon CSE overexpression, whereas this attenuation was largely prevented by DTT (Supplementary Figure S7C). Together, it can be postulated that S-sulfhydration is involved in the antifibrotic effects of CSE.

S-sulfhydration at $Smad3^{C121}$ is a functional target for CSE-mediated antifibrotic effects. Among the differentially S-sulfhydrated proteins identified by LC-MS/MS, we focused on Smad3, the key transcription factor in SSc fibrosis, which was S-sulfhydrated at Cys121 (Fold change $[FC]_{SSc/Control}$ = 0.427, P = 0.0007; Figure 4B). The modified biotin-switch assay confirmed reduced SSH-Smad3 levels in SSc dermal fibroblasts compared with normal controls (Figure 4E). Notably, CSE overexpression increased SSH-Smad3 levels, whereas this effect was partly abolished by the reducing agent DTT (Supplementary Figure S7D). These findings suggest that Smad3 undergoes CSE-dependent S-sulfhydration.

To determine whether Cys121 is the CSE-mediated S-sulfhydrated site of Smad3, we generated fibroblasts transiently expressing the Smad3 C121S mutant (Cys121→Ser; $Smad3^{C121S}$) and overexpressed CSE in fibroblasts expressing $Smad3^{WT}$ or $Smad3^{C121S}$. As expected, SSH-Smad3 levels were significantly increased upon CSE overexpression in fibroblasts expressing $Smad3^{WT}$, whereas this modification was largely prohibited by the C121S mutation (Figure 5A), indicating that Cys121 is the primary site of S-sulfhydration in Smad3.

Interestingly, Cys121 is part of the zinc finger domain within the MH1 domain of Smad3, which is essential for DNA binding (Figure 5B). S-sulfhydration of zinc-coordinating Cys can lead to structural/functional changes in proteins.[34] In addition, Cys121 is relatively conserved across multiple species (Figure 5C), emphasizing its functional significance. To investigate whether S-sulfhydration at Cys121 on Smad3 (SSH-Smad3) induces allosteric effects on its MH1 domain, we performed molecular

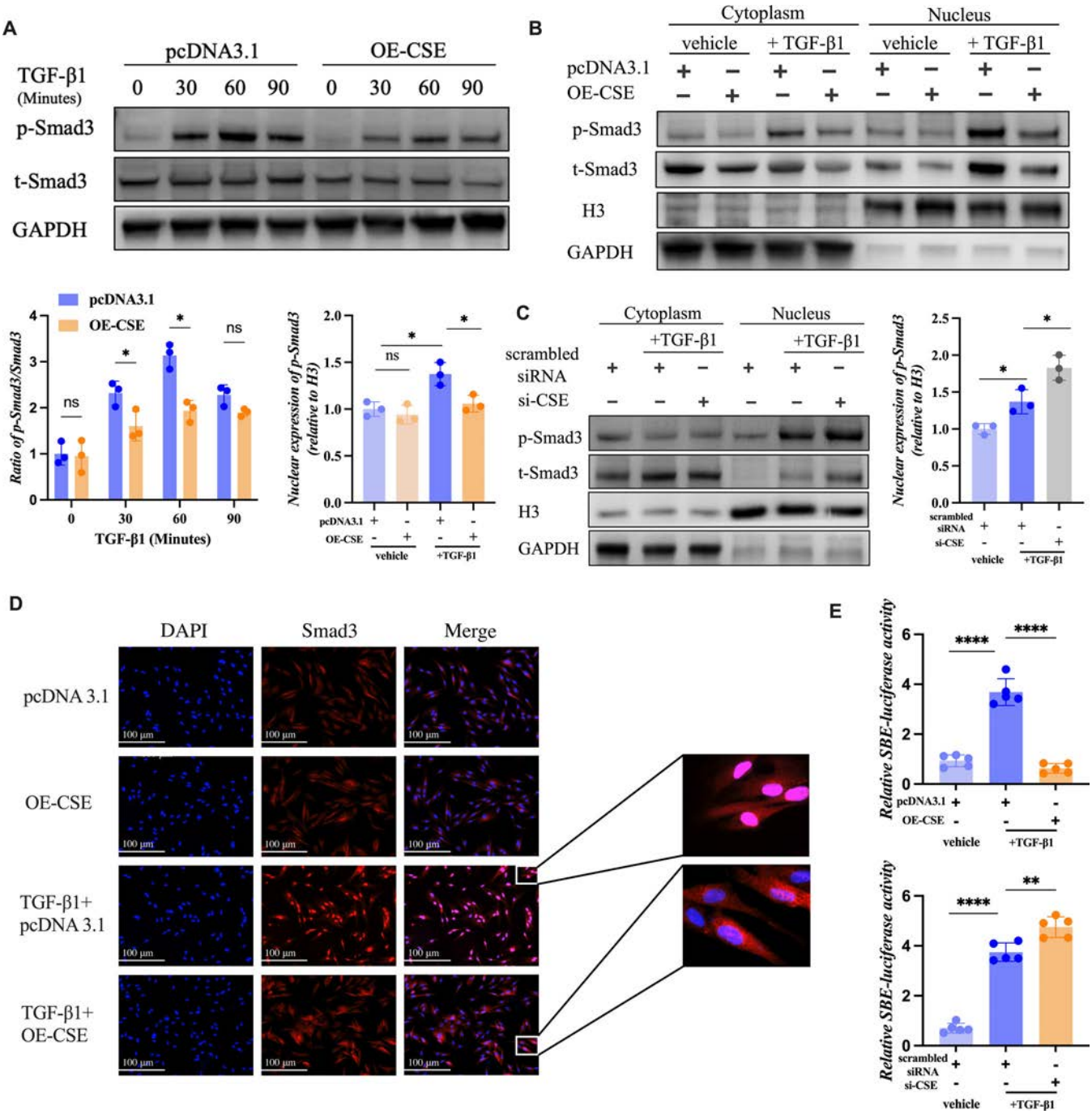

Figure 3. Effects of cystathionine γ-lyase (CSE) on Smad3 phosphorylation, nuclear translocation, and Smad3-binding element (SBE)-luciferase transcriptional activity in fibroblasts. (A) Fibroblasts transfected with CSE overexpression (OE-CSE; control: pcDNA3.1, empty vector) were exposed to transforming growth factor β 1 (TGFβ1; 10 ng/mL) for 30, 60, and 90 minutes. Western blotting was used to detect phosphorylated Smad3 (p-Smad3) relative to total Smad3 (t-Smad3; n = 3). $P > 0.05$ is nonsignificant (ns); $^{*}P < 0.05$. (B and D) CSE-overexpressing fibroblasts were treated with TGFβ1 for 60 minutes. (B) The nuclear p-Smad3 was determined by Western blotting, with H3 (Histone 3) as the internal standard for nuclear fractions (n = 3). (D) Immunofluorescence was performed to visualize the subcellular localization of Smad3 (scale bar, 100 μm; DAPI, blue; Smad3, red). (C) CSE-knockdown fibroblasts were treated with TGFβ1 for 60 minutes; Western blotting detected the nuclear p-Smad3 (n = 3). $^{*}P < 0.05$. (E) Fibroblasts were cotransfected with plasmids SBE-luciferase, Renilla luciferase, and either OE-CSE (control: pcDNA3.1) or small interfering CSE (si-CSE; control: scrambled small interfering RNA [siRNA]), followed by TGFβ1 stimulation for 24 hours. Smad3 transcriptional activity was quantified as the SBE-to-Renilla luciferase ratio (n = 5). $^{**}P < 0.01$; $^{****}P < 0.0001$ versus control. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/art.70085/abstract.

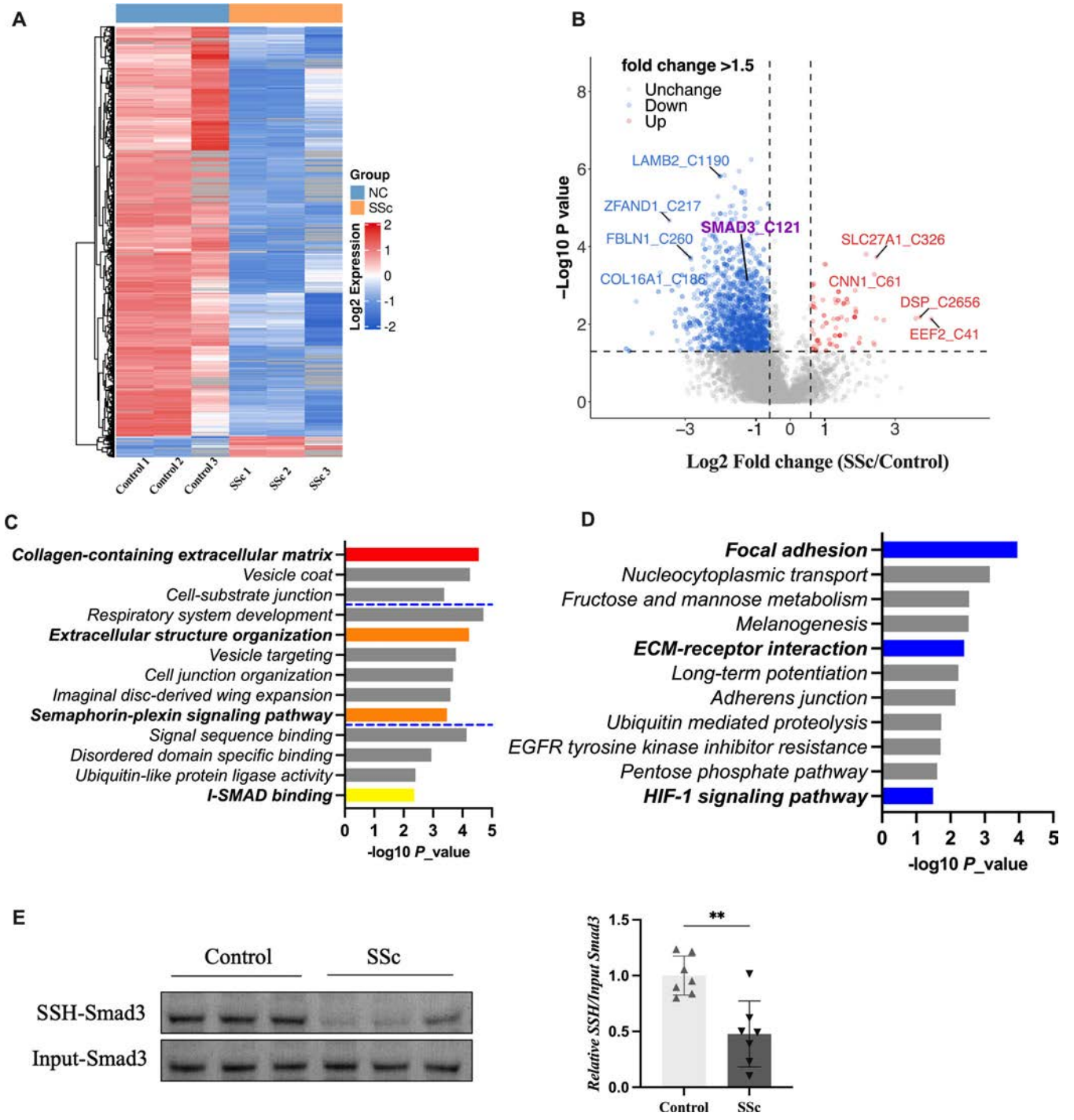

Figure 4. S-sulfhydration is involved in cystathionine γ-lyase-mediated antifibrotic effects in systemic sclerosis (SSc). (A) Heatmap of differentially S-sulfhydrated proteins (n = 3) in dermal fibroblasts from patients with SSc and healthy controls. Color intensity indicates relative abundance, with blue representing lower abundance and red representing higher abundance. (B) Volcano plot of differentially S-sulfhydrated proteins comparing SSc and controls (n = 3). The vertical dashed lines indicate the fold change cutoff (> 1.5), and the horizontal dashed line represents the significance threshold ($P < 0.05$). Representative up-regulated (red) and down-regulated (blue) proteins are highlighted. (C) Gene Ontology (GO) enrichment analysis of differentially S-sulfhydrated proteins, with fibrosis-related GO terms highlighted as follows: cellular component (red), biologic process (orange), and molecular function (yellow; n = 3). Blue dashed lines separate the three GO categories. (D) Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis of differentially S-sulfhydrated proteins. Pathways significantly associated with fibrosis are highlighted in blue (n = 3). (E) Relative levels of S-sulfhydrated Smad3 (SSH-Smad3) in fibroblasts from patients with SSc and controls were analyzed by modified biotin-switch assay combined with Western blotting, with SSH-Smad3 signals normalized to input Smad3 (n = 7). $^{**}P < 0.01$ versus control. NC, healthy control. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/art.70085/abstract.

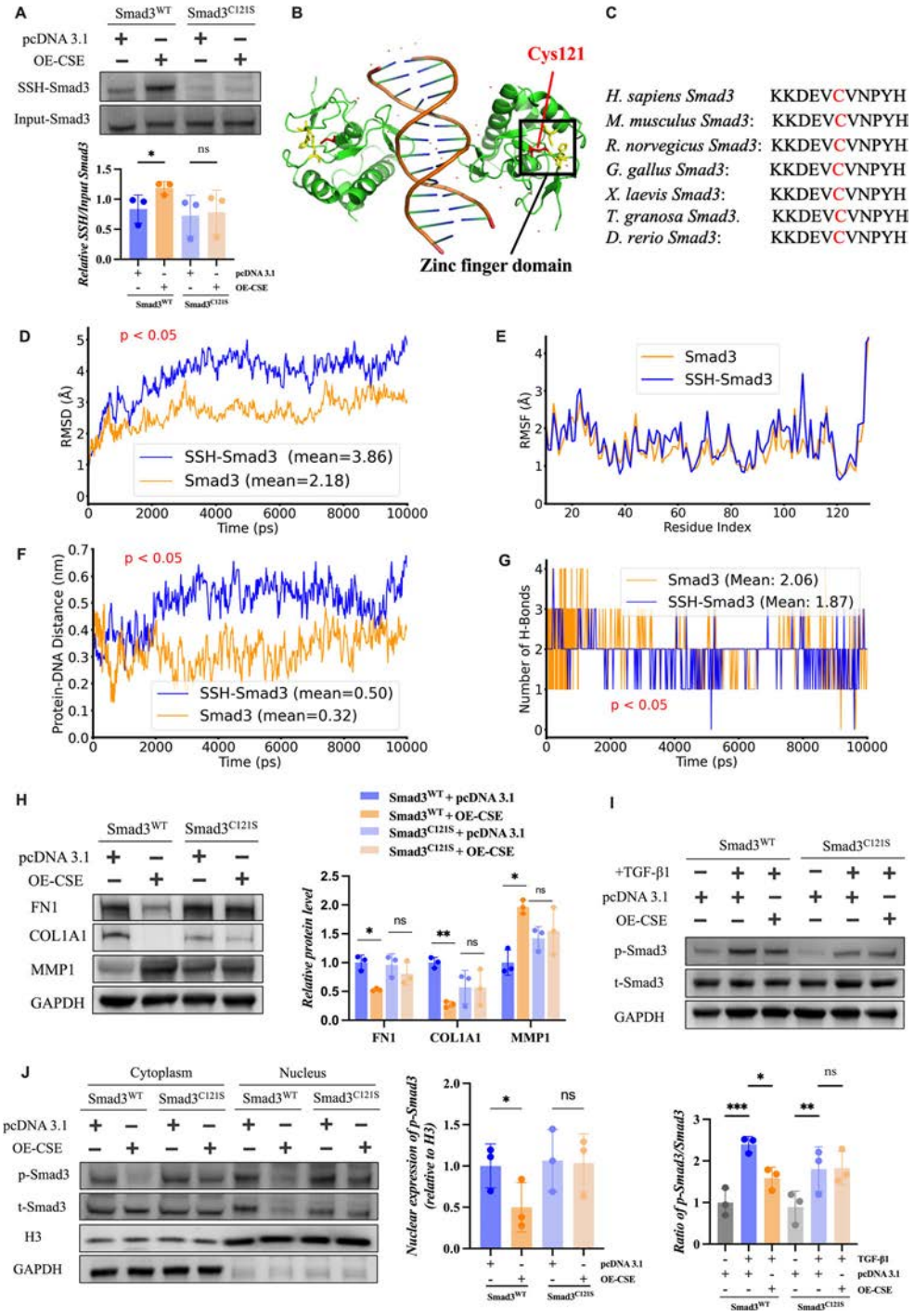

Figure 5. Smad3^{C121} is an S-sulfhydration target critical for cystathionine γ-lyase (CSE) antifibrotic effects. To investigate the structural and functional significance of CSE-mediated S-sulfhydration at cysteine (Cys) 121 of Smad3 (SSH-Smad3), we assessed S-sulfhydrated Smad3 levels, performed molecular dynamics (MD) simulations, and conducted fibroblast validation. (A) SSH-Smad3 levels were assessed in fibroblasts expressing Smad3^{WT} or Smad3^{C121S} following CSE overexpression (OE-CSE, pcDNA 3.1 empty vector control). $P > 0.05$ is nonsignificant (ns); *$P < 0.05$ versus control. (B) Structure of the Smad3 MH1 domain bound to DNA (Protein Data Bank [PDB]: 1MHD). (C) Cys121 of Smad3 is evolutionarily conserved in vertebrates. (D–G) MD simulations comparing SSH-Smad3 and unmodified Smad3 to assess the structural impact of S-sulfhydration. Shown are (D) RMSD (root-mean-square deviation, structural deviations), (E) RMSF (residue fluctuations), (F) protein–DNA distance, and (G) number of protein–DNA hydrogen bonds. (H–J) Functional validation was performed by OE-CSE in fibroblasts expressing Smad3^{WT} or Smad3^{C121S}. (H) FN1, COL1A1, and MMP1 protein levels were quantified by Western blotting (n = 3). $P > 0.05$ is ns; *$P < 0.05$; ** $P < 0.01$ versus control. (I–J) Fibroblasts were additionally treated with transforming growth factor β 1 (TGFβ1) for one hour before harvesting. (I) Smad3 phosphorylation is shown. $P > 0.05$ is ns; *$P < 0.05$; ** $P < 0.01$; ***$P < 0.001$ versus control. (J) Smad3 nuclear localization is shown, with H3 (Histone 3) as the nuclear control (n = 3). $P > 0.05$ is ns; *$P < 0.05$ versus control. p-Smad3, phosphorylated Smad3. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/art.70085/abstract.

dynamics (MD) simulations. Compared with nonmodified Smad3, the root-mean-square deviation (RMSD) of SSH-Smad3 was higher (SSH-Smad3 vs Smad3, 3.8631 Å vs 2.1825 Å, $P < 0.05$), indicating decreased MH1 domain stability (Figure 5D). Consistently, the residue fluctuation plot revealed higher average residue fluctuations in the MH1 domain of SSH-Smad3, particularly after Val60, corresponding to the zinc finger domain (Figure 5E). Smad3–DNA interactions were further assessed by measuring the average protein–DNA distance and the number of protein–DNA hydrogen bonds. Compared to nonmodified Smad3, SSH-Smad3 was relatively further away from DNA (SSH-Smad3 vs Smad3, 0.50 nm vs 0.32 nm, $P < 0.05$) and formed fewer hydrogen bonds with DNA (SSH-Smad3 vs Smad3, 1.87 vs 2.06, $P < 0.05$), indicating reduced DNA-binding affinity (Figure 5F and G). Overall, MD simulation revealed that S-sulfhydration at Cys121 could slightly loosen its structure at the atomic level, which is not conducive to its transcription function.

Based on this, we next examined the functional significance of this modification in the antifibrotic effects of CSE, using fibroblasts expressing $Smad3^{WT}$ or $Smad3^{C121S}$. Upon CSE overexpression, a decrease in COL1A1 and FN1 and an increase in MMP1 were observed in the $Smad3^{WT}$ group. However, these alterations did not occur in the $Smad3^{C121S}$ group, implying that the prevention of ECM deposition by CSE could be dependent on S-sulfhydrated Smad3 (Figure 5H). Notably, the fibroblasts expressing $Smad3^{C121S}$ did not exhibit CSE-induced inhibition of Smad3 phosphorylation and nuclear translocation, compared to fibroblasts expressing $Smad3^{WT}$ (Figure 5I and J). Collectively, these data demonstrated that CSE-induced S-sulfhydration of Smad3 at Cys121 controls its antifibrotic effects.

CSE controls BLM-induced dermal fibrosis in mice. We generated BLM-induced scleroderma mice models to further investigate the effect of CSE on dermal fibrosis in vivo. Mice were infected with AAV-CSE to induce CSE overexpression. PAG administration was used to inactivate CSE. After an eight-week experimental period, compared with controls, the CSE and SSH-Smad3 levels were significantly decreased in BLM-treated mice but were reversed by AAV-CSE administration. PAG treatment decreased SSH-Smad3 levels in the PBS-treated group, but no further significant decrease was observed in BLM-treated mice, likely due to the already extremely low SSH-Smad3 levels caused by BLM treatment (Figure 6A and B). Furthermore, skin histologic analysis showed an obvious dermal thickening and collagen deposition induced by BLM, which were alleviated by CSE overexpression and aggravated by PAG treatment (Figure 6C and D). The above results were consistent with changes in ECM deposition markers in mice with CSE overexpression, including decreased COL1A1 and FN1 and increased MMP1. After PAG injection, although no interesting changes in FN1 and MMP1 were observed, COL1A1 was significantly elevated (Figure 6E). Moreover, immunofluorescence analysis further confirmed that CSE overexpression reduced p-Smad3 expression in BLM-induced skin fibrosis (Supplementary Figure S8), consistent with the biochemical and histologic findings. To further evaluate the in vivo effect of H_2S, we also treated BLM-induced fibrotic mice with Gyy4137. Gyy4137 administration markedly attenuated dermal fibrosis, as evidenced by reduced collagen deposition and decreased dermal thickness in Masson staining (Supplementary Figure S9). Overall, these findings supported a therapeutic effect mediated by CSE on dermal fibrosis in vivo, potentially involving S-sulfhydration of Smad3.

Enhanced CSE ameliorated BLM-induced pulmonary fibrosis in mice. Pulmonary fibrosis is the second most common manifestation of SSc following skin fibrosis. To analyze whether enhanced CSE could alleviate it, we established BLM-induced pulmonary fibrosis mouse model and overexpressed CSE via AAV-CSE infection. After seven weeks, SSH-Smad3 levels were reduced by BLM and promoted by CSE overexpression, in parallel with changes in CSE expression (Supplementary Figure S10A and B). Histologic analysis revealed notable alveolar septum thickening and excessive collagen deposition induced by BLM, which was partially mitigated by enhanced CSE (Figure 6F). Changes in ECM deposition marker expression (COL1A1 and FN1) were consistent with those observed in histology, suggesting that enhanced CSE ameliorated pulmonary fibrosis in vivo (Supplementary Figure S10C and D).

DISCUSSION

SSc is a severe multisystem fibrotic disease with a complex pathogenesis. Elevated serum homocysteine levels in SSc suggest impairment of the CSE/H_2S axis. Here, we confirmed that CSE/H_2S levels were reduced in SSc, closely associated with skin lesion severity, fibroblast activation, and ECM deposition. Proteomics and MD simulation further revealed S-sulfhydration as essential for CSE/H_2S's antifibrotic effects. To our knowledge, this is the first study to emphasize the role of S-sulfhydration in SSc and even in fibrotic disease.

Prior studies have highlighted the role of CSE/H_2S axis in fibrosis, such as its involvement in atrial fibrosis and lung fibrosis through modulation of oxidative stress and endothelial metabolism.[35,36] However, its molecular mechanisms in SSc remain unclear.[37] Here, we demonstrated that CSE silencing or pharmacological inhibition significantly enhanced ECM deposition, characterized by up-regulated COL1A1 and FN1 and down-regulated MMP1. Conversely, CSE overexpression or H_2S donor treatment mitigated fibrotic features in SSc-derived fibroblasts, including reduced ECM deposition, α-SMA expression, and cell migration. Together, these findings strongly support its antifibrotic role in SSc. Notably, given the pleiotropic biologic functions of H_2S, including regulation of mitochondrial integrity,

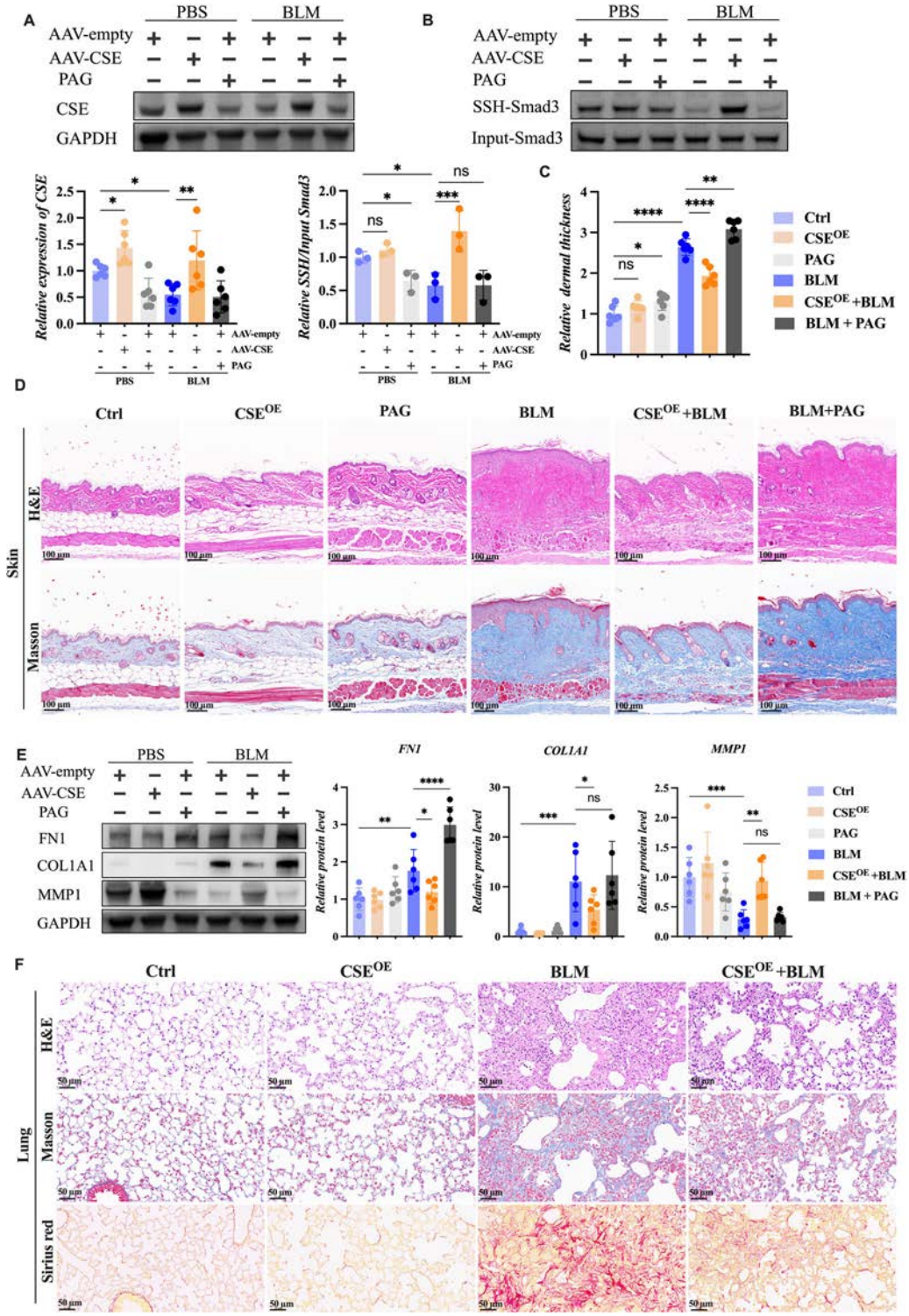

Figure 6. Cystathionine γ-lyase (CSE) regulates bleomycin (BLM)-induced fibrosis in mice. Adeno-associated virus (AAV)-CSE was administered to induce CSE overexpression (CSE^{OE}), with AAV-empty as the negative control (Ctrl); propargylglycine (PAG) was applied to inhibit CSE activity. (A and B) Representative Western blot images and summarized data showing CSE protein levels [(A) n = 6] and S-sulfhydrated Smad3 (SSH-Smad3) levels [(B) n = 3] in murine skin tissues. $P > 0.05$ is nonsignificant (ns); $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$ versus Ctrl or BLM treated alone. (C and D) Skin histopathology and dermal thickness assessed by hematoxylin and eosin (H&E) and Masson trichrome staining (scale bar, 100 μm; n = 6). $P > 0.05$ is ns; $^{*}P < 0.05$; $^{**}P < 0.01$; $^{****}P < 0.0001$ versus Ctrl or BLM treated alone. (E) Western blot analysis comparing FN1, COL1A1, and MMP1 levels in murine skin tissues (n = 6). $P > 0.05$ is ns; $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$; $^{****}P < 0.0001$ versus Ctrl or BLM treated alone. (F) Histologic changes in pulmonary tissues assessed by H&E, Masson trichrome staining, and Sirius red staining analysis (scale bar, 50 μm; n = 6). PBS, phosphate buffered saline. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/art.70085/abstract.

NAD^+ metabolism, and antioxidant responses,[38,39] additional mechanisms beyond S-sulfhydration may also contribute, warranting cautious interpretation of H_2S-donor experiments.

Mechanistically, S-sulfhydration is increasingly recognized as a critical mechanism by which CSE regulates cellular processes. This modification regulates cellular signaling by altering enzymatic activity, protein localization, protein–protein interactions, and protein stability.[40] Studies estimate that up to 30% of cellular proteins could undergo S-sulfhydration, regulating inflammation and metabolism and contributing to maintaining cellular homeostasis.[41] Despite its recognized importance, no studies have investigated the role of S-sulfhydration in fibrogenesis, particularly in SSc. Here, using S-sulfhydration proteomics, we observed a global reduction in S-sulfhydration in SSc fibroblasts, consistent with low CSE expression. Notably, many S-sulfhydrated proteins were enriched in fibrosis-related pathways, aligning with our observation that reducing agent DTT abrogated the antifibrotic effects of CSE. These findings emphasized the necessity of S-sulfhydration in CSE function. However, because DTT is a broad thiol-reducing agent rather than a specific inhibitor of S-sulfhydration, and healthy control and SSc skin samples were obtained from different anatomic sites, these results should be interpreted cautiously.

Among all identified S-sulfhydration targets, Smad3 is of particular interest given its central role in SSc fibrosis, in which its downstream signaling drives myofibroblast activation, ECM deposition, and tissue remodeling.[32] Our findings demonstrated that CSE overexpression suppressed Smad3 phosphorylation, nuclear accumulation, and SBE-driven transcriptional activity, thereby emphasizing that the antifibrotic effects of CSE are closely linked to Smad3 signaling. Importantly, we identified S-sulfhydration of Smad3 at Cys121 as a novel regulatory mechanism in SSc fibrosis. Reduced S-sulfhydration at this site in SSc was restored by CSE overexpression, whereas mutation of Cys121 abolished S-sulfhydration, partly impaired CSE-mediated regulation of Smad3 signaling, and consequently enhanced ECM deposition. These findings highlight S-sulfhydration at Cys121 of Smad3 as a functional target mediating the antifibrotic effects of CSE.

Structurally, Cys121 resides within the MH1 domain of Smad3, a critical region for its DNA binding. The interaction between the MH1 domain and the SBE motif (GTCTAGAC) is stabilized by Cys121 together with Cys64, Cys109, and His126, which together coordinate with a zinc atom to form a zinc finger motif.[42] This motif is redox sensitive and essential for maintaining proper folding and DNA-binding capacity, and oxidative modification of zinc-coordinating residues can lead to zinc release and consequent conformational and functional changes.[43] As observed in zinc finger proteins such as ERR-γ, carbonylation reduced its DNA-binding ability, thereby down-regulating obesity-related genes.[44] Our MD simulations revealed atomic-level structural and dynamic changes in Smad3 upon S-sulfhydration. Combined with our cellular experiments, we surmised that S-sulfhydration at Cys121 could loosen the MH1 domain, impair DNA binding, and thereby attenuate Smad3-dependent transcription and fibrosis. Additionally, the allosteric effect of this modification on Smad3 phosphorylation may be attributed to altered accessibility of its phosphorylation sites, which requires further investigation.

AAV vectors are well-established tools for in vivo gene delivery, with demonstrated safety and long-term efficacy in treating inherited blindness and neurologic disorders.[45] Here, AAV-CSE delivered subcutaneously and intratracheally induced CSE overexpression in murine skin and lungs, mitigating BLM-induced fibrosis. Because prolonged subcutaneous BLM exposure may also cause mild pulmonary involvement, future studies may explore whether the dermal fibrosis model used here exhibits any accompanying lung alterations. Given that the in vivo results were not based on $Smad3^{Cys121}$ mutant mice, we could not rule out the possibility that other mechanisms are involved in CSE-mediated antifibrosis. Furthermore, viral or nanoparticle-based CSE delivery and slow-releasing H_2S donors, such as Gyy4137 or SG1002, may represent promising antifibrotic strategies.

Beyond S-sulfhydration, Smad3 activity is also regulated by other PTMs. For instance, ubiquitin-like modifier (SUMO)ylation at specific lysine residues facilitates Smad3's nuclear anchoring, whereas ubiquitination at the linker region or MH2 domain drives its degradation.[46,47] The crosstalk between S-sulfhydration and other PTMs, especially in fibrosis, warrants further investigation. Notably, our S-sulfhydration proteomics also identified additional promising candidates for future studies.

Thiol modifications represent a complex regulatory network in which S-sulfhydration, S-nitrosylation, and other Cys-based modifications may coexist or interconvert, thereby influencing protein function. For example, S-nitrosylation of EphB2 promotes liver fibrosis, and S- nitrosylated DJ-1 has been implicated in fibrotic regulation.[48,49] Moreover, S-sulfhydration of Smad3 at Cys64 has been shown to reduce its DNA-binding activity in vascular disease,[22] supporting the notion that Smad3 function can be fine-tuned by multiple Cys modifications. In this context, our data identify S-sulfhydration of Smad3 at Cys121 as a key regulatory event in SSc, whereas the potential contribution of additional thiol modifications cannot be fully excluded. Taken together, these considerations emphasize the complexity of thiol regulation in Smad3 and underscore the need to dissect the roles of distinct Cys modifications in SSc.

Notably, SSc fibroblasts exist in a state of oxidative stress, characterized by Nrf2 down-regulation and increased reactive oxygen species (ROS) production, which drive inflammation and fibrosis.[50] Endogenous H_2S and thiol modifications can counteract oxidative stress; for instance, S-sulfhydration has been shown to activate Nrf2, up-regulate antioxidant enzymes such as SOD2, and reduce excessive ROS.[51] These observations suggest that the antifibrotic effects observed in our study may involve redox

regulation and crosstalk with other thiol modifications rather than being solely dependent on the CSE/H_2S pathway.

In summary, we demonstrate that CSE-mediated S-sulfhydration serves as a key antifibrotic mechanism in SSc. Reduced CSE levels lead to decreased S-sulfhydration of Smad3, fine-tuning its structure and amplifying Smad3-dependent profibrotic signaling, thereby promoting myofibroblast activation and ECM deposition and ultimately aggravating SSc fibrosis. Enhanced CSE expression mitigates ECM production both in vitro and in BLM-induced fibrosis models. Notably, we identify Cys121 of Smad3 as the specific S-sulfhydration target, underscoring the therapeutic potential of targeting CSE-dependent S-sulfhydration in SSc.

AUTHOR CONTRIBUTIONS

All authors contributed to at least one of the following manuscript preparation roles: conceptualization AND/OR methodology, software, investigation, formal analysis, data curation, visualization, and validation AND drafting or reviewing/editing the final draft. As corresponding authors, Drs Yaqian Shi and Rong Xiao confirm that all authors have provided the final approval of the version to be published, and take responsibility for the affirmations regarding article submission (eg, not under consideration by another journal), the integrity of the data presented, and the statements regarding compliance with institutional review board/Declaration of Helsinki requirements.

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Impact of Evolving Treatment Patterns on Interstitial Lung Disease Progression in Systemic Sclerosis Using the European Scleroderma Trials and Research Database

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Objective. The treatment landscape for systemic sclerosis-associated interstitial lung disease (SSc-ILD) has evolved with increasingly available immunosuppressive therapies (ISTs) and antifibrotic treatments. However, their real-world use remains unclear. The objective of this study was to analyze treatment trends and the effect of IST and antifibrotic treatments on ILD progression using the European Scleroderma Trials and Research database.

Methods. We included patients with SSc-ILD meeting the 2013 American College of Rheumatology/EULAR criteria with high-resolution computed tomography–confirmed ILD, pulmonary function, and therapy data, grouped into four time periods (≤2006, 2007–2011, 2012–2016, and ≥2017). We analyzed IST initiation, switching, discontinuation, and combination therapy. ILD progression was defined as a decline in the percentage of predicted forced vital capacity of 5% or greater or the percentage of predicted diffusing capacity of the lungs for carbon monoxide of 10% or greater over 12 ± 3 months.

Results. Among 1,409 patients, IST use at first evaluation increased significantly from 13.6% (≤2006) to 57.4% (≥2017) ($P < 0.001$). Mycophenolate mofetil emerged as the most prescribed IST (7% to 57%) ($P < 0.001$). Combination therapy rose from 17.9% to 26.9% ($P < 0.001$), whereas ILD progression rates declined from 21.3% (2007–2011) to 12.1% (≥2017) ($P < 0.001$). In the 2017 and later cohort, logistic regression showed shorter disease duration (odds ratio [OR] 0.991, 95% confidence interval [CI] 0.987–0.996; $P < 0.001$) and myositis (OR 9.9, 95% CI 1.94–51.76; $P = 0.006$) were associated with therapy initiation, whereas switching was higher in patients with a higher modified Rodnan skin score (OR 1.03, 95% CI 1.00–1.06; $P = 0.035$) and in patients with arthritis (OR 3.03, 95% CI 1.55–5.94; $P = 0.001$). Last, combination therapy was associated with younger age, higher dyspnea class, and arthritis.

Conclusion. Our findings reveal a significant evolution in clinical practice. However, continued disease progression emphasizes the need for more effective therapeutic approaches.

INTRODUCTION

Interstitial lung disease (ILD) is a major complication in systemic sclerosis (SSc) and contributes significantly to both morbidity and mortality.[1–3] Over the past two decades, the treatment landscape for SSc-ILD has evolved considerably, with growing recognition of the role of immunosuppression.[4,5] The pivotal Scleroderma Lung Study (SLS) I in 2006 demonstrated the

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benefits of cyclophosphamide (CYC) in stabilizing lung function in patients with SSc-ILD compared with placebo.[6] This was later confirmed by the SLS II in 2016, which not only reinforced the role of immunosuppression but also established mycophenolate mofetil (MMF) as the cornerstone for SSc-ILD given its reduced toxicity compared with CYC.[7] Since then, additional treatment options, including tocilizumab,[8,9] rituximab (RTX),[8,10] and nintedanib,[11] have been investigated. The approvals of tocilizumab by the US Food and Drug Administration in 2021 and nintedanib worldwide in 2019, further impacted the management of SSc-ILD.[12] Furthermore, the results of a randomized controlled trial (RCT) comparing RTX with CYC and a RCT performed in Japan comparing RTX with placebo, which led to the approval of RTX in Japan, have solidified the use of RTX in the armamentarium of SSc-ILD.[8,10] Based on this evidence, the recently updated EULAR recommendation on SSc management suggested four immunosuppressive drugs (MMF, CYC, RTX, and tocilizumab) and one antifibrotic drug (nintedanib) for the treatment of SSc-ILD.[13]

Based on the increasing number of available treatments, several key questions evolve, such as the impact of novel therapies on the treatment landscape, particularly regarding the modification of treatment patterns. Given that disease severity, extrapulmonary involvement, and comorbidities play a crucial role in treatment decisions, understanding their impact on treatment choices over time is critical.[14,15] Moreover, with novel therapies being introduced, it is crucial to determine whether they are truly integrated into clinical practice.[16] Importantly, the increasing treatment armamentarium has major implications for the design of future SSc-ILD RCTs.[17] It is therefore critical to determine the specific treatments currently used and to assess the disease behavior on these treatments. This study aims to provide a comprehensive analysis of the treatment patterns for SSc-ILD using real-life data from the European Scleroderma Trials and Research (EUSTAR) database to generate important and novel insights to shape the design of future SSc-ILD trials, particularly regarding the allowance of background therapy.

METHODS

Study design and population. Patients with SSc from the EUSTAR database fulfilling the 2013 American College of Rheumatology/EULAR SSc classification criteria[18]; with radiologically confirmed ILD based on high-resolution computed tomography (HRCT); available pulmonary function tests, including percentage of predicted forced vital capacity (%pFVC) and percentage of predicted diffusing capacity of the lungs for carbon monoxide (%pDLco); and treatment information at baseline and after 12 ± 3 months were included in the study (EUSTAR CP number 138). The structure of the EUSTAR database and minimum essential data set have been described previously.[19,20]

The study population was segregated into four five-year long distinct cohorts based on the period in which patients were first evaluated and treated. We segregated the periods based on the first evidence-based medications assessed in randomized clinical trials for SSc-ILD, CYC in SLS I, and mycophenolate in SLS 2:

1. ≤2006: pre SLS I study publication.[6]
2. 2007–2011: post SLS I study publication.[6]
3. 2012–2016: pre SLS II study publication.[7]
4. ≥2017: post SLS II study publication.[7]

Each patient was assigned to one of these four periods based on the calendar year of their first EUSTAR assessment (index visit). Patients were then observed longitudinally, but all subsequent visits and outcomes were attributed to that index period.

Data collection and treatment patterns. Data collected included patient demographics (age, sex, disease duration), clinical characteristics (SSc subtype, SSc autoantibody profile, organ involvement), smoking status, and baseline lung function, including %pFVC and %pDLco. Treatment data included type and duration of immunosuppressive therapies (ISTs) and antifibrotic treatments, and treatment modifications (initiation, switching, and discontinuation).

IST included a daily prednisone dose of at least 10 mg, conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) (CYC, MMF, methotrexate, and azathioprine), and biologic DMARDs (bDMARDs) (RTX, tocilizumab, and abatacept). Antifibrotic agents included nintedanib and pirfenidone. The following definitions for treatment modifications were used.

- Treatment switching: change from one therapy to another during follow-up.
- Treatment discontinuation: stopping the primary therapy without initiation of another therapy.
- Unmodified treatment: no change in therapy throughout the study period.
- Combination therapy: the concurrent use of two or more therapies for at least three consecutive months.

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Outcome measures. The primary objective of this study was to assess treatment patterns and patient characteristics of treated patients from before 2006 until today. Treatment patterns included initiation of treatment at patients' first assessment, switches, discontinuations, and combination therapies compared across the four treatment periods. The secondary objective was to assess the impact of ISTs and antifibrotic treatments over a three-year follow-up period on ILD progression. Follow-up for each patient began at the index EUSTAR and ended after the index visit, death, lung transplantation, or the last EUSTAR visit available within that 36-month window at the earliest. Visits beyond 36 months were not considered for outcome analyses. ILD progression was defined as a decline in %pFVC of 5% or greater or a decline in %pDLco 10% or greater over 12 ± 3 months. As subanalysis, we assessed ILD progression in antitopoisomerase-I antibody (ATA) positive patients to enrich for a more severe SSc-ILD cohort and because these patients are preferably included in RCTs.

Contemporary cohort combination therapy analysis. To inform the design of future RCTs we assessed current treatment patterns in patients from the latest, contemporary period (≥2017). The analyses included a detailed description of the different treatment courses with a focus on combination therapies and clinical characteristics associated with treatment initiation, switch, discontinuation, and combination. We defined "treatment course" as any course of therapy with a specific drug or combination of drugs per individual patient. To reduce variability, we applied uniform mapping rules (generic names only; combination defined by ≥3-month overlap) and excluded courses with unresolved inconsistencies.

Statistical analysis. Descriptive statistics were used to summarize baseline characteristics and treatment patterns across the four periods using means ± standard deviations and proportions, as appropriate. Continuous variables were analyzed using analysis of variance for normally distributed data and Kruskal-Wallis tests for nonnormally distributed data. Categorical variables were compared using chi-square or Fisher exact tests, as appropriate. Bonferroni's correction was applied to counteract the problem of multiple comparisons.

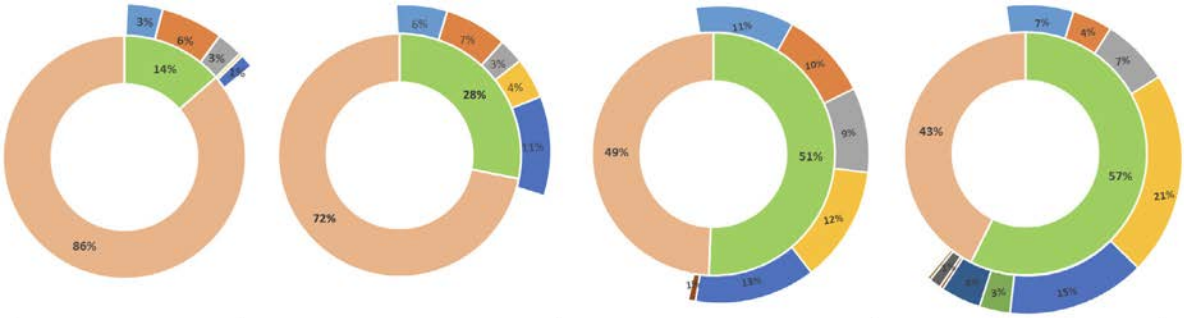
Univariable and multivariable logistic regression analyses with odds ratio (OR) and 95% confidence interval (CI) were applied to analyze the impact of clinical characteristics on IST and antifibrotic therapy introduction, switch, discontinuation, and combination therapy in the contemporary period. Given that our main focus was ILD, candidate baseline variables associated with treatment modifications were selected based on reports from the published literature and expert opinion on the factors associated with severe ILD and/or ILD progression: sex, age, reflux/dysphagia symptoms, SSc subtype, antibody status (ATA, anticentromere antibody, anti-RNA polymerase III antibody [ARA]), baseline %pFVC, baseline %pDLco, disease duration, skin involvement measured by modified Rodnan skin score (mRSS), C-reactive protein elevation, dyspnea class, synovitis, and myositis. Missing data on the candidate predictors were not imputed. Variables were included if missing values were lower than 30%. In multivariable models, variables were selected with a threshold of $P = 0.1$, and 10 events per variable were needed. All analyses were performed using SPSS Statistics version 26 (IBM, Armonk, NY). Missing values were reported but not imputed. A P value of <0.05 was considered statistically significant.

Local ethics committees (when required according to local legislation) of the respective EUSTAR centers approved the collection of data. Data are available on reasonable request. Anonymized data can be shared based on EUSTAR approval and regulations.

RESULTS

Changes in immunosuppressive treatments over time. First, we wanted to assess whether treatment patterns changed over time. A total of 1,409 patients with SSc-ILD were included across the four periods. The mean age at diagnosis was 54.7 ± 9.3 years, and 78.4% of the study population were women. The distribution of patients across the four treatment periods was as follows: (1) ≤2006: 236 patients (16.7%); (2) 2007–2011: 558 patients (39.6%); (3) 2012–2016: 338 patients (23.9%); and (4) ≥2017: 277 patients (19.7%). We found that the use of ISTs increased significantly, rising from 13.6% in the period 1, to 28.1% in period 2, then 50.6% in period 3, and peaking in period 4 with 57.4% ($P < 0.001$) (Figure 1). Antifibrotic therapies were first used in the contemporary period. Across the study periods, novel therapies were progressively introduced, leading to substantial changes in treatments used. MMF increased from 3% in the 2006 and earlier cohort to 24% in the 2017 and later cohort ($P < 0.001$), with 21% of treated patients receiving it as monotherapy. The use of CYC decreased from 18.7% among all ISTs in the 2006 and earlier cohort to 13.8% among all ISTs in the 2017 and later cohort ($P < 0.001$). Azathioprine decreased from 25% among ISTs in the 2006 and earlier cohort to 13.8% in the 2017 and later cohort ($P < 0.001$). Among csDMARDs, MMF was the most common treatment and was used by 29.6% of patients in the 2012 to 2016 cohort, increasing to 45.5% in the 2017 and later cohort ($P < 0.001$). Regarding biologics, RTX was the most used therapy, peaking at 46.4% among biologics in the 2017 and later cohort (see Figure 1).

Switching therapies increased from 2.5% in the 2006 and earlier cohort to 14% in the 2017 and later cohort ($P < 0.001$). The percentage of patients who discontinued therapies rose from 0% in the 2006 and earlier cohort to 24.0% in 2017 and later cohort ($P < 0.001$), whereas the proportion of patients with unmodified treatment decreased from 97.5% in the 2006 and



Treatment	≤2006	2007-2011	2012-2016	≥2017	P-value
IST, n (%)	32 (13.6)	157 (28,1)	171 (50.6)	159 (57.4)	<0,001
Azathioprine, n(%)	8 (3.4)	33 (5.9)	41 (12.1)	22 (7.9)	<0,001
Steroids ≥ 10 mg/d, n(%)	14 (5.9)	40 (7.2)	37 (10.9)	13 (4.7)	0,022
Cyclophosphamide, n(%)	6 (2.5)	16 (2.9)	35 (10.4)	22 (7.9)	<0,001
Mycophenolate,n (%)	7 (3.0)	26 (4.7)	48 (14.2)	66 (23.8)	<0,001
Methotrexate, n(%)	3 (1.3)	64 (11.5)	50 (14.8)	45 (16.2)	<0,001
Tocilizumab, n(%)	0	0	0	10 (3.6)	<0,001
Rituximab, n(%)	0	0	3 (0.9)	13 (4.7)	<0,001
Abatacept, n(%)	0	0	2 (0.9)	1 (0.4)	<0,001
Nintedanib, n(%)	0	0	0	4 (1.4)	0,002
Pirfenidone, n(%)	0	0	0	1 (0.4)	0,364
DMARD, n(%)	23 (9.7)	134 (24.0)	163 (48.2)	158 (57.0)	<0,001
csDMARD, n(%)	23 (9.7)	134 (24.0)	162 (47.9)	145 (52.3)	<0,001
bDMARD, n(%)	0	0	3 (0.9)	28 (10.1)	<0,001
Switch, %	2.5	6.7	8.2	14.0	<0,001
Discontinuation, %	0	3.8	20	24	<0,001
Unmodified, %	97.5	89.5	71.8	62	<0,001
Combination, %	17.9	18.1	19.7	26.9	<0.001

Figure 1. Changes of the treatment landscape of SSc-ILD over time. bDMARD, biologic disease-modifying antirheumatic drugs; csDMARD; conventional synthetic DMARD; IST, immunosuppressive therapy; SSc-ILD, systemic sclerosis-associated interstitial lung disease.

earlier cohort to 62.0% in the 2017 and later cohort ($P < 0.001$). Last, the frequency of combination treatments increased from 17.9% in the 2006 and earlier cohort to 26.9% in the 2017 and later cohort ($P < 0.001$).

The profiles of patients with SSc-ILD over time. Next, we wanted to assess whether the characteristics of SSc-ILD treated patients changed over time. Characteristics of the entire SSc-ILD cohorts across the four time periods were similar except for statistically significant differences in median disease duration, an increase in sine-scleroderma patients, and a significant reduction in patients with myositis (Supplementary Table 1). When analyzing the characteristics of treated patients with SSc-ILD across the last three periods, excluding period 1 because of the limited number of treated cases (n = 32), we observed a significant increase in the median age at treatment initiation from period 2 to period 4 (Table 1). Additionally, patients in period 4 presented lower %pFVC and %pDLco values. A progressive reduction in the prevalence of concomitant inflammatory arthritis was also noted, decreasing from 23.1% in period 2 to 17.9% in period 3 and 12.2% in period 4 ($P = 0.042$). Similarly, the prevalence of myositis declined from 32.0% in period 2 to 17.5% in period 3 and 14.5% in period 4 ($P = 0.038$). An increasing prevalence of ARA positivity was observed, rising from 1.9% in period 2 to 2.4% in period 3 and 8.7% in period 4 ($P = 0.038$) (Table 1). Including treated patients from period 1, we could also confirm a significant increase in the median age at treatment initiation from period 1 to period 4, a significant increase in the percentage of male patients treated (from 9.3% in period 1 to 28.3% in period 4; $P = 0.028$) and a decrease in the rate of patients with concomitant myositis (from 29.0% in period 1 to 14.5% in period 4; $P = 0.038$) (see Supplementary Table 2). The overall rate of deaths (within 5 years since the first evaluation) among treated patients belonging to the four periods was as follows: 1 (3.1%) in period 1; 7 (4.5%) in period 2; 11 (6.4%) in period 3; and 8 (5.0%) in period 4 ($P = 0.803$). Conversely, lung transplantation rates among the same cohorts were as follows: 1 of 32 (3.1%) in period 1; 3 of 157 (1.9%) in period 2; 3 of 171 (1.7%) in period 3; and 1 of 159 (0.6%) in period 4 ($P = 0.660$).

Impact of immunosuppressive treatment patterns on ILD progression. Last, we analyzed the impact of IST and antifibrotic therapies across the different time periods in patients with SSc-ILD on ILD progression. Period 1 was excluded from the analyses given the low number of treated patients. Over a follow-up period of three years, the number of progressive events decreased significantly across the periods; from 115 of 540 (21.3%) in period 2; to 146 of 1061 (13.8%) in period 3; and 160 of 1320 (12.1%) in period 4 ($P < 0.001$), respectively (Figure 2). We conducted the same analyses in ATA-positive patients, enriching for a more severe SSc-ILD cohort. ATA-positive patients represented 56% of the SSc-ILD population across the four periods (136, 311, 185, and 154 patients in periods 1 to 4, respectively). Even in this subgroup, the proportion of progressive events decreased significantly over time, from 73 of 318 (23.0%) in period 2 to 84 of 563 (14.9%) in period 3 and 83 of 654 (12.7%) in period 4 ($P \leq 0.001$).

Table 1. Demographic and clinical features of patients with SSc-ILD treated at first-time assessment across the three periods (total 487 patients)*

Time period	2007–2011 (N = 157)	2012–2016 (N = 171)	≥2017 (N = 159)	*P* value
Age, mean (SD), years	52.1 (12.6)	52.1 (12.8)	55.8 (11.8)	**0.010**
Male, n (%)	34 (21.7)	41 (24.0)	45 (28.3)	0.387
Disease duration, median (IQR), months	55.0 (28.2–115.5)	55.5 (25.0–98.0)	53.5 (18.0–95.0)	0.562
%pDLco, mean (SD)	62.5 (18.6)	55.1 (18.6)	59.4 (19.1)	**0.003**
%pFVC, mean (SD)	87.7 (19.9)	80.5 (19.7)	81.4 (21.0)	**0.006**
Known smoking status	18	122	128	0.258
Ever smoker, n (%)	3 (16.6)	43 (35.2)	47 (36.7)	
Known skin involvement status, n (%)	156	162	79	
Sine scleroderma	3 (1.9)	7 (4.3)	6 (7.6)	0.111
Limited cutaneous	61 (39.1)	69 (42.6)	27 (34.2)	0.456
Diffuse cutaneous	92 (59.0)	86 (53.1)	46 (58.2)	0.549
Stomach symptoms, n (%)	39/156 (25.0)	41/167 (24.5)	35/156 (22.4)	0.876
Intestinal symptoms, n (%)	25/155 (16.7)	27/167 (16.2)	33/156 (21.1)	0.479
Scleroderma renal crisis, n (%)	3 (1.9)	2 (1.2)	1 (0.6)	0.615
Digital ulcers, n (%)	62/138 (44.9)	64/144 (43.7)	69/155 (44.5)	0.918
Inflammatory arthritis, n (%)	36/156 (23.1)	30/168 (17.9)	19/156 (12.2)	**0.042**
Myositis, n (%)	40/156 (32.0)	29/166 (17.5)	23/158 (14.5)	**0.038**
PAH, n (%)	0/29 (0)	1/44 (2.3)	0/33 (0)	0.999
Known antibodies status, n (%)	155	161	148	
Anticentromere	18 (11.6)	13 (8.1)	8 (5.4)	0.192
Antitopoisomerase	95 (61.3)	104 (64.5)	94 (63.5)	0.826
Anti-RNA-polymerase III	3 (1.9)	4 (2.4)	13 (8.7)	**0.038**

* %pDLco, % predicted diffusing capacity of the lungs for carbon monoxide; %pFVC, %-predicted forced vital capacity; IQR, interquartile range; PAH, pulmonary arterial hypertension; SSc-ILD, systemic sclerosis-associated interstitial lung disease.

We then analyzed what modifications were made after the first progressive event among the three cohorts in patients already on ISTs and/or antifibrotic therapy, and we observed that there was a significant increase in combination therapies and switching therapies from period 2 to period 4 (see Table 2).

Current treatment patterns. To characterize the treatment pattern of patients with SSc-ILD in the contemporary cohort, we performed a detailed analysis of patients belonging to period 4 (≥2017). Among 277 patients, 118 were untreated, and among the treated, a total of 377 MMF-based treatment courses were identified. MMF was used as monotherapy in 166 (44%) treatment courses, whereas it was combined with RTX in 143 (38%) courses, with nintedanib in 61 (16%) courses and with tocilizumab in 37 (10%) courses (Figure 3A). In 24 (6.4%) courses MMF was used in triple combination with RTX and nintedanib. Methotrexate was used in monotherapy in 86 (46%) courses; in combination with tocilizumab in 45 cases (24%); with RTX in 40 (21.5%); and with nintedanib in 11 (5.9%) courses. In eight courses (4.3%) methotrexate was used in triple combination (Figure 3B). Rituximab (n = 257) was in the majority of cases used in double combination (175 cases, 68%), with MMF being the most common and only in 50 courses (19%) as monotherapy. In 32 (12%) regimens RTX was used in triple combination (Figure 3C). Last, tocilizumab-based courses accounted for a total of 122 cases with 22 (18%) used as monotherapy. The majority included combination therapies with MTX (45 cases, 36.9%). Triple combination was observed in 24 (9.3%) cases (Figure 3D).

A total of 14% treatments were switched in the contemporary cohort. After switching, a decrease in csDMARD therapies was observed (pre-switch use of 90.1% to post-switch use of 85.5%), whereas an increase in bDMARD therapies was observed from 27% to 51%. The type of csDMARD and bDMARD post switching did not significantly change, with MMF being the most common csDMARD, and RTX the most common bDMARD (see Figure 4).

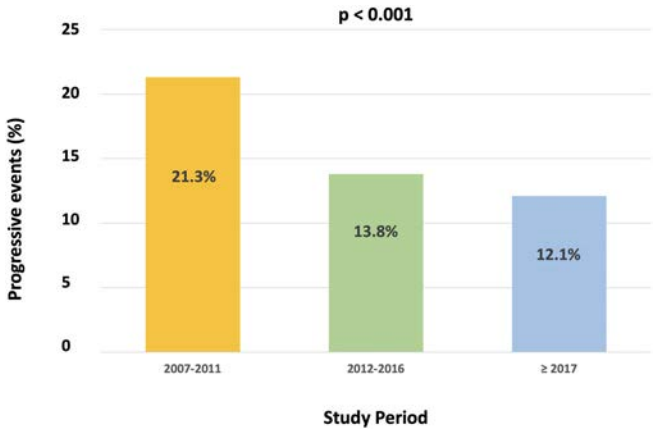


Figure 2. Number of progressive events in patients with SSc-ILD treated with immunosuppressive and/or antifibrotic drugs among the three cohorts segregated by time. SSc-ILD, systemic sclerosis-associated interstitial lung disease. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/art.70043/abstract.

Table 2. Treatment modifications after the first progressive event in patients on immunosuppressive and/or antifibrotic therapy belonging to period 2: 2007–2011, period 3: 2012–2016, and period 4: ≥2017*

Treatment modification	Period 2 (N = 115)	Period 3 (N = 146)	Period 4 (N = 160)	*P* value
Switch, n (%)	11 (9.6)	13 (8.9)	27 (16.9)	**0.049**
Discontinuation, n (%)	6 (5.2)	10 (6.8)	9 (5.6)	0.870
Retained same drug, n (%)	98 (85.2)	121 (82.9)	124 (77.5)	0.238
Combination, n (%)	24 (20.9)	27 (18.5)	52 (32.5)	**0.011**

* Bolded values significant $P < 0.05$.

The impact of clinical characteristics on treatment patterns in the contemporary cohort. We wanted to assess which clinical characteristics influenced treatment choices in the contemporary cohort, so we conducted univariable and multivariable logistic regression analyses (Supplementary Tables 3–6). We identified that shorter disease duration was significantly associated with IST and antifibrotic therapy initiation at the first evaluation (OR 0.991, 95% CI 0.987–0.996; $P < 0.001$). Additionally, the presence of concomitant myositis was strongly linked to IST and antifibrotic therapy initiation (OR 9.934, 95% CI 1.936–51.764; $P = 0.006$). The likelihood of switching treatments was significantly higher in patients with a higher mRSS (OR 1.031, 95% CI 1.002–1.062; $P = 0.035$) and in patients with arthritis (OR 3.034, 95% CI 1.551–5.936; $P = 0.001$). No clinical feature was found to be significantly associated with treatment discontinuation. Throughout the study period, the use of combination therapy was associated with younger age (OR 0.968, 95% CI 0.953–0.985; $P < 0.001$), higher dyspnea class (OR 1.557, 95%

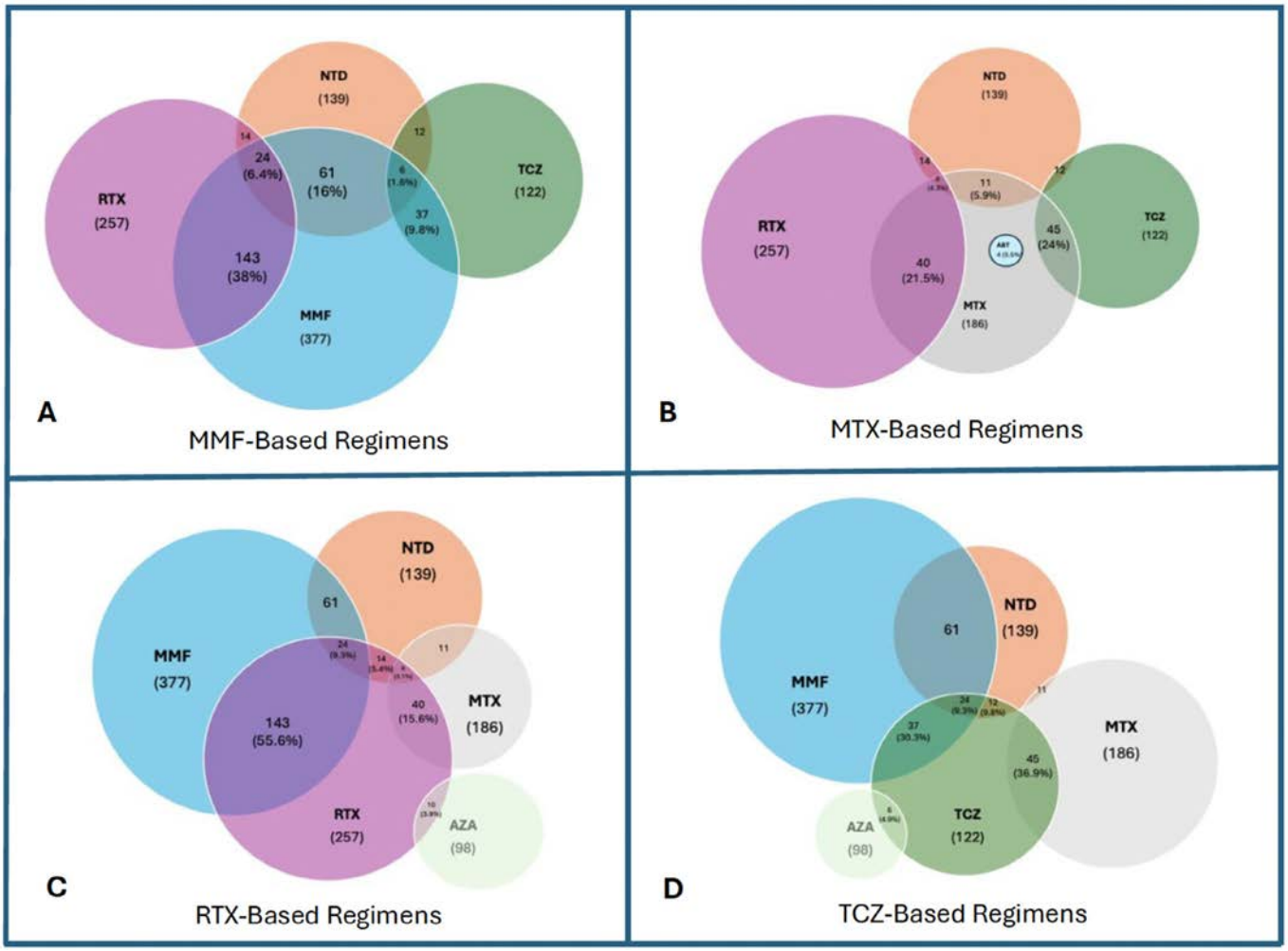


Figure 3. Treatment courses in patients treated in year 2017 or after according to the DMARD-based regimen: (A) MMF-based courses; (B) MTX-based courses; (C) RTX-based courses; and (D) TCZ-based courses. AZA, azathioprine; DMARD, disease-modifying antirheumatic drug; MMF, mycophenolate mofetil; MTX, methotrexate; NTD, nintedanib; RTX, rituximab; TCZ, tocilizumab. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/art.70043/abstract.

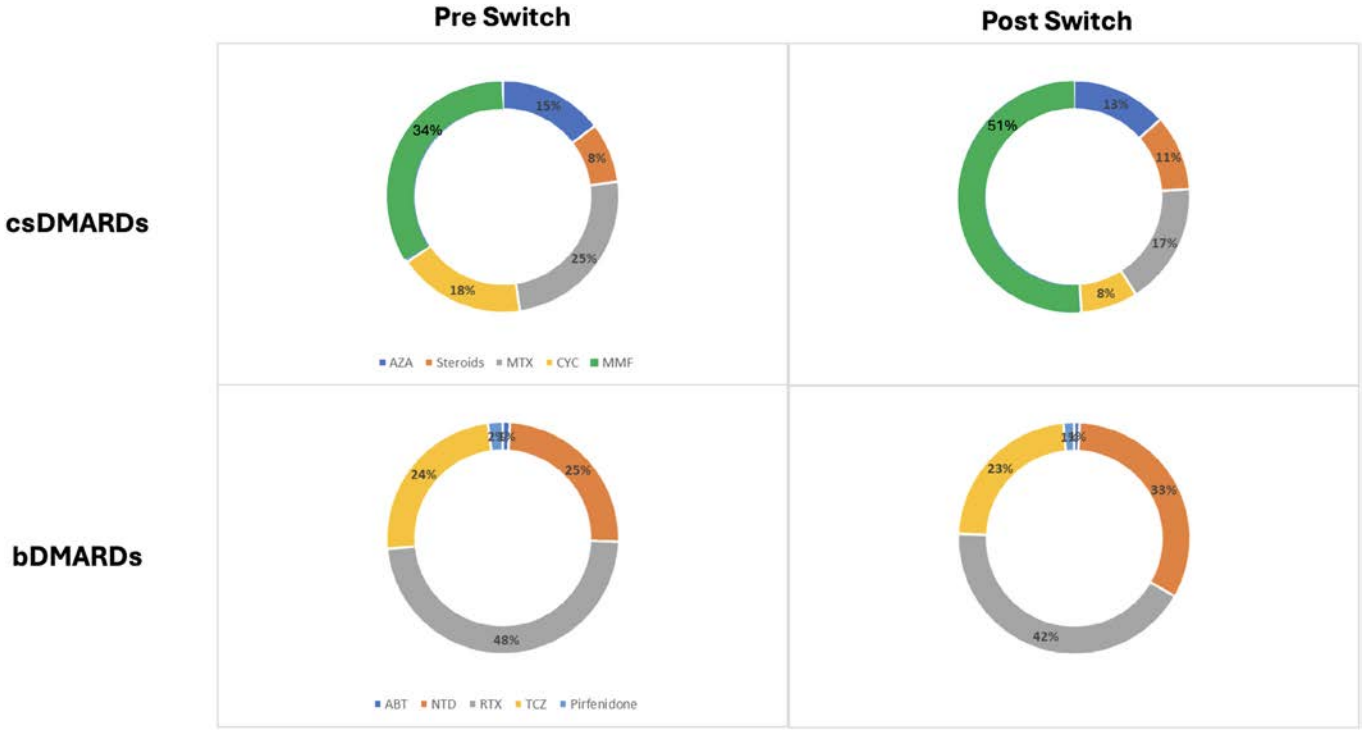


Figure 4. The use of csDMARDs and bDMARDs in patients with SSc-ILD switching therapies in the contemporary period. ABT, abatacept; AZA, azathioprine; bDMARDs, biologic synthetic disease-modifying antirheumatic drugs; cDMARDs, conventional synthetic DMARDs; CYC, cyclophosphamide; MMF, mycophenolate mofetil; MTX, methotrexate; NTD, nintedanib; RTX, rituximab; SSc-ILD, systemic sclerosis-associated interstitial lung disease; TCZ, tocilizumab. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/art.70043/abstract.

CI 1.189–2.039; $P = 0.001$), and inflammatory arthritis (OR 2.560, 95% CI 1.354–4.840; $P = 0.004$).

DISCUSSION

Our study provides novel insights into the change of IST and antifibrotic treatment patterns for patients with SSc-ILD over the past decades using a large and multicenter real-world SSc-ILD cohort from the EUSTAR database. Our findings highlight a substantial shift in clinical practice, showing the integration of new therapeutic agents and evolving treatment strategies that are driven by increasing evidence and expanded therapeutic options.

The first key observation is the significant increase of patients treated with IST and/or antifibrotic treatment since their first evaluation, with a peak reached in the contemporary cohort, in which more than 50% of patients are treated. This trend was already observed in a 2018 EUSTAR study,[21] which showed that although the majority (>70%) of patients with SSc-ILD receive IST at some point, its use was still not widespread, especially in early patients. Watchful waiting and close monitoring were commonly employed in the early stages, with IST initiation typically reserved for patients with moderate lung function impairment. In the present study, we further explored this aspect by analyzing patients at their first evaluation across four distinct time periods, demonstrating how the watchful waiting strategy has been progressively replaced by earlier treatment initiation. Nevertheless, 43% of patients with SSc-ILD still do not receive IST at their first evaluation.

Although the overall patient profile did not change dramatically over time, we observed a progressive refinement in the features of patients initiated on IST and/or antifibrotic therapies based on ILD characteristics in the contemporary cohort. Older patients with SSc-ILD were more frequently started on IST and/or antifibrotic therapy at their first evaluation. At the same time, extrapulmonary involvement—such as inflammatory arthritis and myositis, which may have previously driven treatment decisions—was significantly less represented in the contemporary cohort. Similarly, the prevalence of sine-scleroderma patients within the overall SSc-ILD cohort was lower in more recent diagnoses. This shift reflects a growing understanding of SSc-ILD.[22] This has also been incorporated in the design of the most recent clinical trials focusing on ILD, in which patients regardless of their cutaneous subset are included, such as in the SENSCIS and FIBRONEED-ILD trials.[11,23,24]

We also identified an increasing complexity of treatment regimens, with physicians not only integrating novel therapies such as RTX, tocilizumab, and nintedanib but also increasingly using combination therapies and treatment-switching strategies.

Although minimal variability in visit frequency or completeness of date fields across centers cannot be excluded, the use of predefined structured variables ensured consistency in treatment classification throughout the registry. We observed limited use of nintedanib. This aligns with the study window (2017–2022) of contemporary patients, which overlaps only the initial post-approval years in Europe and the United States, and therefore more likely reflects recent adoption than underuse in current care.

Previous EUSTAR studies partly highlighted that the use of advanced therapies were incorporated in the clinical practice of EUSTAR centers even in combination with other csDMARDs.[25–28] Nonetheless, our study for the first time highlights how these changes have impacted the progression of patients with SSc-ILD and how treatment strategies have evolved over time.

This trend reflects a more tailored, patient-centered approach to SSc-ILD management, allowing for dynamic treatment adjustments based on individual responses. Moreover, our analysis highlights that combination therapies have been preferentially used in younger patients with a higher dyspnea class and concomitant presence of inflammatory arthritis, emphasizing the growing clinical need for intensified therapeutic regimens in young patients who already have pulmonary disability due to the underlying ILD. The increasing use of these strategies underscores the significant unmet need for more evidence for sophisticated and combined approaches, including upfront and sequential combination strategies, to overcome therapeutic limitations and enhance disease control.[29] This appears to be particularly relevant for patients who have already received first-line IST and/or antifibrotic therapy. In those who progressed despite treatment, we observed a significant increase over time in the use of combination and switching strategies. This underscores how physicians are increasingly and proactively adapting treatment for nonresponsive patients, integrating newly approved drugs and/or layering them onto existing regimens.[16] However, the evidence supporting combination treatment regimens—when to modify them and which patients are best suited for such an approach—remains limited. High-quality data are available only from the SENSCIS trial,[11] which evaluated the efficacy and safety of a single combination (MMF and nintedanib).[30] In contrast, the use of nintedanib in combination with other drugs or in triple therapy regimens has been reported only in retrospective studies.[31,32] Furthermore, data on other agents, such as RTX and tocilizumab, are even more scarce[32–36] because major clinical trials did not allow concurrent ISTs.[16]

Our findings also demonstrate that early IST initiation has become standard practice in SSc-ILD management. MMF has emerged as a cornerstone drug, serving as the backbone for many combination regimens with biologics and nintedanib. As shorter disease duration emerged as a predictor for IST and/or antifibrotic therapy initiation at the first evaluation in contemporary patients, this has important implications for the design of future clinical trials. Short disease duration is indeed an inclusion criterion in clinical trials, and given that the majority of patients with SSc-ILD receive IST at their first evaluation, trial design must reflect this reality, ensuring that investigational therapies are evaluated in the context of background treatment.[37] Furthermore, to align with clinical practice and our findings, it is essential to acknowledge the use of various background therapies beyond MMF and nintedanib, including RTX and tocilizumab. These agents are now part of the approved treatment landscape for SSc-ILD and should be considered as background therapies and/or control arms in future trials.[38] Even in the most recent SSc-ILD trials, many of these drugs remain prohibited, with washout periods often required. This may contribute to low patient enrollment rates and an increased number of screening failures.[17]

This crucial aspect should also be interpreted within the broader context that, despite the apparent benefits of evolving treatment strategies, prognosis for patients with SSc-ILD remains unsatisfactory. Although our findings suggest that broader use of treatment may have contributed to reduced short-term ILD progression rates, a substantial proportion of patients still experience disease worsening. This has been observed not only in our analysis but also in previous studies conducted within the EUSTAR network in recent years.[39] They report that 30% of patients experience disease progression annually, regardless of treatment status. Furthermore, in our study, we found that the proportion of patients experiencing progressive events has remained relatively stable, with rates of approximately 14% in period 3 and 12% in period 4. This underscores the urgent need for more effective therapeutic options and treatment regimens, especially because even a 5% decrease in the %pFVC in one year has been shown to be associated with increased mortality.[40]

This study has some limitations. First, the lack of serial HRCT data and the earlier detection of milder disease and/or a more treatment-responsive phenotype over more recent years could contribute to the observed improvements and prevent a direct assessment of radiologic ILD progression, limiting our ability to correlate treatment strategies with imaging-based outcomes.[41] Second, although we examined IST and antifibrotic treatment patterns, we did not assess whether treatment initiation was solely driven by ILD indication or by other SSc-related manifestations. Third, safety data, including adverse events, were not analyzed because side effects are not systematically recorded in the EUSTAR database. Finally, our study does not account for patient adherence or compliance with given therapies, which could influence real-world treatment effectiveness. These limitations highlight the need for future research integrating imaging data, safety outcomes, and adherence metrics to provide a more comprehensive understanding of IST and antifibrotic impact in SSc-ILD. Nonetheless, the ability of EUSTAR to capture real-life practice in many patients with a temporal continuum represents a major strength of our work. It paves the way and is instrumental for the design of future trials.

In conclusion, this study reveals a clear change in the management of SSc-ILD, which is nowadays characterized by treatment initiation at a patient's first evaluation in most patients with SSc-ILD, the widespread use of ILD specific treatment options, and the increasing use of combination and switch strategies. As treatment paradigms continue to evolve, future research must integrate these real-world patterns into clinical trial design and explore novel therapeutic targets to further improve patient outcomes. Despite significant progress, the prognosis for SSc-ILD remains suboptimal, emphasizing the ongoing need for innovative treatment approaches and refined patient stratification strategies.

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AUTHOR CONTRIBUTIONS

All authors contributed to at least one of the following manuscript preparation roles: conceptualization AND/OR methodology, software, investigation, formal analysis, data curation, visualization, and validation AND drafting or reviewing/editing the final draft. As corresponding author, Dr Hoffmann-Vold confirms that all authors have provided the final approval of the version to be published and takes responsibility for the affirmations regarding article submission (eg, not under consideration by another journal), the integrity of the data presented, and the statements regarding compliance with institutional review board/Declaration of Helsinki requirements.

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A Metabolomic Signature Predicts Gout Flare Clinical Outcome Associated With Colchicine Prophylaxis

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Objective. This study investigated that serum metabolomics, before urate-lowering therapy (ULT) initiation, could serve as a biomarker for responsiveness to colchicine prophylaxis in patients with gout commencing treat-to-target ULT.

Methods. We studied a multicenter prospective cohort (n = 409) initiating treat-to-target ULT plus colchicine prophylaxis. Untargeted metabolomics were measured at enrollment. We defined putative colchicine response or colchicine nonresponse as no flare or one or more flares, respectively, during six months after first colchicine dose. Cox regression and machine learning models defined the metabolomic signatures associated with reported flare activity on colchicine prophylaxis in the cohort.

Results. In our cohort, 36.9% participants experienced at least one flare. Many inflammation-related metabolites were differentially abundant in the recurrent flare group and correlated with recurrent flare risk. A significant association was found between a four-metabolite risk score and gout flare activity (adjusted hazard ratio 3.21, 95% confidence interval [CI] 2.24–4.59), independent of the adjusted clinical factors. The machine learning model, which incorporated the top-ranked metabolites selected by multivariable methods with unbiased variable selection along with traditional clinical factors, reached an area under the receiver operating characteristic of 0.771 (95% CI 0.713–0.828) and 0.724 (95% CI 0.611–0.837) for predicting flare risk in the discovery and validation cohort, respectively.

Conclusion. Metabolomic profile–defined inflammation status was associated with gout flare outcomes in ULT initiators receiving colchicine prophylaxis. Identification of these novel metabolomic predictive signatures before ULT could potentially help optimize clinical decision-making for flare prophylaxis colchicine dosing and duration in the first six months after initiation of treat-to-target ULT in gout.

INTRODUCTION

Gout flare is painful, debilitating, and unpredictable. Gout flare is associated with considerable and painful morbidity and with systemic inflammation linked to increased risk of postflare cardiovascular events (myocardial infarction, stroke, and venous thromboembolism).[1,2] Urate-lowering therapy (ULT) initiation promotes an early increase in gout flare frequency in many patients with gout. Oral low-dose colchicine is the first-line anti-inflammatory prophylaxis drug after initiating treat-to-target ULT.[3,4] However, optimal dosing and duration of colchicine flare prophylaxis remain unclear.[5] Furthermore, only approximately 70% of patients have been reported who completely respond to gout flare colchicine prophylaxis. These observations, and the

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potential drug interactions and side effects of colchicine,[6] highlight the unmet need for robust biomarkers to predict therapeutic outcomes of flares when treating hyperuricemia and to individually tailor colchicine regimens.

Predictive factors for gout flares include ULT initiation, patient age, baseline serum uric acid (sUA), monosodium urate (MSU) crystal burden, and the presence or absence of palpable tophus.[7,8] Gout flares induced by ULT initiation are associated with the remodeling and release of MSU crystals at cartilage surfaces and other intra-articular sites as sUA levels decline.[9,10] A recent randomized trial concluded that placebo was not noninferior to colchicine flare prophylaxis.[5] The mean gout flares per month were 0.61 vs 0.35, respectively, during the first six months of dose-titration allopurinol. A network meta-analysis further confirmed the benefit of colchicine prophylaxis, with a reduced flare incidence seen using both fixed-dose ULT and dose titration.[11]

This study explored the potential of metabolomics to provide novel, predictive insights into gout flare risk as a proxy for colchicine response. Dysregulated metabolism is known to modulate both inflammatory responses and the drug's efficacy. Notably, cellular and gut microbiota–derived metabolites can influence the host immune system and have emerged as promising biomarkers in various inflammatory diseases.[12] For instance, the itaconate level has been shown to regulate the anti-inflammatory effects of glucocorticoids.[13] In gout specifically, alterations in bile acid and purine metabolism were linked to differences in flare burden.[14] Hence, we profiled the serum metabolome in a Chinese gout cohort at the initiation of colchicine prophylaxis.

MATERIALS AND METHODS

Study population and design. The multicenter cohort was started in 2019 at the Affiliated Hospital of Qingdao University, Xiang'an Hospital of Xiamen University, and Shanghai 10th People's Hospital separately. The Qingdao cohort and Xiang'an cohort were assigned as the discovery cohort, with the Shanghai cohort as an independent validation set (Figure 1). All participants met the 2015 American College of Rheumatology/EULAR gout classification criteria[15] and the following inclusion criteria: (1) aged between 18 and 70 years, (2) without malignant diseases, (3) estimated glomerular filtration rate (eGFR) >60 mL/min/1.73m^2, and (4) not experiencing an acute flare. Participant data, including demographics, physical examination (subcutaneous palpable tophus), medications, and serum samples, were collected at enrollment. Serum biochemical variables, including sUA, were measured with enzyme colorimetric methods by an Automatic Biochemical Analyzer (Roche, Germany). All the patients started ULT with either febuxostat or benzbromarone based on the treat-to-target principle. Anti-inflammatory prophylaxis with colchicine (0.5 mg twice daily) was prescribed for six months. The study was approved by the Ethics Committee of the Affiliated Hospital of Qingdao University, and written informed consent was provided by all participants.

Participants visited the clinic every two to four weeks or when they developed a flare (for confirmation by a rheumatologist). Study drug discontinuation was confirmed at each visit by asking participants whether they took the drugs as prescribed. The occurrence of a gout flare was validated by two expert rheumatologists. Flares were defined as a clinically evident episode of acute joint inflammation with manifestations of joint pain, swelling, or tenderness.[16] Participants were separated into a recurrent flare group (those who experienced at least one gout flare) and a nonflare group (those who experienced no gout flare) during the six months after the first colchicine dose. People who were lost to follow-up or stopped anti-inflammatory prophylaxis before completing three months were excluded. Patients were censored for the following reasons: an episode of flare, loss to follow-up, discontinuation of colchicine prophylaxis, or the end of follow-up (six months).

Untargeted metabolomics profiling. Untargeted metabolomics assays were performed based on published protocols.[14] In brief, 50 μL of serum samples was mixed with 200 μL ice-cold methanol at 4°C with an internal standard and incubated for 15 minutes. After vortexing and centrifugation for 14,000 revolutions per minute at 4°C, the supernatant was collected. A quality control (QC) sample was prepared by pooling serum samples aliquots. Ultra-high–performance liquid chromatography (Nexera UHPLC LC-30A, SHIMADZU Technologies) coupled to a quadruple time-of-flight mass spectrometer (AB 6600 TripleTOF, SCIEX) was used to acquire data in a data-dependent acquisition mode in both positive and negative ionization modes (Shanghai Applied Protein Technology Co, Ltd). Liquid chromatography separation was performed using Waters ACQUITY UPLC BEH Amide column (100 mm × 2.1 mm, 1.7 μm). The raw data (.wiff files) were converted to mzML format using ProteoWizard software (version 3.0.23132, https://proteowizard.sourceforge.io/). R package "XCMS" was used to perform metabolomics analysis. Tandem mass spectrometry spectra were extracted for each mass spectrometry feature, which were identified using our in-house metabolite database and public database, including Human Metabolome Database, MassBank of North America, MassBank, and Global Natural Products Social Molecular Networking, according to Metabolomics Standards Initiative. Features with coefficient of variation in QC > 30% were excluded. More details about data process were provided in the supplementary materials.

Statistical analysis. Characteristics of the patients were described in both cohorts. For the metabolome-wide, unsupervised principal component analysis (PCA) and supervised orthogonal partial least-squares discriminant analysis (OPLSDA) were performed by R package "MixOmics" "ropls." Differential

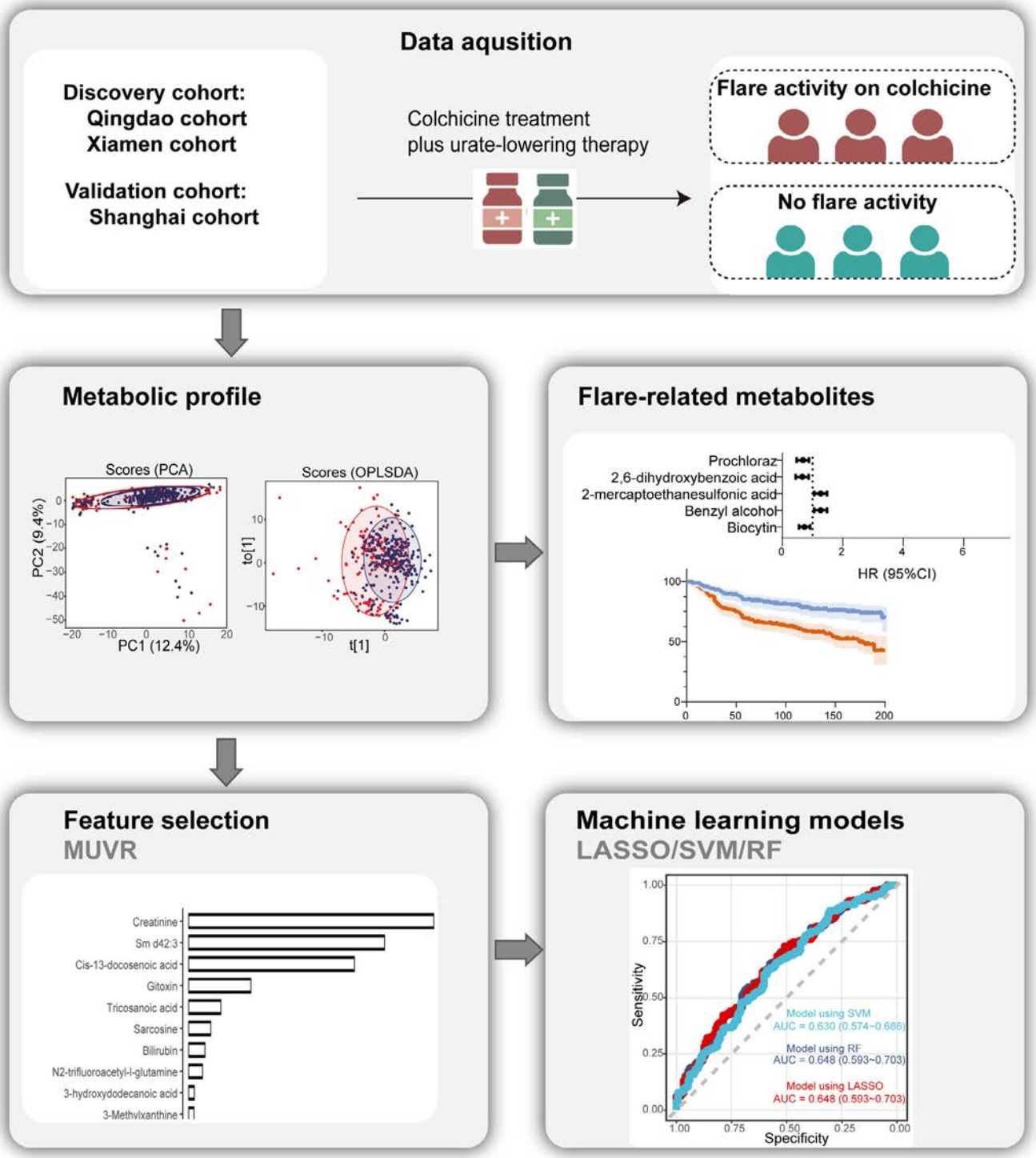

Figure 1. Study design. AUC, area under the operating characteristic curve; CI, confidence interval; HR, hazard ratio; LASSO, least absolute shrinkage and selection operator model; MUVR, multivariable methods with unbiased variable selection; OPLSDA, orthogonal partial least-squares discrimination analysis; PC1, principal component 1; PC2, principal component 2; PCA, principal component analysis; RF, random forest; SVM, support vector machine.

metabolites were initially screened based on an integrated criteria combining a variable importance in projection (VIP) score derived from the OPLSDA model and *P* value from the Mann-Whitney U test. The Benjamini-Hochberg procedure for false discovery rate (FDR) control was used to adjust for multiple comparisons. To investigate cross-talk among metabolic pathways, a global

metabolic network based on Kyoto Encyclopedia of Genes and Genomes was constructed by R package "FELLA." Differential metabolites were used for network analysis, and nodes with $P < 0.05$ were filtered into subnetwork, which was imported to Cytoscape for visualization. Multivariable Cox proportional hazards regression models were performed with adjustment for age, body mass index (BMI), duration of gout, tophus, liver disease, baseline sUA, and flare frequency in the preceding year, and with P values adjusted for multiple testing using FDR. Schoenfeld residuals were used to assess the proportional hazards assumption. A stepwise Cox regression was performed applying the forward selection method based on the likelihood ratio test. Model performance was evaluated using the Harrell's concordance index (C-index) via R package "rms," validated with 1,000 bootstrap repetitions. The patients were grouped by the median risk score, and survival analysis was performed by R package "survminer." The associations between the metabolites and flare frequency during follow-up was assessed using Poisson regression, obtained rate ratios, and 95% confidence interval (CI) per SD change. Metabolomics-based molecular subtyping was performed by hierarchical cluster method.

Biomarker selection was performed with multivariable methods with unbiased variable selection (MUVR). MUVR analysis was performed on all metabolites. We employed 10-fold repeated double cross-validation (rdCV) using the "caret" package in R, enabling robust variable selection and model validation. For the final predictive model, we selected the top five metabolites based on importance scores, defined as those most frequently chosen as predictors across the rdCV iterations. This threshold balanced model simplicity with predictive performance because incorporating additional variables did not yield substantial improvements in classification accuracy during internal validation. Least absolute shrinkage and selection operator (LASSO) regression, random forest, and support vector machine were trained in the cohort. Area under the receiver operating characteristic (AUC) curve was used to assess model performance. Metabolites intensities were normalized to a range of 0 to 1 to construct machine learning models. We conducted sensitivity analyses to evaluate the robustness of our results. First, all missing metabolite values were imputed using half of the minimum observed value. Second, we removed those participants who displayed as outliers in PCA analysis in constructing models. All statistical analysis was conducted in R (version 4.3.1) or SPSS software (version 21.0).

RESULTS

Cohort characteristics. In total, 409 male participants were included in the study (Supplementary Figure 1). Thirty-eight patients were excluded because of loss to follow-up (n = 12) or early discontinuation of prophylaxis (primarily due to common colchicine-related side effects such as diarrhea and nausea) (n = 26) before completing the three-month period. The median follow-up duration was 112 days. In the discovery cohort, 104 participants experienced at least one gout flare, whereas 215 participants did not develop a flare during the follow-up period. The recurrent flare group exhibited a longer duration, more frequent flares in the preceding year, and a higher proportion of palpable tophaceous gout compared with the nonflare group (Table 1). There were no significant differences in other

Table 1. Baseline characteristics between nonflare and recurrent flare group*

Characteristics	Non-flare group (n = 215)	Recurrent flare group (n = 104)	*P* value
Age, median (IQR), years	40 (32–52)	42 (32–55)	0.715
BMI, median (IQR), kg/m^2	27.0 (24.8–29.3)	27.6 (25.6–30.1)	0.080
Duration of gout, median (IQR), years	5 (2–8)	7 (5–11)	<0.001
Flare frequency in the preceding year, median (IQR)	2 (1–3)	2.5 (1–5)	<0.001
Tophus, n (%)	53 (24.7)	47 (45.6)	<0.001
Laboratory measures, median (IQR)			
Serum urate, μmol/L	513 (425–595)	534 (424–596)	0.559
FBG, mmol/L	5.5 (5.2–6.0)	5.5 (5.1–6.0)	0.780
Triglyceride, mmol/L	1.8 (1.3–2.6)	1.7 (1.2–2.4)	0.413
Total cholesterol, mmol/L	4.9 (4.4–5.7)	4.9 (4.3–5.8)	0.852
eGFR, mL/(min/1.73 m^2)	89.8 (76.4–103.5)	92.7 (82.9–106.9)	0.158
Comorbidities, n (%)			
Nephrolithiasis	12 (5.9)	5 (5.3)	0.822
Hypertension	49 (24.1)	26 (27.4)	0.549
Diabetes	5 (2.5)	3 (3.2)	1.000
Coronary heart disease	4 (2.0)	3 (3.2)	0.826
Dyslipidemia	18 (8.9)	7 (7.4)	0.664
Liver disease	19 (9.4)	17 (17.9)	0.035

* For categorical variables, data are presented as n (%) and compared using the chi-square test. For continuous variables, values are presented median (IQR) and compared using Mann-Whitney U test where appropriate. Dyslipidemia includes hypertriglyceridemia and hypercholesteremia. Liver disease refers to alcoholic fatty liver disease and nonalcoholic fatty liver disease. BMI, body mass index; eGFR, estimated glomerular filtration rate; FBG, fasting blood glucose; IQR, interquartile range.

clinical characteristics or biochemical markers between the two groups, including sUA, lipid levels, and eGFR. In the validation cohort, 47 of 90 participants experienced at least one gout flare (Supplementary Table 1).

Metabolic profiles between nonflare group and recurrent flare group. The untargeted platform identified a total of 992 metabolites of known structures. We observed a separate metabolic profile in the PCA and OPLSDA analysis (Figure 2A and 2B) between the nonflare and recurrent flare groups at baseline in the overall cohort. A total of 18 samples (9 belong to recurrent flare and 9 nonflare) with low principal component 2 (PC2) scores were identified as outliers (Supplementary Table 2). They had lower sUA levels but no other notable clinical differences from the cohort. There was a total of 58 metabolites significantly altered between the two groups (VIP > 1, $P < 0.05$) (Supplementary Figure 2). After FDR correction, however, no metabolites remained statistically significant (all FDR > 0.1). These findings indicated that slight changes in the absolute differences from baseline levels may not be sufficient to differentiate the long-term flare risk. Among these nominally significant metabolites, leukotriene B4 was the most markedly elevated (2.8-fold) (Figure 2C) in the recurrent flare group; the amino acids creatine, sarcosine, and L-canavanine were moderately elevated; and the most markedly decreased metabolites were lipids and lipid-like molecules. The dysregulated metabolic networks unraveled by FELLA were involved in amino acid metabolism and inflammation-related signaling pathway (Figure 2D).

Metabolic biomarkers for flare prediction. After adjustment for age, BMI, duration of gout, tophus, liver disease, baseline sUA, and flare frequency in the preceding year, three metabolites (Phe-ile, Phe-leu, and Chelidonic acid) were significantly associated with flare activity (FDR < 0.05) (Supplementary Figure 3, Supplementary Table 3). When a more lenient FDR threshold of <0.2 was adopted in light of the exploratory aims, a total of 13 metabolites were observed. After stepwise selection, a set of four metabolites (nortriptyline, Ile-Val, alfuzosin, and methanone: (6-hydroxy-1-pentyl-1h-indol-3-yl)-1-naphthalenyl) were retained in the final model. We then calculated the metabolite risk score (MRS) by summing their regression coefficients (Supplementary Table 4). Following the exclusion of potential prescribed drug–related metabolites (nortriptyline, terazosin, and alfuzosin) from the 13 candidates, three metabolites continued to demonstrate a significant association (Supplementary Table 5). After adjustment for age, BMI, duration of gout, tophus, liver disease, baseline sUA, and flare frequency in the preceding year, the MRS was significantly associated with flare activity (adjusted hazard ratio [HR] 3.21, 95% CI 2.24–4.59) (Figure 3A). Based on the bootstrap-validated analysis, the combined model integrating clinical variables with the MRS demonstrated improved predictive performance, yielding an optimism-corrected C-index of 0.704 compared to 0.651 for the clinical-only model. Subsequently, the patients were 50/50 split to high-MRS vs low-MRS group according to median risk score cutoff –0.029. Compared to the low-MRS group, a significantly higher proportion of individuals in the high-MRS group experienced flares (Figure 3B). We also investigated the effect of MRS among patients with different baseline flare burdens (defined as infrequent or frequent flare groups according to a flare frequency of <2 or ≥2 episodes in the prior year). The MRS demonstrated a good ability to discriminate flare risk across frequent subgroup but not in the infrequent group (Figure 3C). These findings demonstrate the potential of this metabolite panel to predict flare risk in patients who flared frequently in the last year. For participants with recurrent gout flares, a total of 84 flare cases were documented among 256 participants who had flare frequency data during the follow-up period. After adjustment with age, BMI, duration, sUA, tophus, liver disease, and the flare frequency in the preceding year, nortriptyline, N-oleyl-leucine, and alfuzosin level was significantly associated with gout flare rate (Supplementary Table 6).

To select metabolites to predict flare risk as a proxy for colchicine response, MUVR was used to screen potential biomarkers. After multiple training, all metabolites performed well to predict recurrent flare. According to variables' importance rank (Figure 4A), the top-ranked five metabolites were used to construct the prediction models (LASSO regression, random forest, and support vector machine) (Supplementary Figure 4). Given their similar discriminatory performance, the LASSO model was ultimately selected as the primary model for reporting based on its superior model simplicity, interpretability of results, and potential for clinical translation. Formulas of the LASSO prediction model were shown in Supplementary Table 7. Metabolites (creatinine, Sm d42:3, Cis-13-docosenoic acid, gitoxin, and tricosanoic acid) along with clinical factors (age, BMI, sUA, duration of gout, tophus, and flare frequency in the preceding year) yielded the greatest AUC compared with the metabolites alone (Supplementary Figure 5). Overall, the AUC achieved 0.771 (95% CI 0.713–0.828) in the discovery cohort and 0.724 (95% CI 0.611–0.837) in the validation cohort (Figure 4B). Of note, the addition of traditional clinical variables improved the prediction models based on metabolites.

Sensitivity analyses confirmed the robustness of our main findings. Specifically, the key differential metabolites identified remained consistent when using the data set with half-minimum imputation (Supplementary Table 8). The MRS was significantly associated with flare activity (adjusted HR 3.18, 95% CI 2.20–4.55). The performance of the LASSO model remained

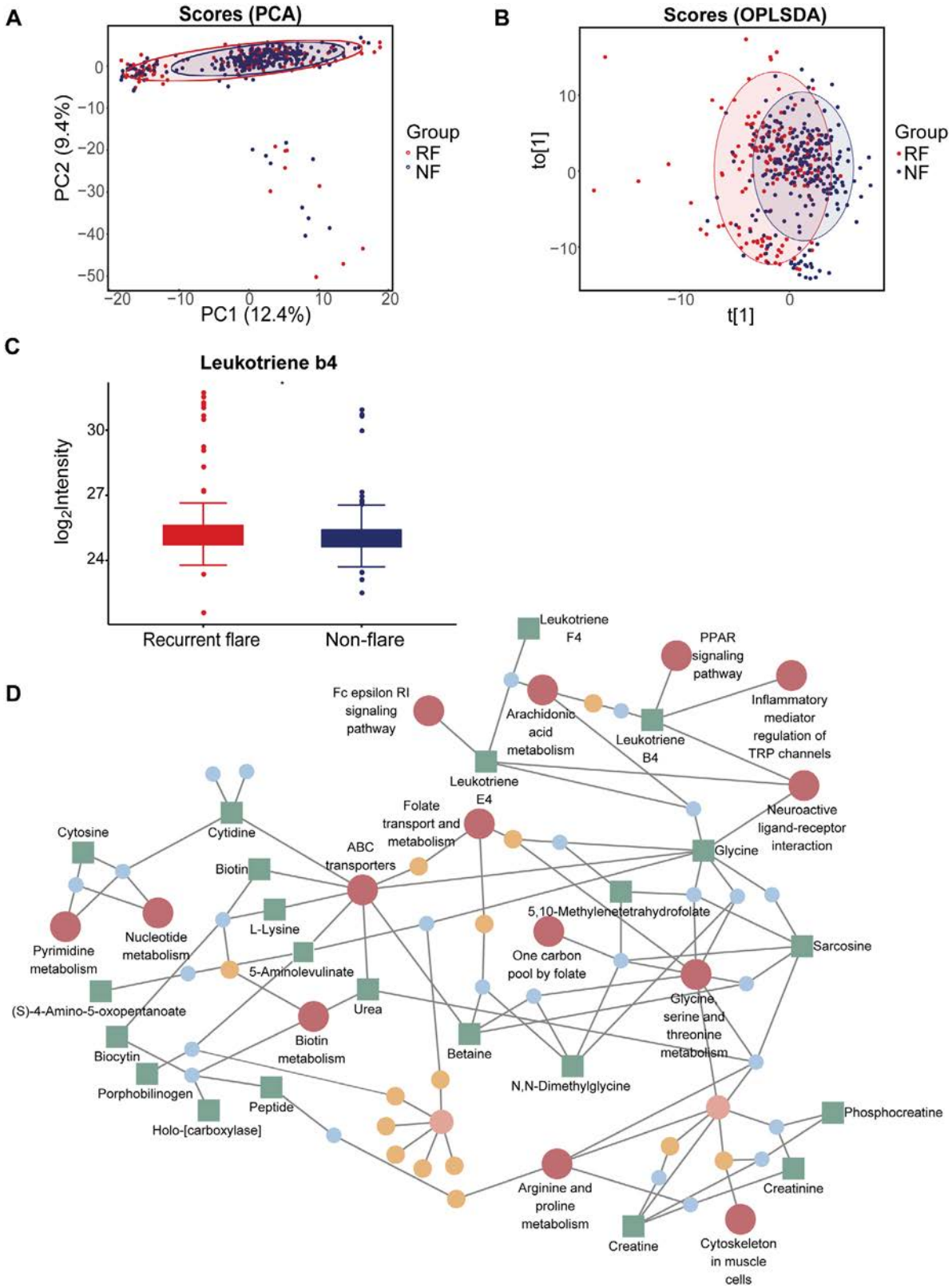

Figure 2. Dysregulation of metabolic profile between nonflare and recurrent flare group. (A) PCA of patients. (B) OPLSDA based on metabolic features. The horizontal axis (t [1]) represents the scores of the predictive component, and the vertical axis (to [1]) represents the scores of the orthogonal component. (C) Expression of leukotriene B4. (D) Subnetwork analysis of significantly disturbed metabolic pathways. The blue, yellow, and orange nodes represent reaction, enzyme, and module, respectively. NF, nonflare group; OPLSDA, orthogonal partial least-squares discrimination analysis; PC1, principal component 1; PC2, principal component 2; PCA, principal component analysis; RF, recurrent flare group. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/art.70094/abstract.

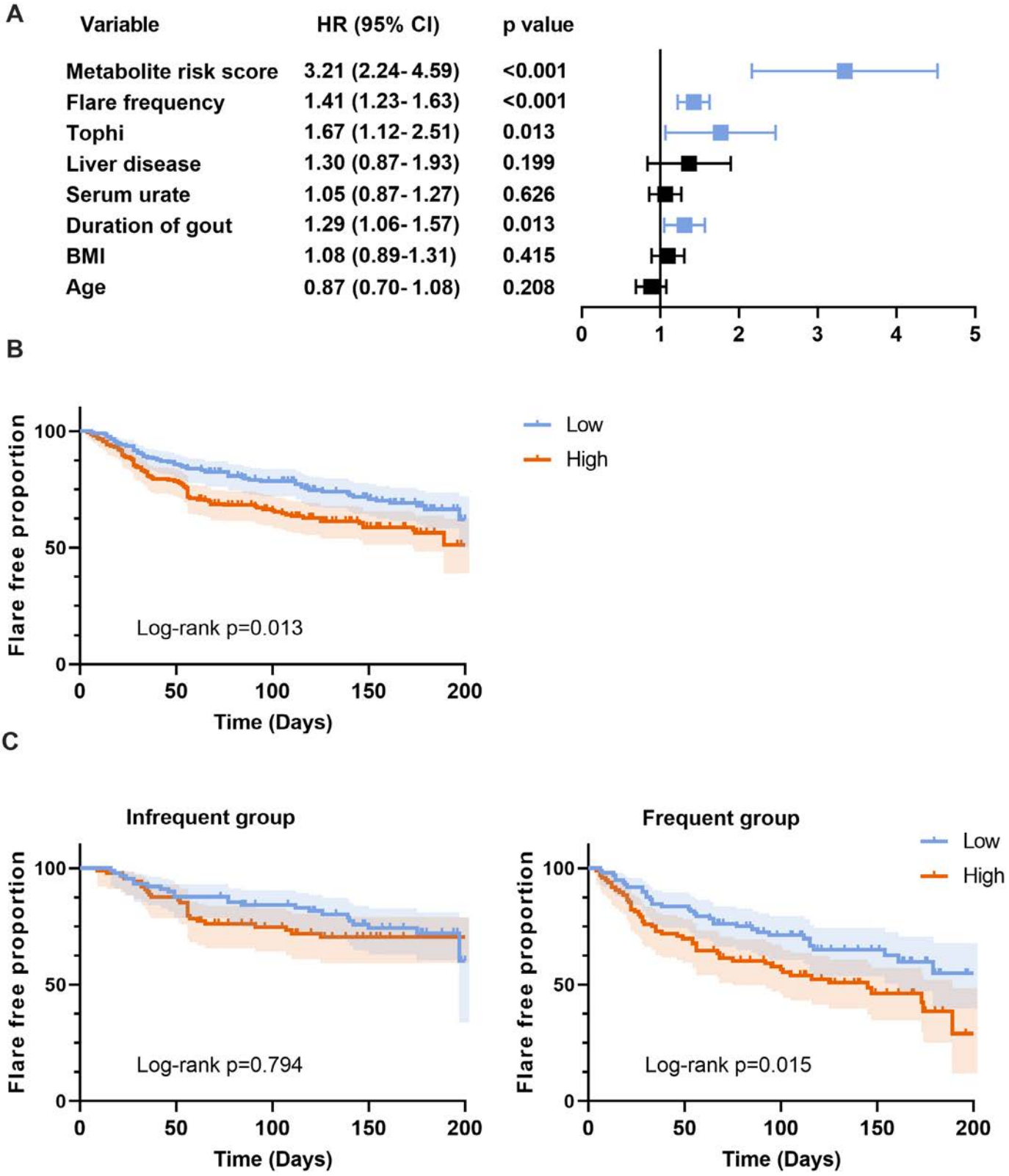

Figure 3. Metabolite risk score associated with flare activity on colchicine. (A) Multivariable Cox regression between variables and flare activity on colchicine. All clinical continuous variables were *z*-score normalization. (B) Kaplan-Meier plots comparing high and low groups of metabolic risk score. (C) Kaplan-Meier plots comparing high and low groups of metabolite risk score in infrequent and frequent flare group at baseline. The high and low score groups were defined based on the median value (–0.029) of metabolite risk score. BMI, body mass index; CI, confidence interval; HR, hazard ratio. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/art.70094/abstract.

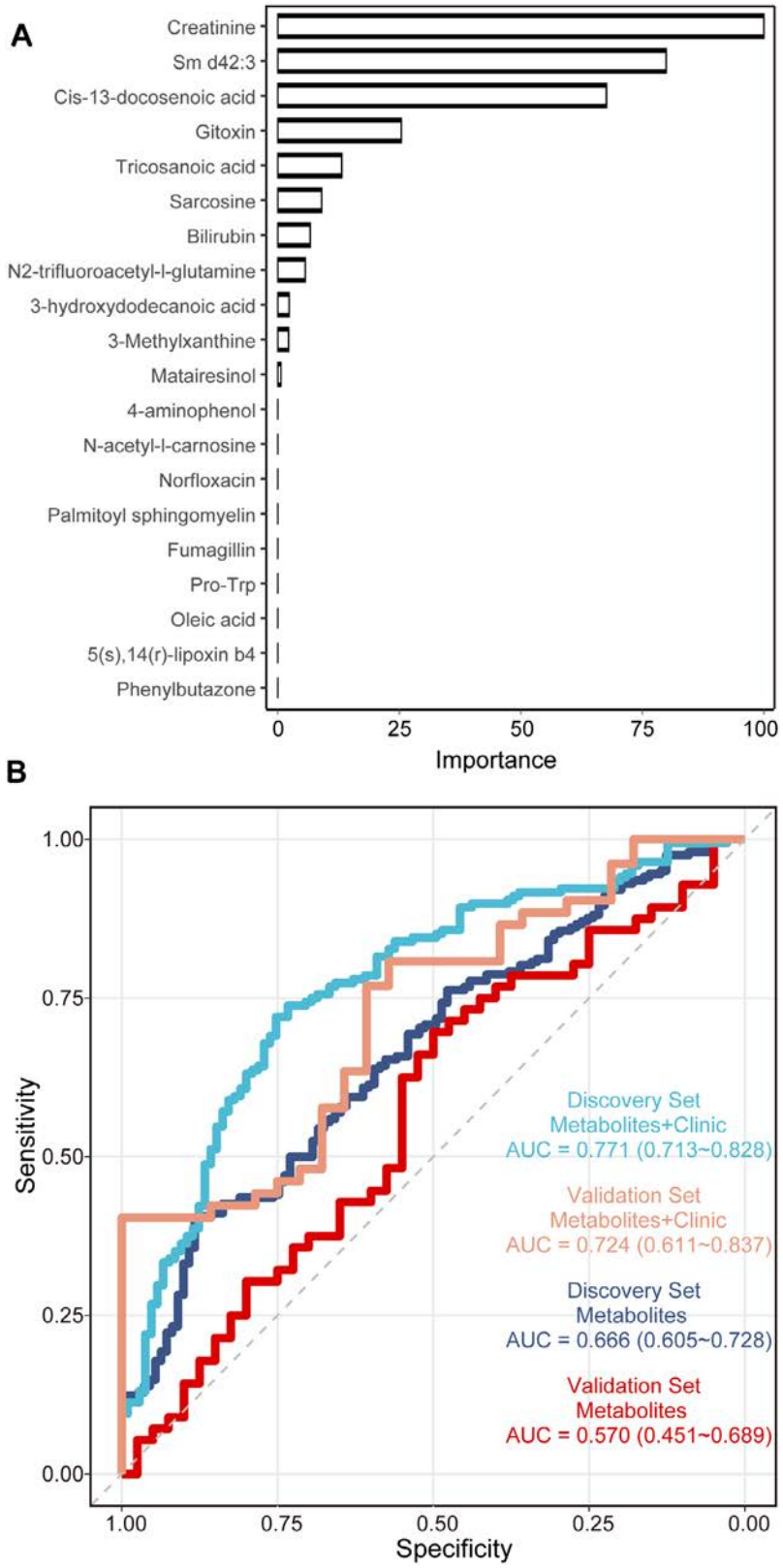

Figure 4. Model performance for flare activity with top metabolites and clinical variables based on least absolute shrinkage and selection operator regression. (A) Importance of top-ranked metabolites derived from the multivariable methods with unbiased variable selection algorithm. (B) Model performance for predicting recurrent flare. Metabolites were creatinine, Sm d42:3, Cis-13-docosenoic acid, gitoxin, and tricosanoic acid. Clinical characteristics were age, body mass index, serum urate, duration of gout, tophus, and flare frequency in the preceding year. AUC, area under the receiver operating characteristic curve. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/art.70094/abstract.

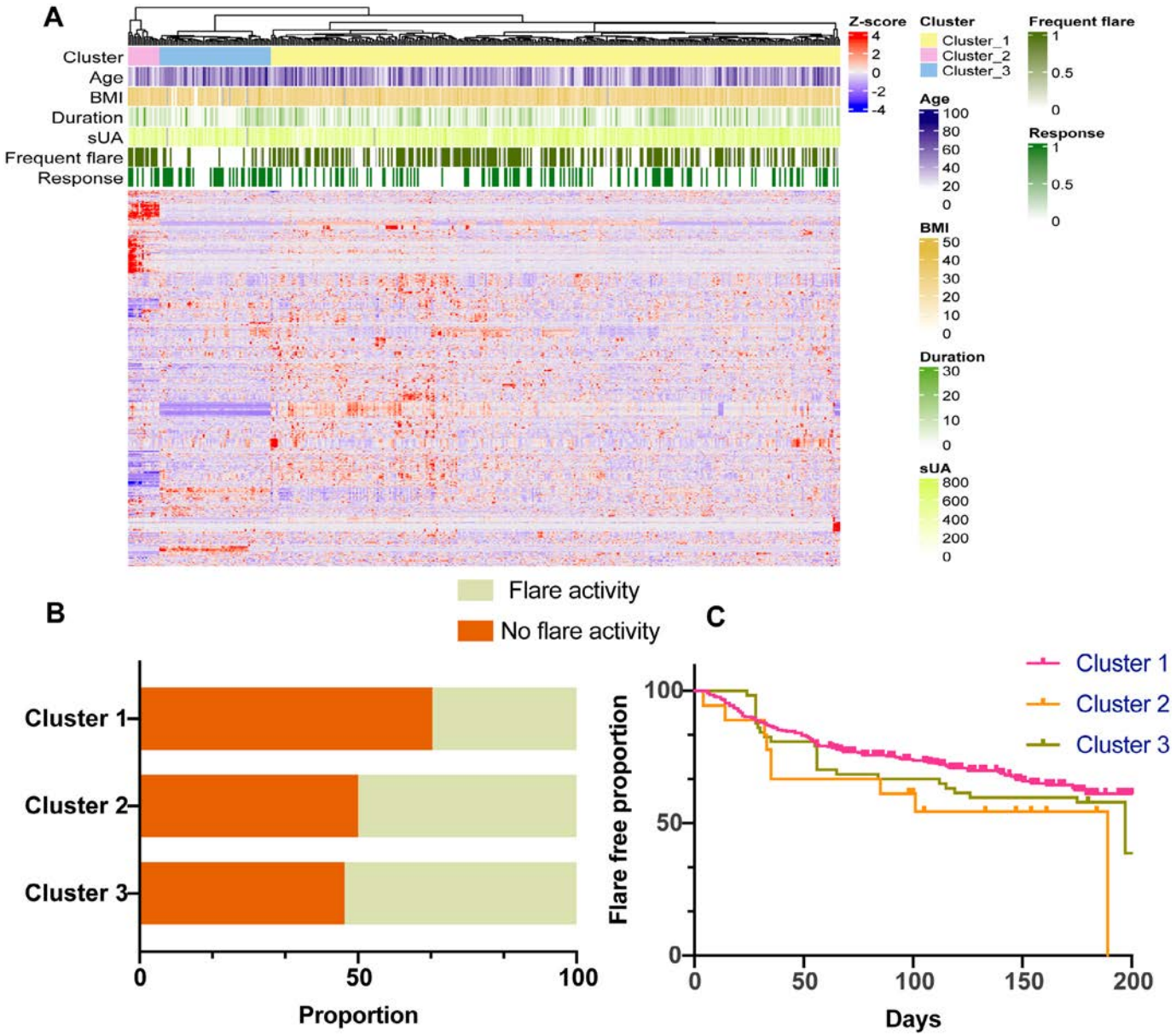

Figure 5. Clustering analysis based on hierarchical cluster. (A) Heatmap analysis among three clusters. (B) Proportion of flare risk among three clusters. (C) Kaplan-Meier plots comparing three clusters. BMI, body mass index; sUA, serum uric acid. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/art.70094/abstract.

stable in the half-minimum imputed data set (Supplementary Figure 6). Furthermore, after removing 18 outlier samples identified in PC2 of PCA analysis, the MRS was significantly associated with flare activity (adjusted HR 3.00, 95% CI 1.82–4.94), and the performance of the LASSO model remained stable (Supplementary Figure 7).

Metabolomics-based molecular subtyping. To stratify patients with gout according to clinical features and outcomes, metabolome data were integrated into three clusters (cluster 1, n = 327; cluster 2, n = 18; cluster 3, n = 64) by hierarchical clustering (Figure 5A). Therapeutic response was thereby investigated. Each cluster exhibited distinct metabolite expression patterns, with cluster 1 the most. Among three clusters, age and sUA level were significantly different (Supplementary Table 9). Flare frequency in the prior year demonstrated notable difference, with 82.4% of cluster 2 experiencing frequent flares (≥2). Flare activity on colchicine prophylaxis also significantly differed (Figure 5B), with cluster 1 showing the best response. However, the time to first flare did not differ among the three clusters (log rank $P = 0.194$; Figure 5C).

DISCUSSION

In this study, metabolomic profiling was divergent between those with no or some gout flare activity with colchicine

prophylaxis within the first months of ULT. Inflammation-related metabolites prospectively emerge as biomarkers of gout flare outcome on colchicine prophylaxis. Moreover, we demonstrate a metabolic risk score and a panel of metabolites to be predictive for early flare activity despite colchicine prophylaxis.

Not all patients initiating ULT develop gout flares, or increase their flare burden from baseline, in the first 2 years of therapy. Here, 36.9% participants experienced at least one flare in the first few months of colchicine prophylaxis, slightly lower than that reported in the STOP gout trial, in which 44.1% experienced at least one flare during 24-weeks follow-up.[7] Prior flare burden, palpable tophus, and urate fluctuation are potential predictors of gout flare.[17–19] The potential relationship between metabolomic signatures and outcomes following colchicine prophylaxis remains unexplored.

In this study, we demonstrate that specific differential metabolomic signatures are associated with early flare activity, including inflammation-modulating metabolites. Certain metabolites and pathways linked here with flare burden on colchicine have previously been implicated in inflammatory diseases and, in some cases, gout. At baseline, leukotriene B4 was significantly increased in the recurrent group, which acts as an endogenous ligand for the nuclear receptor PPARα. It is a phagocyte chemotaxis and activator,[20] increases during acute flares,[21] and is a known target of some anti-inflammatory drugs.[22] These nominally significant metabolites indicated the pathways of PPAR, and amino acid metabolism might have coordinated perturbations preceding colchicine treatment. Further investigation specifically targeting these pathways will provide deeper mechanistic insights. Multiple pathways of amino acid metabolism modulate inflammatory responses.[12] Here, enrichment of metabolites such as Ile-Val was associated with flare burden during colchicine prophylaxis. Level of amino acid metabolites have been shown to serve as a predictor of the incidence of hospitalized gout.[23] Indoles and derivatives [methanone, (6-hydroxy-1-pentyl-1h-indol-3-yl)-1-naphthalenyl], generated in part via gut microbiota tryptophan metabolism, can modulate the host immune system.[24] Based on these metabolites, we constructed an MRS that demonstrated efficacy in identifying high-risk flares, especially for the frequent flare group. This efficacy was further enhanced when integrating MRS with traditional clinical factors.

Our study reveals multiple metabolites are predictive for the risk of gout flare based on machine learning models. Many of these associations have strong biologic plausibility. Specifically, creatinine was a predictive factor for flare activity, reflecting possible regulation of inflammation strongly associated with renal impairment and type 2 diabetes.[25] Cis-13-docosenoic acid known as erucic acid, is a ligand for PPARδ/γ and has anti-inflammatory properties via PPARδ and NLRP3 inflammasome signaling pathway.[26,27] These metabolites demonstrated an ability to predict gout flare risk, aligning with the findings of a recent prospective cohort,[28] whereas this study focused on prophylaxis-modified metabolic signatures in ULT starters. We assessed the predictive value of clinical features and metabolomic signatures alone and their combination. The addition of metabolomic data provided incremental predictive value, a finding that aligns with and is further supported by the results from Cox proportional hazards models.

There are limitations to this study. First, all included participants were men and their treatment assignment was not randomized in our cohort design. In this study, febuxostat or benzbromarone use were predominantly prescribed for urate lowering, which could limit generalizability to the many populations where allopurinol is primarily prescribed (due to marked differences in HLA-B*5801 allele frequency). Moreover, excluding dropouts may limit prediction generalizability. Adverse effects–related dropouts may represent a distinct metabolic subgroup (eg, extreme colchicine metabolizers), suggesting future monitoring incorporating dropout risk stratification. Second, we did not take into account the effects of different ULT regimens on flare risk. That said, a recent post hoc analysis revealed comparable flare risk regardless of ULT type or dose escalation.[7] Third, gout flares are often unreported,[29] which limits studies of this nature. Fourth, although our model predicts flare risk during standardized six-month prophylaxis, its applicability to longer prophylaxis durations (>6 months) or alternative dosing regimens requires validation in independent cohorts. Fifth, we did not account for other potential confounders, nor did we incorporate competing risk or frailty models into our analysis. The potential pathways and metabolites representing promising targets related to colchicine response require further validation. Although single imputation methods such as k-nearest neighbor do not formally propagate imputation uncertainty, the low overall missing rate (most variables <5%) reduces the potential impact. Moreover, the high consistency of outcomes across different imputation methods in our sensitivity analyses supports the robustness of the reported findings.

In conclusion, this study demonstrates that specific metabolites, beyond clinical factors alone, can predict the outcome of gout flare activity within the first months of treat-to-target ULT coupled with low-dose colchicine flare prophylaxis. This predictive capability is particularly evident in patients experiencing frequent flares. A novel metabolomic signature may help to individualize and optimize gout flare prophylaxis therapy in the early period of treat-to-target ULT.

AUTHOR CONTRIBUTIONS

All authors contributed to at least one of the following manuscript preparation roles: conceptualization AND/OR methodology, software, investigation, formal analysis, data curation, visualization, and validation AND drafting or reviewing/editing the final draft. As corresponding author, Drs Terkeltaub and Li confirm that all authors have provided the final approval of the version to be published and take responsibility for the affirmations regarding article submission (eg, not under consideration by another journal), the integrity of the data presented, and the

statements regarding compliance with institutional review board/ Declaration of Helsinki requirements.

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Type I Interferon Signature is Associated With Lung Disease, Drug-Associated Immune Reactions, and Genetic Variation in Interferon-Linked Pathways in Still Disease

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Objective. To evaluate the relationship across type I interferon (IFN-I)–stimulated gene (ISG) expression, Still disease, and the development of lung disease (LD) and drug-associated immune reactions (DAIR) to interleukin-1 (IL-1) and/or IL-6 inhibitors.

Methods. Whole blood ISG expression was quantified by NanoString array. ISG-28 scores were calculated in consecutive patients with Still or Still-like disease. Exome sequencing with family-based variant prioritization identified candidate genes harboring rare candidate causative variants. Lists of candidate genes were subjected to functional enrichment analysis.

Results. Among 57 patients (32 children, 25 adults), 16 had elevated ISG-28 scores. This group exhibited higher prevalence of LD (0.44 vs 0.1, $P = 0.007$) and DAIR (0.63 vs 0.17, $P = 0.003$) and lower IL-6 inhibitor use (0 vs 0.25, $P = 0.048$) compared to others. No significant differences were found in the rates of macrophage activation syndrome, active disease, elevated IL-18, or current IL-1 inhibition. The combination of HLA-DRB1*15 with high ISG-28 scores is associated with LD and DAIR with high specificity, whereas absence of both biomarkers had high negative predictive value. Candidate genes from high ISG-28 individuals were enriched in IFN-related pathways, including autophagy, IFN-I production, toll-like receptor signaling, macrophage activation, cytoskeletal organization, and responses to stress.

Conclusion. High IFN-I expression correlates with LD and DAIR in Still disease, linked to rare genetic variation in immune pathways. Combining high ISG-28 with HLA-DRB1*15 significantly improves post hoc stratification of patients for these complications. If prospectively validated, these findings may guide molecular risk assessment and targeted therapies, including IFN-I directed treatments in Still disease with IFN-I signature.

INTRODUCTION

Still disease is a severe inflammatory condition that affects people of all ages. In children, it is classified by the International League of Associations for Rheumatology (ILAR) as the systemic subtype of juvenile idiopathic arthritis, whereas the adult form is called adult-onset Still disease (AOSD).[1,2] International efforts have recognized that together, they compose a spectrum of the same disorder, collectively referred to as Still disease.[3] Regardless of age, the disease is characterized by recurrent episodes of high-

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spiking fever, a classic evanescent salmon-colored rash, arthralgia or arthritis, generalized lymphadenopathy, hepatosplenomegaly, and serositis.[1–3] Up to 20% of the cases can be complicated with macrophage activation syndrome (MAS), a life-threatening form of secondary hemophagocytic lymphohistiocytosis.[3]

Historically, Still disease did not manifest clinically apparent lung involvement, outside of a few isolated case descriptions.[4] That changed in the early 2010s, when reports of severe cardiopulmonary complications emerged in patients with Still disease, with an initial mortality rate approaching 70%.[4–7] Characterized mainly by septal thickening, pulmonary alveolar proteinosis with significant clubbing, and/or pulmonary arterial hypertension (PAH), these patients differed from the isolated cases described in the literature in their character, as well as their prevalence and severity. Risk factors for the development of lung disease (LD) included onset before two years of age, high levels of interleukin-18 (IL-18), recurrent episodes of MAS, presence of trisomy 21, and carriage of HLA-DRB1*15 alleles.[4–6,8]

It was also observed that almost all patients with LD had been treated with biologic drugs targeting IL-1 or IL-6. Notably, these patients had much higher-than-expected rates of adverse drug reactions to anakinra, canakinumab, and tocilizumab. Up to a third of the patients who received tocilizumab experienced anaphylaxis, a term that encompasses clinically indistinguishable IgE and non-IgE mediated reactions.[5,6,9] Other features atypical of Still disease, such as fixed, pruritic rash and eosinophilia, were also highly prevalent among patients with LD. Retrospective studies discovered that a subset of patients with Still disease treated with these drugs, including almost all patients with LD, developed a group of symptoms that were classified as drug reaction with eosinophilia and systemic symptoms (DRESS).[6,8,10] Although the mechanism underlying this group of features is unknown, two main hypotheses have emerged: the drug reaction hypothesis and the cytokine plasticity hypothesis.[11] The first proposes that LD represents an extreme feature of drug reactions to IL-1 and IL-6 inhibitors. The second proposes that LD and the constellation of anaphylaxis, injection site reactions, peripheral eosinophilia, and pruritic eruptions result specifically from the inhibition of IL-1 or IL-6, via compensatory cytokine shifting toward Th2 responses. Acknowledging the lack of consensus about the origin of these features but wishing to establish a unifying term to describe this unique combination of immediate and delayed-onset signs and symptoms, we will henceforth refer to these as drug-associated immune reactions (DAIR). Regardless of the underlying mechanism, the association between DAIR and the development of LD has been demonstrated in multiple studies.[5,6,10,12–14]

It has also been repeatedly illustrated that both the development of LD and DAIR are strongly associated with HLA-DRB1*15 alleles.[8,10,12–14] It is increasingly recommended to screen patients for this allele to identify those at high risk for LD and complications.[8,12,15,16] However, it is also recognized that not all patients with his HLA type develop LD, and approximately 20% of patients with LD do not have the risk allele, suggesting that other mechanisms beyond this genetic risk factor are at play. There is an urgent need to identify factors that contribute to the risk of developing LD and DAIR to identify the patients at the highest risk and to find alternative therapeutic options.

Although previous studies have suggested that interferons (IFNs) might play a role in the pathophysiology of Still LD,[5,7,17] most of them have focused on the role of type II IFN (IFN-II), with less attention paid to a potential role of IFN-I. In this study, we aimed to evaluate the role of IFN-I in a cohort of children and adults with Still disease.

PATIENTS AND METHODS

Study design. The study cohort included consecutive enrollees in a natural history study of Still disease at the NIH between July 2017 and April 2023. Participants were self-referred or referred by their primary rheumatologists, meeting the ILAR criteria for systemic juvenile idiopathic arthritis (sJIA),[1] meeting the Yamaguchi et al criteria for AOSD,[2] or seeking evaluation of Still-like conditions without fully meeting these criteria (henceforth, collectively referred to as Still disease). Exclusion criteria for enrollment in our protocol included inability to provide informed consent (either by the patient or by a parent or guardian) or the presence of any medical condition that, in the opinion of the investigators, would confuse the interpretation of the study. Visits were scheduled at the convenience of the patients and were not timed to any specific clinical scenario (such as flares or disease onset). Although there was no prohibition of any specific therapy, participants were not brought to the clinic while clinically unstable. Clinical and laboratory data were collected from the enrollment visit. If blood samples were not obtained at the enrollment visit, clinical data from the first study visit with a corresponding blood sample were substituted.

Clinical data. Clinical and demographic data were collected using a standardized data collection form. Demographic data included age at disease onset, age at visit, disease duration, biologic sex, and current medication use. Race and ethnicity were self-reported and selected from a fixed set of categories. Disease activity was measured by the Systemic Juvenile Arthritis Disease Activity Score 10 (sJADAS10) collected at the time of the visit.[18,19] Disease activity cutoffs included active disease (sJADAS10 > 2.9), moderate disease activity (sJADAS10 > 10 and ≤ 20.6), and high disease activity (sJADAS10 > 20.6). Cases in which patient global scores were missing were not included in the analysis of sJADAS10 as a continuous variable; however, these cases were included in categorical analyses of disease activity if their values would fall within a specific category regardless of their patient global score. High-dose steroid therapy was defined as ≥20 mg of prednisone equivalent in adults, ≥0.5 mg/kg

in children, or intermittent intravenous steroids. MAS was defined by the 2016 Ravelli et al criteria,[20] and subclinical MAS was defined as hyperferritinemia >1,000 μg/L with elevated liver enzymes. All cases were reviewed retrospectively for LD, defined as the presence of diffuse interstitial LD identified by reports of thoracic computed tomography, PAH measured by echocardiogram or cardiac catheterization, or significant abnormality on pulmonary function testing without other known explanation. All cases were retrospectively reviewed for DAIR to IL-1 and IL-6 inhibitors, here defined as the development of anaphylaxis to IL-1 and IL-6 medications, severe injection site reactions that led to discontinuation of a drug, or the development of a generalized pruritic eruption upon drug initiation or upon tapering steroids while on drug (for cases in which the medication was initiated in the setting of high-dose steroid therapy). Participants in whom pruritic eruptions were present at initial presentation were included in this group if they experienced marked worsening or change in characteristic of the rash upon exposure to the medications. Other information collected about DAIR included the development of the following while on IL-1 or IL-6 inhibitors: absolute eosinophil count (AEC) >500 or >1,000, elevated liver enzymes more than two times the upper limit of normal without another explanation, development of MAS while on medication, and maximum eosinophil count while on medication.

Biomarkers. Expression of IFN-stimulated genes (ISGs) was quantified in whole blood RNA using custom NanoString assays normalized by housekeeping gene expression. IFN-I signature was measured as ISG-28 scores, calculated by the geometric mean of 28 genes (Supplementary Table 1).[21,22] IFN-II signature was measured by *CXCL9* expression.[22] IL-18 and CXCL9 levels were measured by Olink Target 48 cytokine panel. Samples exceeding the assay limit of detection (15,461 pg/mL) were diluted and reanalyzed. Samples with discrepant results after dilution were excluded from analysis. HLA-DRB1*15 alleles were either determined by clinical next generation sequencing or extracted from exome sequencing data using HLA-LA (version 1.0.4).

Exome sequencing. Participants and their parents had exome sequencing performed by Otogenetics Corporation (Atlanta, GA) using Agilent (Agilent Technologies, Santa Clara, CA) capture kits and Illumina HiSeq 2500 (Illumina, San Diego, CA) sequencers. Variant calling was performed with an in-house variant discovery pipeline modeled after the Genome Analysis Toolkit (GATK) best practices (Broad Institute) for identifying germline short variants (single-nucleotide polymorphisms [SNPs] and indels). Paired-end reads in FASTQ format from each DNA sample were processed according to the GATK data preprocessing guideline. The reads were aligned to human reference genome hg19 using Burrows–Wheeler Aligner and underwent data cleanup to remove sequencing biases with Picard. Variant calling was done based on the GATK best practice for germline short variants (SNPs and indels). HaplotypeCaller was used to produce per-sample Genomic Variant Call Format (GVCF) files. Per-sample GVCFs from the HaplotypeCaller were jointly called to generate multisample VCF files using GATK CombineGVCFs and GenotypeGVCFs tools, and variants were annotated using ANNOVAR. Variants were manually reviewed by expert bioinformatician (ZD) to exclude poor quality variants (eg, strand bias, low read count) and variants in genes that are not reliable for short read sequencing.

Pathway analysis. Family-based variant prioritization of rare (minor allele frequency < 0.01) de novo, recessive (homozygous or compound heterozygous), and X-linked variants was used to generate a list of candidate causative variants for further analysis. Additionally, genes containing biologically relevant rare variants were added to the candidate list. For functional enrichment analysis, overrepresentation analysis (ORA) was performed with the Web-based Gene Set Analysis Toolkit (WebGestalt) (2024 version)[23] to examine gene ontologies (biologic process, cellular component, molecular function), pathways (Kyoto Encyclopedia of Genes and Genomes, Reactome, Panther), diseases (Online Mendelian Inheritance in Man), phenotypes (human phenotype ontology), and the Hallmark50 gene sets. The Benjamini–Hochberg method was used for adjusting for multiple comparisons. Categories were included if they had between 5 and 2000 analytes. When necessary, redundancy reduction was performed with the weighted set cover method. A complementary analysis of gene ontology–biological process (GO:BP) was performed using Enrichr.[24]

Statistical analysis. Continuous variables were summarized by reporting the median and interquartile range (IQR). Categorical variables were reported by count and proportion. Relationships between continuous variables were evaluated with Spearman's correlation. Relationships between categorical variables were evaluated by two-tailed Fisher exact test, with the significance level set at 0.05. Relationships between continuous and categorical variables were evaluated with Mann–Whitney U test. Statistical analysis was performed in R (version 4.3.2; The R Foundation). Figures were generated in R using ggpplot2 (version 3.5.0).

Ethics approval. All study procedures were performed in compliance with relevant laws and institutional guidelines, observing privacy rights of human participants. Informed consent was obtained from the participants or from their parents when the participant was a minor. This study was approved by the NIH institutional review board (18-AR0081, 11-AR-0223) and was conducted in accordance with the World Medical Association Declaration of Helsinki.

Data availability statement. The data that support the findings of this study (trio exome sequencing data) are being submitted to the publicly available Database of Genotypes and Phenotypes at (https://dbgap.ncbi.nlm.nih.gov/home/). Accession numbers for the data will be available at the time the publication is released in print.

RESULTS

Demographic characteristics of the cohort. The cohort included 57 unique participants evaluated for Still disease in our quaternary care clinic, including 32 children (<18 years old) and 25 adults (Table 1, Supplementary Tables 2 and 3). Most participants were White, 73.7% were female, and all had established Still disease with median disease duration of 3.3 years. Approximately one third of participants had a history of MAS, but only one met Ravelli et al criteria at the time of visit. Eleven participants (19.3%) had LD, all of whom had DAIR, and six additional participants had DAIR without LD. All participants were HLA typed, with 18 (31.6%) carrying HLA-DRB1*15 alleles. Although most participants had active disease by sJADAS10 at the time of the visit, most had normal laboratory parameters (Supplementary Table 4).

A subset of patients with Still disease displays with an elevated ISG expression signature. The examination of IFN signatures in our cohort with the ISG-28 score identified a distinct group of 16 outlier patients, roughly the first quartile, with high ISG-28 scores that exceeded the upper limit of the 95% confidence interval (CI) of healthy individuals (Figure 1A).[21] Elevation of the ISG-28 score was largely driven by IFN-I (Figure 1B–F). Plotting the strongest IFN-I (*MX1*) and IFN-II (*CXCL9*) induced genes[22] against one another revealed skewing of the high ISG-28 patients toward IFN-I (Figure 1B). Consistent with this, ISG-28- more strongly correlated with the expression of *MX1* than *CXCL9* (Figure 1C and D). Classic IFN-I–induced genes also displayed more significant induction in high ISG-28 patients than did *CXCL9* (Figure 1E and F).[22] Elevated ISG-28 scores were not explained by disease activity, showing no correlation with the sJADAS10, IL-18, C-reactive protein, or ferritin (Supplementary Figure 1A–D).

Elevated ISG-28 is associated with DAIR and LD, bolstering association of HLA-DRB1*15 with these complications. The clinical characteristics of the patients in the high ISG-28 group differed from those in rest of the cohort in several important ways (Figure 1G, Table 1, Supplementary Figure 2, Supplementary Table 5). The features most strongly associated with high ISG-28 scores were DAIR (P = 0.003, odds ratio [OR] = 7.3 [95% CI 1.7–34.3]) and LD (P = 0.007, OR = 6.9 [95% CI 1.4–39.7]). Anaphylaxis (P = 0.032) and pruritic eruptions and severe injection site reactions (P = 0.025) were also associated with a high ISG-28. Although no member of the high ISG-28 group was receiving IL-6 directed therapy, the use of high-dose steroids or IL-1 inhibitors did not statistically differ between the groups. The high ISG-28 group also showed a nonsignificant trend toward higher rates of HLA-DRB1*15 positivity and historical MAS than the rest of the cohort.

To evaluate the relationship between the IFN signature and HLA-DRB1*15, the cohort was stratified by these variables, and the rates of DAIR and LD were examined in the subgroups (Figure 2A–B). Although the rate of DAIR was 45.5% in the HLA-DRB1*15-only group and 33.3% in the elevated ISG-28–only group, 100% of the group with both variables had DAIR. The specificity of HLA-DRB1*15 alone for the development of DAIR was 0.84, but that rose to 1.0 with the addition of a high ISG-28 score.

Similarly in LD, the specificity of HLA-DRB1*15 alone for the development of LD was 0.78, but it rose to 0.93 when combined with a high ISG-28 score. The negative predictive values of HLA-DRB1*15 for DAIR and LD also improved with the addition of a high ISG-28 score, rising from 0.86 to 0.93 for DAIR and 0.92 to 1.0 for LD. Therefore, the combination of high ISG-28 and HLA-DRB1*15 results in the most accurate post hoc identification of the groups of patients with the highest and lowest frequencies of these complications in our study.

Characteristics of patients with LD. Among the 11 patients with LD in our study, 7 had sJIA, 3 had AOSD, and 1 had Still-like disease (Supplementary Tables 6 and 7). Patients with LD were more likely to carry HLA-DRB1*15 (72.7% vs 21.7%, P = 0.002), to have a history of MAS (72.7% vs 30.4%, P = 0.007), to be on high-dose steroids at the visit (81.8% vs 21.7%, P = 0.0004), to have high disease activity (30% vs 5%, P = 0.0483), and to have a history of anaphylaxis or delayed drug reactions to IL-1 and/or IL-6 inhibitors. There was a nonsignificant trend toward higher levels of IL-18 in the LD group (median 5,796.8 vs 943.6 pg/mL, P = 0.077). There was no difference in frequency of patients with age at onset <2 years old or in CXCL9 protein levels in the LD group compared to the rest of the cohort.

Features of DAIR in the cohort. Seventeen (29.8%) participants had a history of DAIR, with most exhibiting more than one feature (Figure 3, Supplementary Table 8). Most commonly, the history of DAIR was remote to study enrollment, with a median time from the last feature of the reaction to the measurement of ISG-28 being 259 days (IQR 11.5–560.5). Even though eosinophilia was not used in the definition of DAIR, patients in the DAIR group had marked elevation of maximum AEC while on IL-1 or IL-6 inhibitors compared to the group without it (median 1.07 vs 0.20, P = 0.000095; Figure 3). Of the patients without DAIR, none had AEC ≥1k/mcl while on IL-1 or IL-6 inhibitors, whereas only 5 of 23 had AEC ≥0.5k/mcL. All patients with LD had a history of DAIR, and in our cohort, these two features were strongly associated (11 of 11 vs 6 of 44, $P = 1 \times 10^{-7}$). Moreover, patients with LD

Table 1. Clinical characteristics of the cohort divided by IFN score*

	n	High IFN (n = 16)	Low IFN (n = 41)	Full cohort (N = 57)	*P* value
Diagnosis					
sJIA	57	8 (50)	17 (41.5)	25 (43.9)	0.570
AOSD	57	4 (25)	16 (39)	20 (35.1)	0.371
Still-like disease	57	4 (25)	8 (19.5)	12 (21.1)	0.723
Female sex	57	11 (68.8)	31 (75.6)	42 (73.7)	0.739
Age at visit, y	57	15 (7.9–27.8)	16.5 (7.5–33.2)	16.1 (7.5–33.2)	0.812
Age at onset, y	57	11 (3.5–25)	8 (2.3–27)	10 (2.3–27)	0.950
Disease duration, y	57	3.4 (2.9–6)	3.3 (1.9–7)	3.3 (2.1–6.3)	0.840
Race					0.705
White	57	13 (81.2)	34 (82.9)	47 (82.5)	
Black or African American	57	2 (12.5)	1 (2.4)	3 (5.3)	
Asian	57	0 (0)	2 (4.9)	2 (3.5)	
Multiple races	57	1 (6.2)	3 (7.3)	4 (7)	
Unknown	57	0 (0)	1 (2.4)	1 (1.8)	
Ethnicity					0.657
Not Latino or Hispanic	57	15 (93.8)	33 (80.5)	48 (84.2)	
Latino or Hispanic	57	1 (6.2)	5 (12.2)	6 (10.5)	
Unknown	57	0 (0)	3 (7.3)	3 (5.3)	
HLA-DRB1*15 positive	57	7 (43.8)	11 (26.8)	18 (31.6)	0.341
History of MAS	57	8 (50)	14 (34.1)	22 (38.6)	
Ravelli et al[20]	57	7 (43.8)	9 (22)	16 (28.1)	0.115
Subclinical	57	1 (6.2)	5 (12.2)	6 (10.5)	0.366
History of LD	57	7 (43.8)	4 (9.8)	11 (19.3)	0.007
ILD	57	5 (45.5)	3 (75)	8 (72.7)	
PAH	57	4 (57.1)	1 (25)	5 (45.5)	
Isolated reduced DLco	57	1 (14.3)	1 (25)	2 (18.2)	
History of exposure to IL-1 or IL-6 inhibitors[a]	57	15 (93.8)	32 (78)	47 (82.5)	0.253
History of DAIR					0.003
Yes	57	10 (62.5)	7 (17.1)	17 (29.8)	
No	57	5 (31.2)	23 (56.1)	28 (49.1)	
Not exposed	57	1 (6.3)	9 (22)	10 (17.5)	
Undetermined[b]	57	0 (0)	2 (4.9)	2 (3.5)	
Current IL-1 inhibition	56	8 (50)	14 (35)	22 (39.3)	0.369
Current IL-6 inhibition	56	0 (0)	10 (25)	10 (17.9)	0.048
Current high-dose steroids	57	6 (37.5)	13 (31.7)	19 (33.3)	0.758
sJADAS10	44	8.5 (3.6–11.2)	7.7 (4.3–15.5)	8.1 (4.2–14.6)	0.647
Active disease[c]	47	13 (86.7)	28 (87.5)	41 (87.2)	1
MoDA/HDA	45	5 (33.3)	12 (40)	17 (37.8)	0.752
HDA	50	1 (6.2)	4 (11.8)	5 (10)	1
IL-18 level, pg/mL[d]	45	1,635.4 (475.7–16,751.5)	944.8 (375.8–4,991.1)	945.9 (379.4–7,327.9)	0.561
IL-18 > 15,461, pg/mL	50	6 (40)	7 (20)	14 (28)	0.170
ISG-28	57	2,138.7 (1,322.4–2,968.3)	432.5 (348.8–535.3)	516.5 (403.4–851.5)	3.5×10^{-14}

* Continuous variables are presented as median (Q1–Q3); categorical variables are presented as n (% of nonmissing values). AOSD, adult-onset Still disease; DAIR, drug-associated immune reactions; DLco, diffusing capacity for carbon monoxide; HDA, high disease activity; IFN, interferon; IL, interleukin; ILD, interstitial lung disease; ISG-28, interferon-stimulated gene 28; LD, lung disease; MAS, macrophage activation syndrome; MoDA, moderate disease activity; NSAID, nonsteroidal anti-inflammatory drug; PAH, pulmonary arterial hypertension; Q, quartile; sJADAS10, Systemic Juvenile Arthritis Disease Activity Score 10; sJIA, systemic juvenile idiopathic arthritis.

[a] Patients who were not exposed to IL-1 or IL-6 inhibitors were treated according to the preference of their treating physicians with treatments that included high-dose glucocorticoids, methotrexate, hydroxychloroquine, NSAIDs, tofacitinib, mycophenolate mofetil, adalimumab, and colchicine.

[b] There were two patients in the low IFN group who had confounding features that did not allow for a determination regarding DAIR to IL-1 and/or IL-6 biologics.

[c] Active disease: sJADAS > 2.9; MoDA: sJADAS10 > 10 and ≤ 20.6; HDA: sJADAS10 > 20.6. One participant with an sJADAS10 score of 20.3 without a patient global score was included in the HDA group, based on the inference that this participant with highly active disease would have a patient global score of at least 0.3 of 10 and was likely to meet the cutoff of 20.6 for HDA.

[d] Three samples with discordant results after dilution were excluded from this analysis. Two samples above limit of detection were not available for dilution.

had higher maximum AEC while on IL-1 or IL-6 inhibitors than did patients without LD, regardless of DAIR status (median 1.10 vs 0.32, $P = 0.01$). Despite not being a part of the definition of DAIR, elevation of liver enzymes >2 × the upper limit of normal while on IL-1 or IL-6 inhibitors was more common in patients who had DAIR (13 of 16 vs 5 of 28, $P = 0.00007$). Two patients had

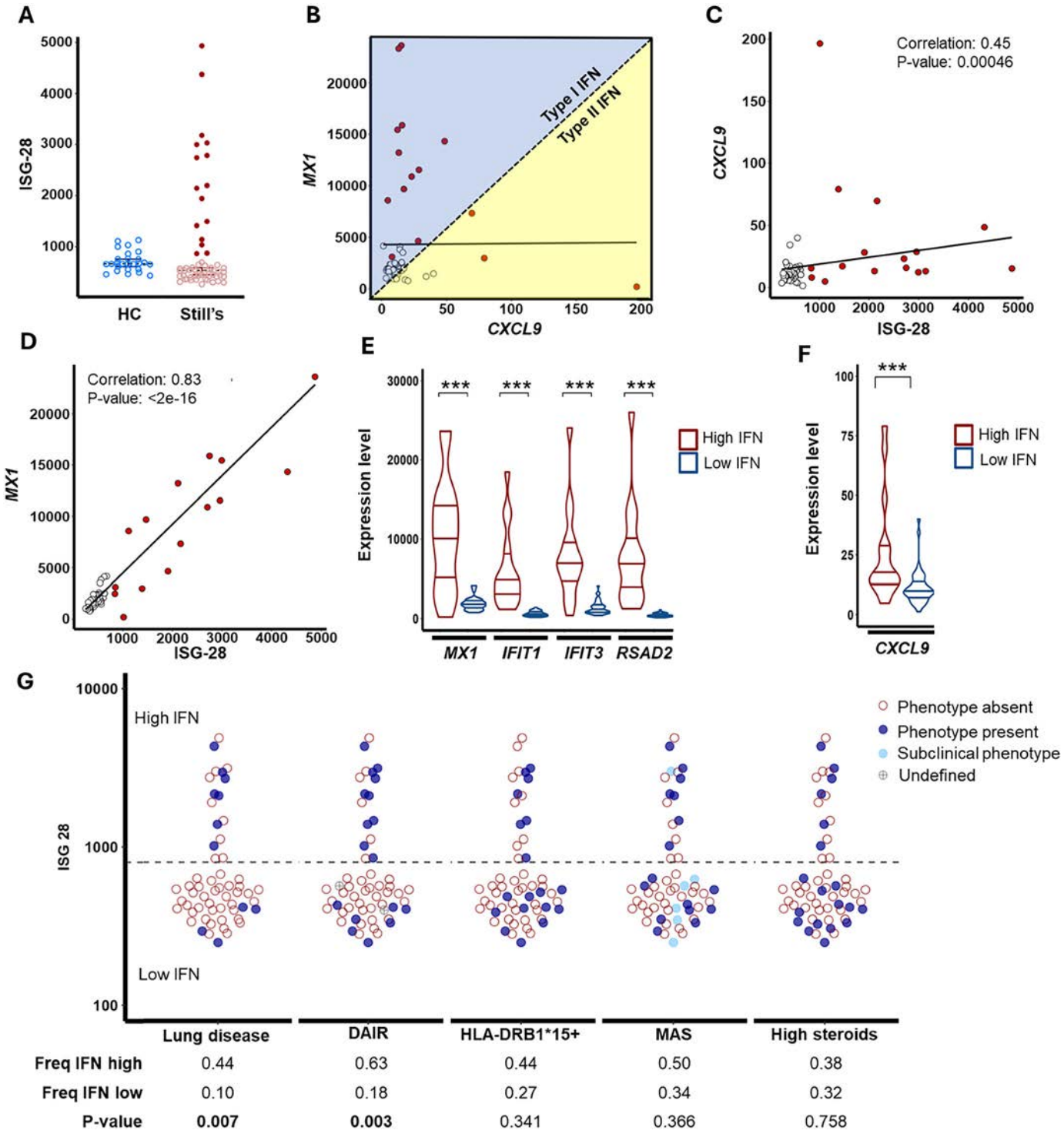
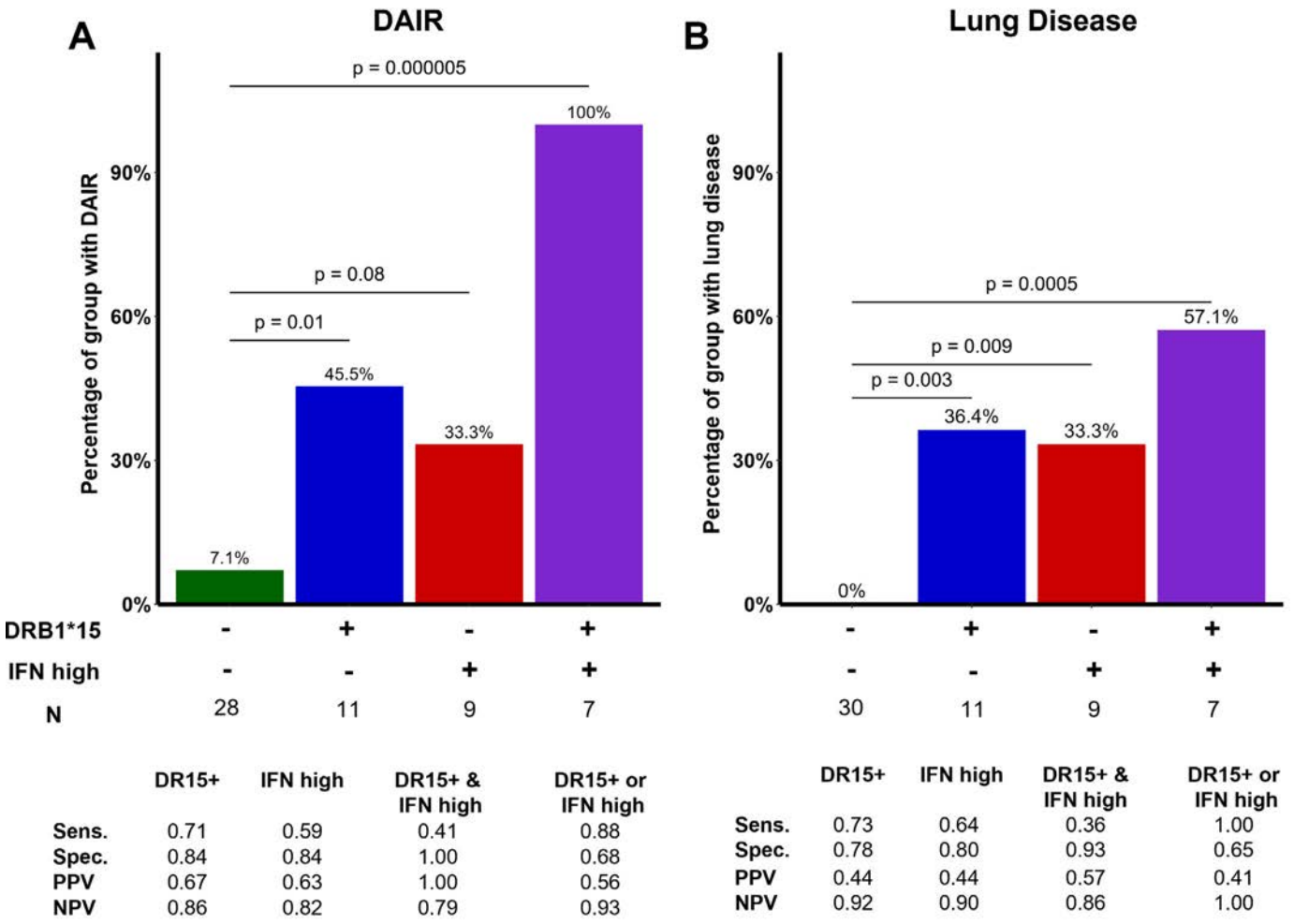


Figure 1. Type I interferon signature in Stills disease. ISG-28 scores from healthy individuals[12] and patients with Stills disease are displayed in panel A. The upper limit of the 95% confidence interval in healthy individuals defined the upper limit of normal as 734.4. Patients with ISG-28 scores above that threshold (high ISG-28) are marked as solid red dots. (B) Expression of *MX1* and *CXCL9* are plotted against one another. (C–D) Spearman's correlation of the ISG-28 score with expression of *CXCL9* and *MX1*, respectively. (E–F) Violin plots display (E) interferon alpha-specific and (F) interferon gamma-specific genes in patients with Stills disease with and without high ISG-28. Comparison between groups with high and low interferon was performed by Mann–Whitney U test. (G) Clinical features are projected onto plots of ISG-28 score, shown in logarithmic scale to facilitate visualization. Each phenotype is graphed separately, with phenotype frequencies of the high ISG-28 and low ISG-28 groups noted below. Comparisons were performed with two-tailed Fisher exact test with significance at 0.05. Error bars in (A) indicate the median and 95% confidence interval, whereas those in (E) and (F) reflect the median and interquartile range. DAIR, drug-associated immune reactions; Freq, frequency; HC, healthy controls; IFN, interferon; ISG-28, interferon-stimulated gene 28; MAS, macrophage activation syndrome.



	DR15+	IFN high	DR15+ & IFN high	DR15+ or IFN high
Sens.	0.71	0.59	0.41	0.88
Spec.	0.84	0.84	1.00	0.68
PPV	0.67	0.63	1.00	0.56
NPV	0.86	0.82	0.79	0.93

	DR15+	IFN high	DR15+ & IFN high	DR15+ or IFN high
Sens.	0.73	0.64	0.36	1.00
Spec.	0.78	0.80	0.93	0.65
PPV	0.44	0.44	0.57	0.41
NPV	0.92	0.90	0.86	1.00

Figure 2. HLA-DRB1*15 and a high ISG-28 score are associated with lung disease and DAIR in Still disease. The prevalence of DAIR and lung disease in the Still cohort, stratified by HLA-DRB1*15 and high ISG-28 status, are displayed in panels A and B, respectively. Performance characteristics of the HLA-DRB1*15 and ISG-28 to identify DAIR and lung disease are presented in tabular format under the bar plots. Two patients with indeterminate DAIR status were excluded from the DAIR analysis. Comparisons between groups were performed using two-tailed Fisher exact test. DAIR, drug-associated immune reactions; ISG-28, interferon-stimulated gene 28; IFN, interferon; NPV, negative predictive value; PPV, positive predictive value.

confounding circumstances that prevented unambiguous classification of DAIR. One had a longstanding history of pruritic cold urticaria preceding diagnosis of Still, which prevented a clear determination of worsening of symptoms with canakinumab. The second had an influenza infection and used other medications at the time of DAIR, which precluded clear attribution to anakinra.

Patients with Still disease with IFN-I signature display enrichment of candidate causative variants in pathways connected to regulation and production of IFN-I. In the monogenic interferonopathies, genetic variation leads to accentuated IFN-I signaling.[7] Given that the IFN-I signature in our cohort was strongly associated with historical development of DAIR to IL-1 and/or IL-6 inhibitors and LD, but not with variables indicative of current clinical status, we hypothesized that high-impact genetic variation may contribute to this IFN-I signature. To evaluate this hypothesis, we performed trio exome sequencing and family-based variant prioritization in all probands for whom parental samples were available (n = 39). We stratified this cohort based on ISG-28 scores to examine the 16 patients that had elevated ISG-28 scores (high IFN group), an equivalently sized group of 16 patients with the lowest ISG-28 scores (low IFN group), and the full group of 23 patients that did not display an elevated ISG-28 score (non-high IFN group). For each of these groups, we generated a list of genes containing candidate causative variants by selecting rare de novo, recessive, or X-linked variants for each proband (Supplementary Table 9, Supplementary Data). In addition, we included two genes in which biologically relevant variants were discovered (*IL-10*, loss of function[25] and *TLR2*, gain of function; Supplementary Table 10).[26] In the high IFN group, this produced a set of 89 unique candidate genes that,

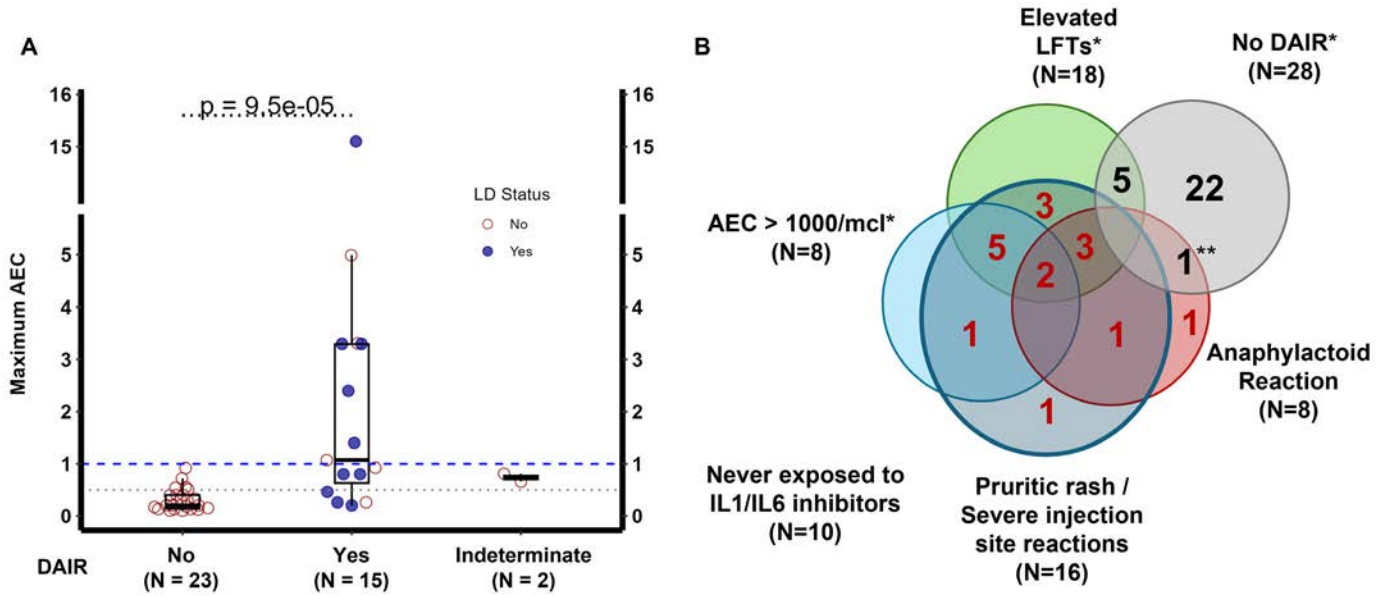


Figure 3. Features of DAIR in Still disease. The maximum AEC (k/mcL) while on IL-1 or IL-6 inhibitors, stratified by DAIR status, is plotted in panel A. Eosinophil count was not assessed during IL-1 or IL-6 inhibitor treatment in 7 patients, including 2 with DAIR and 5 without DAIR. Comparison of the groups with and without DAIR were performed by Mann–Whitney U test. The dashed blue line indicates AEC of 1 k/mcL. The dotted gray line indicates AEC of 0.5 k/mcl. (B) A Venn diagram displays the intersection of features of DAIR in the cohort. Red numbers reflect patients with DAIR to IL-1 and/or IL-6 inhibitors. Two patients with indeterminate DAIR were not included in this analysis. *While on IL-1 or IL-6 inhibitors. **Anaphylaxis to infliximab. AEC, absolute eosinophil count; DAIR, drug-associated immune reactions; IL, interleukin; LD; lung disease; LFT, liver function test.

when subjected to ORA with WebGestalt, revealed enrichment of a group of terms that were relevant to IFN-I and associated phenotypes (Figure 4A–C, Supplementary Tables 11 and 12).

Candidate genes from the high IFN group were most strongly enriched in the Reactome chaperone-mediated autophagy pathway (enrichment ratio 29.8), and autophagy-related terms also displayed significant enrichment in GO:BP. IFN-I production, cell surface toll-like receptor (TLR) signaling, macrophage activation, and various cellular responses to stress also displayed enrichment of candidate genes from the high IFN group. Most candidate genes involved in GO:BP enrichment intersected with more than one process (Figure 5, Supplementary Table 13). There were numerous enriched phenotypes from the Human Phenotype Ontology, but after redundancy reduction, the enriched phenotypes notably included abnormal heart morphology, abnormal joint morphology, and abnormal body weight (Figure 4C), all of which have been described in refractory Still disease. No patient in the high ISG-28 group had congenital heart disease.

As a sensitivity analysis, we repeated the GO:BP analysis of the high IFN group with Enrichr, which uses a Z score based combined score to identify pathway enrichment that can be overlooked by other methods.[24] (Figure 4D, Supplementary Tables 14 and 15). This recapitulated the associations with autophagy and TLR signaling, and the validity of this approach was reinforced by its strong implication of IL-18 production.

Parallel analyses of the low IFN group and the non-high IFN group identified candidate gene lists with 84 and 108 unique genes, respectively. Unlike the high IFN group, neither of these groups displayed evidence of candidate gene enrichment in any GO term or pathway (Supplementary Tables 16 and 17), reinforcing the specificity of these findings to the high IFN subgroup. Additionally, four unaffected parents who transmitted candidate causative variants to their high IFN children also displayed high ISG-28 scores (Supplementary Figure 3).

DISCUSSION

This study identified elevated whole blood IFN-I signatures in a subset of children and adults with Still disease. High ISG-28 was associated with LD and DAIR in the NIH Still disease cohort, which is enriched for patients with refractory disease courses. When the IFN-I signature was combined with HLA-DRB1*15, an established risk factor for LD and DAIR, they together identified these complications more accurately than did either variable alone. The IFN signature was not driven by disease activity or IL-18, nor was it a direct consequence of the DAIR, most of which were temporally remote from evaluation in this study. Instead, patients with elevated ISG-28 carried rare candidate variants that were significantly enriched in IFN-I–related pathways, something not observed in the patients with Still disease without high ISG

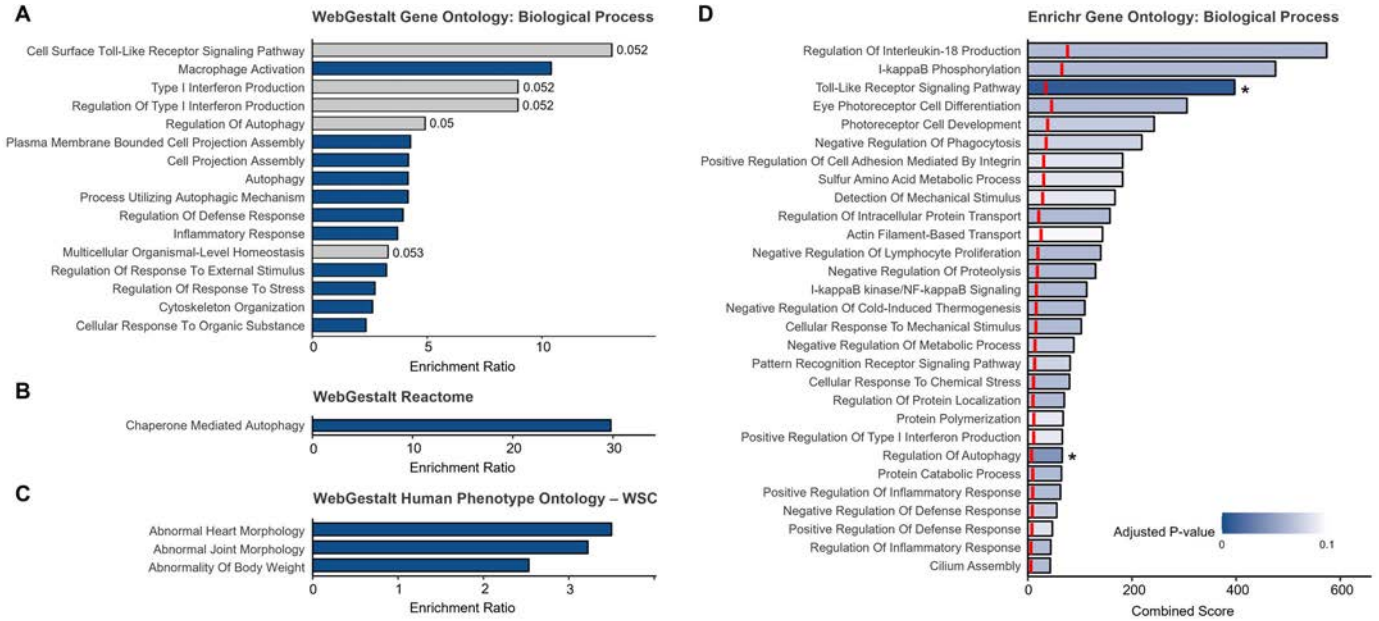


Figure 4. Functional enrichment analysis of candidate genes from the high ISG-28 subgroup of Still disease. Bar plots display the results of overrepresentation analysis of candidate genes from the high ISG-28 Still disease subgroup, as evaluated in WebGestalt. Enriched terms with an adjusted *P* value < 0.06 from (A) the gene ontology–biologic processes terms, (B) Reactome pathways, (C) and Human Phenotype Ontology terms are expressed as enrichment ratios. Adjusted *P* values > 0.05 are listed to the right, and those < 0.05 are highlighted in blue. (D) Bar plots display Enrichr combined scores from overrepresentation analysis of high ISG-28 Still disease candidate genes in gene ontology–biologic process terms with an adjusted *P* value < 0.1 and combined score > 40. Vertical red lines indicate odds ratio, adjusted *P* values are shown as a gradient, and adjusted *P* values < 0.05 are marked with an asterisk. ISG-28, interferon-stimulated gene 28; WSC, weighted set cover.

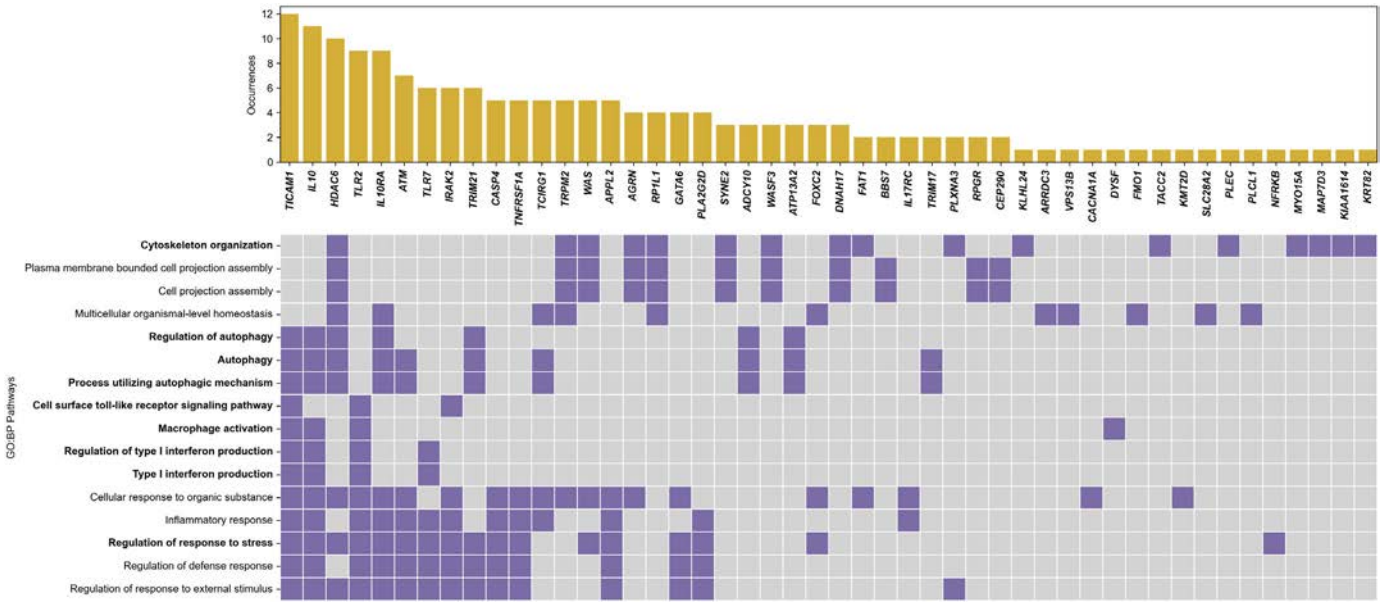


Figure 5. Intersecting patterns of candidate gene enrichment in 16 enriched GO:BP terms. Candidate genes were identified by family-based sequencing and variant prioritization in patients with Still disease with high ISG-28 scores. Functional enrichment analysis identified 16 enriched GO:BP terms that were enriched for these candidate genes. The bar plot displays the number of enriched GO:BP terms in which each gene is contained. The heatmap demonstrates the candidate gene membership of the 16 enriched GO:BP terms. GO:BP terms with plausible connections to the regulation and/or production of type I interferons are shown in bold, ordered based on relatedness determined by hierarchical clustering. GO:BP, gene ontology–biologic process; ISG-28, interferon-stimulated gene 28.

expression, suggesting a genetic contribution to these signatures. Supporting this, a subset of healthy parents who transmitted rare variation in pathway-involved genes to their high ISG-28 children also displayed high ISG-28 scores, as has been described in other nonclassical interferonopathies.[27]

Exome sequencing of a single proband typically identifies over 9,000 rare missense variants,[28] most unrelated to the phenotype of interest. Family-based prioritization of rare de novo, recessive, or X-linked variants yields a smaller set of high-confidence candidate causative variants.[29]

This also prioritizes variant configurations that could plausibly cause disease in sporadically affected probands. Combining this approach with functional enrichment analysis can link phenotypes with contributory genetic variation and specific pathways and processes. In our study, this unexpectedly connected candidate variation in high IFN-I patients with a group of IFN-I linked pathways and processes. Indeed, beyond IFN-I production, cell surface TLR signaling, autophagy, macrophage activation, stress responses, and cytoskeletal derangement can all be connected to the regulation or production of IFN-Is.[30–35]

Activation of cell surface and endosomal TLRs can lead to IFN-I production.[30] Dysregulated TLR signaling has been reported in Still disease, including elevated *TLR7* expression and enhanced MyD88-dependent pathway activation that synergize with IFN-I to promote production of IL-18, a key cytokine in the disease.[36,37] It is therefore plausible that activating variants that link the TLR pathway with Still LD and DAIR, such as the *TLR2* F217S variant,[26] could enhance IFN-I production. Similarly, autophagy, the strongest enriched pathway in the high IFN group, negatively regulates IFN-I production.[38] Several lines of evidence have suggested autophagic impairment in Still disease,[39,40] whereas therapeutic induction of autophagy with rapamycin has produced favorable preliminary results in patients with refractory Still disease.[41,42] Therefore, it is plausible that candidate variants that decrease autophagy could lead to increased production of IFN-I. Together, these examples demonstrate how the pathways identified in our study could plausibly lead to elevated production of IFN observed in Still LD and DAIR.

This is not the first time that IFN-I elevation has been described in Still disease. A study by Rice and colleagues examined IFN-I in 19 children with sJIA.[27] Like our study, they identified a small subgroup of outliers who displayed an IFN-I signature. Noting that all children with IFN-I signatures were receiving IL-1 blockade, the authors speculated that the IFN production was caused by a compensatory cytokine shift. This hypothesis was not supported by our larger study, in which there was no association between IL-1–directed therapy and the presence of the IFN-I signature.

Two studies have also identified increased IFN gene expression and protein levels in subsets of adults with Still disease. The first of these used targeted resequencing to evaluate whether germline or somatic variation in a panel of monogenic interferonopathy genes might underlie the increased IFN-I signatures.[43] Like our study, this study found no evidence to implicate classical monogenic interferonopathy genes in Still disease. However our study leveraged trio exome sequencing, which allowed identification and prioritization of potentially pathogenic variants of all genes.[29] Based on our observations, it is possible that genetic variation in a range of nonclassical interferonopathy genes may instead underlie the high IFN signatures. The second of these studies observed increased IFN production in their patients with Still disease and explored the functional consequences in neutrophils.[44] The authors demonstrated that in response to IFN stimulation, AOSD neutrophils released neutrophil extracellular traps that were enriched with oxidized mitochondrial DNA. They hypothesized that this contributed to disease pathogenesis and demonstrated that this phenomenon could be suppressed by JAK inhibition. If the high IFN-I in Still disease has a genetic basis, then IFN signatures might identify a subgroup of patients in whom JAK inhibition would be effective.

There is also precedent for the involvement of IFN-I in LD, as well as in various DAIR. For example, patients with trisomy 21, who have strong genetically mediated IFN signatures, are at high-risk of developing LD with sJIA.[6,13,45] There is also a well-described connection between IFN-I and the development of PAH, which is one of the main presentations of Still LD.[4,14,46,47] Similarly, conditions associated with increased IFN-I signaling, such as lupus and viral infections, are associated with increased risk of DAIR.[48–51]

Our study raises the possibility that genetic variation could contribute to an IFN-I signature, which is associated with Still LD and DAIR independently of HLA-DRB1*15. The combination of an elevated ISG-28 score and HLA-DRB1*15 strengthened both associations and allowed post hoc identification of patients with the highest and lowest frequencies of these complications with strong positive and negative predictive values. This highlights IFN-I as a rational therapeutic target, supported by emerging evidence that JAK inhibitors, which suppress IFN-I and IFN-II signaling, may effectively treat LD and DAIR in Still disease.[13,41,52] These findings could pave the way for genotype–phenotype stratification to guide precision therapy.

Although recent studies have implicated IFN-I in the development of MAS in Still disease,[37,53] our study did not find significant association between history of MAS and elevated ISG-28 scores. Nonetheless, the one patient with active MAS in our cohort had one of the highest ISG-28 scores. Moreover, association between MAS and LD/DAIR has been described.[5,6] It is therefore possible that the candidate genes identified in our study could also contribute to MAS in these patients, underscoring the complex interplay across IFN pathways, genetic susceptibility, and treatment effects.

A major challenge in the field is the lack of universally accepted definitions for emergent Still disease complications. Although DRESS criteria have been applied to Still LD and

DAIR,[8,54] their appropriateness is questioned due to overlap with active Still features.[11,16] Atypical or pruritic rashes and eosinophilia are considered specific for DAIR[16]; however, two recent studies claimed that eosinophilia is common in Still disease.[12,55] Thus, we focused on characterizing DAIR without considering eosinophilia or less specific features. We observed low-grade eosinophilia frequencies like prior cohorts[12,55]; however, marked eosinophilia (AEC > 1,000 k/mcl) while on IL-1 or IL-6 inhibitors and elevated liver enzymes were only seen in patients with DAIR. Although mild eosinophilia and elevated liver function tests (LFTs) may be common in sJIA and AOSD, significant eosinophilia with LFT elevation should prompt concern for LD and DAIR. Based on this observation, we propose to define pathologic eosinophil elevation as >1,000 k/mcl when evaluating patients with Still disease.

Still LD with associated DAIR emerged after the introduction of IL-1 and IL-6 inhibitors, and although most cases developed in the context of these drugs, rare cases have developed without exposure to them, suggesting involvement of additional factors. HLA-DRB1*15 is strongly associated with LD and DAIR, but associations of this common allele with similar complications in other conditions treated with the same drugs have not been described, indicating disease-specific mechanisms. Our study nominates candidate genes in IFN-I–linked pathways as another potential independent contributor. Additionally, the relationship between LD and DAIR is unclear—they may reflect a spectrum of one condition or distinct entities sharing risk factors. Further research is needed to clarify these complex interactions.

This study has several important strengths. It was performed in a clinic specializing in the care of children and adults with Still disease, generating findings that are applicable to people of all ages. The study cohort was composed of consecutively referred participants with Still disease who were evaluated by our team. All participants were subjected to a standard battery of clinical and laboratory examinations, including HLA testing. This is one of the first studies to evaluate the role of IFN-I in Still LD and DAIR and the first one to identify clinically relevant associations with the signature. This is also the first instance of pathway analysis for identification of variants prioritized by trio exome sequencing in Still disease.

There are also important limitations to the study. First, the study cohort was enriched for patients with treatment refractory disease. Although this does not reflect an incident cohort, it is well suited to investigate the subset of patients with refractory disease—which may account for as many as half of cases. Second, the ISG-28 score was evaluated at a single time point, the enrollment visit, and the stability of this score was not evaluated over time. To properly evaluate the stability of ISG-28 over time will require patient cohorts with routine, longitudinal follow-up data and serial biospecimens. Third, beyond intrinsic (genetic) factors, IFN signatures can also be influenced by extrinsic factors, such as treatments, viral infection, and immune activation status. The high IFN-I signature did not correlate with treatments or disease activity. Additionally, a recent study of our cohort demonstrated an absence of Epstein–Barr virus, cytomegalovirus, or human herpesvirus 6 infection among the high IFN-I patients at study enrollment.[56] Nonetheless, the possibility of occult infection or autoimmunity could not be completely excluded. Fourth, because the ISG-28 was measured at study enrollment and not at the onset of LD or DAIR, the observed correlations reflect post hoc and not prospective association. Prospective validation studies are required to determine whether high ISG-28 is truly a biomarker that correlates with the development of LD and DAIR in patients with incident Still disease and whether type I IFN would be a helpful therapeutic target for these complications. Finally, future studies are necessary to examine the functional effects of the candidate variants identified in the relevant pathways and determine their effects on IFN-I production and signaling.

In conclusion, our study suggests that a genetically linked IFN-I signature in patients with Still disease is associated with the development of LD and DAIR to IL-1 and IL-6 inhibitors. This study provides important new insights into the pathophysiology of Still disease and its complications, and supports a potential role for IFN-I in this subgroup of patients.

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AUTHOR CONTRIBUTIONS

All authors contributed to at least one of the following manuscript preparation roles: conceptualization AND/OR methodology, software, investigation, formal analysis, data curation, visualization, and validation AND drafting or reviewing/editing the final draft. As corresponding author, Dr Ombrello confirms that all authors have provided the final approval of the version to be published and takes responsibility for the affirmations regarding article submission (eg, not under consideration by another journal), the integrity of the data presented, and the statements regarding compliance with institutional review board/Declaration of Helsinki requirements.

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Treatment of a Large Cohort of Childhood Chronic Noninfectious Uveitis in a Multicentric Large Study: Adalimumab Versus Methotrexate as First-Line Therapy

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Objective. Treatment of childhood chronic idiopathic uveitis (cCIU) is predominantly based on studies in juvenile idiopathic arthritis–associated uveitis and expert opinion. Our aim was to report the treatment outcomes of our cohort of cCIU.

Methods. Retrospective multicenter study involving the rheumatology and ophthalmology units at Florence, Italy, and Bristol, United Kingdom. We included children with cCIU, who received at least one systemic treatment. Ocular inflammation and treatment response were assessed according to the standardized uveitis nomenclature.

Results. A total of 116 patients with cCIU received at least one systemic treatment (93 methotrexate, 22 adalimumab, and 1 mycophenolate), whereas 60 of them received an additional second-line treatment (45 adalimumab, 14 mycophenolate, and 1 tocilizumab). Children treated with adalimumab (plus or minus methotrexate) as a first-line therapy were more likely to achieve remission than methotrexate alone ($\chi^2 = 31.35$; $P < 0.001$); furthermore, children treated with methotrexate as a first-line therapy relapsed earlier ($\chi^2 = 4.35$; $P = 0.043$). Children receiving adalimumab were more likely to stop treatment for remission than methotrexate ($\chi^2 = 25.9$; $P < 0.001$). Regarding second-line therapy, children who started adalimumab (plus or minus methotrexate) were more likely to achieve remission than mycophenolate ($\chi^2 = 14.66$; $P = 0.005$). Children with nonanterior uveitis, conversely to the others, were more likely to achieve remission with adalimumab as a first-line therapy than methotrexate ($\chi^2 = 32.3$; $P < 0.001$). Children with nonanterior uveitis, but not children with anterior uveitis, were more likely to stop the first-line treatment when receiving adalimumab than methotrexate ($\chi^2 = 18.56$; $P = 0.001$) due to persistent remission.

Conclusion. Adalimumab shows promise as a potential first-line therapy for cCIU, particularly for posterior segment uveitis. Although effective in anterior uveitis, methotrexate leads children to relapse earlier than adalimumab.

INTRODUCTION

Juvenile idiopathic arthritis (JIA) is the most common cause of chronic uveitis in children, even though the approximately 30% to 40% of childhood uveitis[1] has no known systemic cause and are termed childhood chronic idiopathic uveitis (cCIU) or undifferentiated uveitis. The Standardization of Uveitis Nomenclature (SUN) Working Group divides uveitis into different anatomic subtypes (anterior, intermediate, posterior, and panuveitis).[2–5]

Timely treatment of cCIU is important to prevent ocular complications and blindness. Due to the sparse evidence on cCIU, treatment decisions are predominantly borrowed from studies on chronic uveitis in association with a systemic disease, such as JIA or Behçet disease, or from adult experience.[6–9]

International recommendations advise use of topical and systemic glucocorticoids initially based on the severity and location of the uveitis, with the addition of a disease-modifying antirheumatic drug (DMARD) or biologic agent, depending on the

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severity of disease, specific risk factors, persistent inflammation, or disease relapse.[6,7]

Methotrexate is considered as the first-line DMARD to be used. Adalimumab may be considered as a first-line therapy in which there are severe ocular complications at baseline, although in the United Kingdom, adalimumab is only funded as a second-line treatment for uveitis.[6]

Current treatment recommendations for childhood uveitis relate to JIA-associated uveitis and anterior chronic idiopathic uveitis, and there is little guidance on the treatment of posterior segment uveitis in children.[6,7] The aim of our study was to report the therapeutic approach to a large cohort of cCIU, including all anatomic subtypes of uveitis.

MATERIALS AND METHODS

Study design. This is a retrospective, noninterventional, multicenter study involving cCIU diagnosed before 16 years of age. For the University Hospitals Bristol NHS Foundation Trust in Bristol (United Kingdom), data collection was approved by the hospital trust, and ethics committee approval was not required. Meyer Children's Hospital IRCCS ethics committee approved the study (27/2022) and informed consent was signed by legal guardian.

Setting. This study involved the Rheumatology and Ophthalmology Units of the Meyer Children's Hospital IRCCS (Florence, Italy) and the Rheumatology and Ophthalmology Units of the University of Bristol and Weston NHS Foundation Trust in the United Kingdom.

Study population. Children were included if they attended the rheumatology or the ophthalmology clinics of the two centers between January 1, 2019 and January 31, 2020, had a diagnosis of cCIU defined as persistent uveitis lasting more than three months with relapse less than months after discontinuing treatment according to SUN, no evidence of infection of other systemic disease, onset before 16 years old, have received at least one systemic treatment other than glucocorticoids before 18 years of age, and have a follow-up of at least three months after starting the systemic treatment. Patients were excluded from this study if they had a diagnosis of a systemic disease, previous malignancy, demyelinating disease, or cerebral vasculitis.

Data collection. Data were retrospectively collected from medical records at the onset of the disease, at the start of each systemic therapy, at 3 months (±2 weeks), 6 months (±2 weeks), 12 months (±2 weeks), 2 years (±1 month), 3 years (±1 month), and after each systemic treatment change. The baseline was recorded as the first presentation of disease, which in some cases was not in the hospital follow-up.

The following data were collected: demographics including age, biologic sex at birth, ethnicity, age at onset, duration of disease, and age at diagnosis (calculated considering the first visit when the diagnosis of uveitis was made). When the precise date was not available, and the month and year of onset were the only data accessible, the 15th of the month was considered as onset. Laboratory data included antinuclear antibody (ANA) status, and parameters of inflammation at onset if available (C-reactive protein [normal value <0.5 mg/dl], and erythrocyte sedimentation rate [ESR] [normal value <10 mm/h]) were collected.

Clinical characteristics of uveitis included laterality of uveitis (unilateral or bilateral), anatomic location according to SUN[2] as anterior, intermediate, anterior and intermediate, posterior, and panuveitis. Symptoms at onset were recorded as pain, redness floaters, or blurred vision.

Ocular complications were recorded at onset and at the last available follow-up as present or absent for each eye. The following complications were recorded: cataract, elevated intraocular pressure (>21 mm Hg), ocular hypotony (<5 mm Hg), optic disc swelling, macular edema on optical coherence tomography scan, posterior synechiae, epiretinal membrane, band keratopathy, and choroidal neovascular membrane.

Best corrected visual acuity (VA) was recorded in Logarithm of the Minimum Angle of Resolution (LogMAR), and when this scale was not available, the appropriate conversion was performed according to Schulze-Bonsel et al.[10] VA has been stratified as <0.4 LogMAR, ≥0.4 and <1 LogMAR, and blindness if ≥1 LogMAR.

Ocular inflammatory activity in the anterior chamber was graded using anterior chamber cells on slit-lamp examination according to SUN guidelines. Vitreous haze was assessed by binocular indirect ophthalmoscopy score or National Eye Institute vitreous haze scale.[2,5] Evaluation of retinal or choroidal lesions on slit-lamp examination, presence of active vasculitis on fluorescein angiography (where performed), and presence or absence of cystoid macular edema on optical coherence tomography were recorded. Drug treatments, concomitant therapy, time to treatment effect, duration of treatment, response to treatment, cessation of therapy, and uveitis flares during and after treatment were also recorded.

The response to treatment was assessed according to SUN criteria as follows:

1. Response was defined as the improvement of intraocular inflammation considered as anterior chamber cells, according to the definition of improvement of the SUN Working Group criteria for anterior uveitis.[2] Anterior chamber inflammation was considered "inactive" or controlled if the inflammatory activity was grade 0 cells. Regarding posterior inflammation, the National Eye Institute system for grading vitreous haze was adopted, and the designation "trace" was recorded as 0.5+. Uveitis

was defined as improved and treatment as successful when its activity decreased by two steps in the level of inflammation (anterior chamber cells and/or vitreous haze) with two drops or less per day or decreased to grade 0 at three-months and six-months follow-up (±2) and no declaration of treatment failure due to intolerability or safety concerns at three and six months.
2. Remission on treatment: recorded as present or absent. Remission on treatment is defined as anterior chamber cells ≤0.5, absence of optic disc edema, absence of macular edema, vitreous haze ≤0.5 plus absence of active vasculitis, and the absence of topical and systemic glucocorticoids for three consecutive months.
3. Time to achieve inactive disease, defined as above reported, is counted as months after starting systemic treatment.

The main measures of outcomes considered were the achievement of remission on treatment, the time to achieve inactivity, flare on treatment, the ability to stop the treatment, and time to flare after the withdrawal of treatment.

Statistical analysis. Statistical analysis was performed using SPSS version 29.0 for Windows and STATA version 15 (StataCorp LLC, College Station, TX). Continuous variables were described using median and interquartile range (IQR). For dichotomous and/or categorical variables, proportions were used to assess the clinical characteristic of the population. Statistical significance (*P* value) was assessed at the 0.05 level. Chi-square test and Fisher test were used to compare categorical variables as appropriate, whereas continuous variables were compared using nonparametric tests.

The association between achievement of remission on therapy, relapse on therapy, drug discontinuation due to persistent remission and relapse after drug withdrawal with the therapy, and a selected set of variables was assessed using multivariable logistic regression models. To describe the time to event outcomes (eg, time to remission, time to relapse on treatment), Kaplan-Meier survival curves were generated, and log-rank tests were used to compare survival functions across treatments. The association of these outcomes with treatment and a set of selected variables was assessed using Cox proportional hazards models. Predictors were selected based on clinical hypotheses and included, in addition to therapy, sex, age at onset, disease duration, ANA positivity, ocular complications at presentation, and baseline LogMAR.

Due to the substantial proportion of missing values observed, we employed multiple imputation by chained equations, performing 50 imputations. Only covariates (predictor variables) were imputed; outcomes were left untouched, to preserve the integrity of the observed event data. The number of imputations (50) was chosen because some covariates had missingness rates as high as 30% to 40%, and increasing the number of imputations helps to reduce Monte Carlo error and ensure stable and reliable pooled estimates in cases of high missing data proportions. Multivariate models were then fitted to each of the 50 imputed datasets, and pooled estimates—including coefficients, standard errors, and confidence intervals (CIs)—were derived using Rubin's rules. This strategy ensures that the imputation process does not artificially alter observed outcome distributions, reducing bias in parameter estimation while increasing statistical efficiency despite missing predictor data.

Data statement. Data will be made available on reasonable request to the corresponding author.

RESULTS

There were 146 patients with cCIU (76 boys and 42 ANA positive), of whom 116 met the inclusion criteria for the study (79.4%) (Supplementary Figure 1). All patients had received at least one systemic treatment other than glucocorticoids, and 60 had received a second-line treatment (41.1%) with a median follow-up of 52 months (IQR 35–79). The characteristics of the 116 patients included in the study are summarized in Table 1. We observed that children with panuveitis have a significantly higher ESR ($P = 0.0019$), present a higher number of ocular complications at the onset of the disease ($P = 0.0131$), and have lower VA ($P = 0.0192$) compared with other anatomic subtypes of uveitis (see Table 1). At the onset of the disease, children with posterior segment uveitis were more likely to have impaired VA (<0.4 LogMAR 23 of 33 vs 0.4–1 LogMAR 5 of 15; blindness 2 of 8; $\chi^2 = 8.54$; $P = 0.014$), even when expressed as continuous variables (0.413 vs 0.023; $P = 0.001$).

The median time for the administration of the first systemic treatment was six months (IQR 2–9). Methotrexate was prescribed as the first-line immunosuppressive treatment in 93 children (80.2%), 22 received adalimumab (19%), of whom 5 had concomitant methotrexate, and 1 child was given mycophenolate mofetil (MMF) (0.9%). For second-line treatment, 45 children received adalimumab (75%), 14 received MMF (23.3%), and 1 received tocilizumab (1.7%) (Table 2). At the last available follow-up, we observed that there was a significant improvement in the best corrected VA expressed in LogMAR ($P < 0.001$) and stratified ($P < 0.001$) in the number of children with complications ($P = 0.011$) and in the number of complications ($P < 0.001$) (Supplementary Table 1).

The 22 patients, 5 of them with concomitant methotrexate, receiving adalimumab as first-line therapy were more likely to achieve ocular remission than those on methotrexate alone (20 of 22 vs 41 of 93; $\chi^2 = 31.359$; $P < 0.001$). No difference in time to achieve remission on treatment (Kruskal-Wallis $P = 0.9796$ on those who reached remission; log-rank $\chi^2 = 0.41$; $P = 0.519$; Figure 1A) has been detected between these two

Table 1. Ocular and laboratory characteristics of the population included*

Variable	Whole cohort (n = 116)	Anterior (n = 62; 53.9%)	Intermediate (n = 25; 20.9%)	ant+intermediate (n = 13; 11.3%)	Panuveitis (n = 16; 13.9%)	*P* value[a]
Female sex, n (%)	55 (47.4)	29 (46.8)	11 (44.0)	6 (46.2)	9 (56.3)	0.888
Age at onset, median (IQR)	110 (75–134)	98 (68–136)	118 (105–133)	105 (75–113)	114 (94–132)	0.2998
Duration, median (IQR)	52 (35–79)	47 (33–68)	70 (48–92)	55 (31–60)	59 (42–81)	0.1093
ANA positivity,[b] n (%)	33 (28.5)	23 (37.1)	4 (16.0)	1 (7.8)	5 (31.3)	0.256[c]
ESR,[d] median (IQR), mm/h	10 (2–23)	16 (7–24)	2 (2–9)	9 (6–19)	29 (23–38)	0.0019
CRP,[e] median (IQR), mg/dl	0.1 (0.1–0.3)	0.1 (0.1–0.3)	0.3 (0.1–0.4)	0.2 (0.1–0.6)	0.1 (0.1–0.3)	0.2794
Bilateral uveitis, n (%)	98 (84.5)	51 (82.3)	21 (84.0)	12 (92.3)	14 (87.5)	0.812
Symptomatic uveitis,[f] n (%)	88 (77.9)	43 (70.5)	19 (79.2)	12 (92.3)	14 (93.3)	0.132[g]
Children with complications at onset,[h] n (%)	80 (69.0)	43 (69.4)	15 (60.0)	10 (76.9)	12 (75.0)	0.467
Complications,[h] n (%)	2 (1–4)	2 (1–4)	1 (0–2)	2 (1–4)	2 (2–4)	0.0131
BCVA onset						0.0192
LogMAR,[i] median (IQR)	0.2 (0.0–0.5)	0 (0.0–0.3)	0.4 (0.2–0.8)	0.3 (0.0–0.4)	0.3 (0.0–0.6)	
<0.3, n (%)	49 (42.2)	27 (43.6)	7 (28.0)	8 (61.5)	7 (43.8)	
0.4–1, n (%)	21 (18.1)	6 (9.7)	8 (32.0)	3 (23.1)	4 (25.0)	0.242
>1, n (%)	11 (9.5)	3 (4.8)	4 (16.0)	2 (15.4)	2 (12.5)	

* ANA, antinuclear antibody; ant+intermediate, anterior and intermediate; BCVA, best corrected visual acuity; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IQR, interquartile range; LogMAR, Logarithm of the Minimum Angle of Resolution.
[a] *P* values are computed from chi-square test for categorical variables and from Kruskal-Wallis test for continuous variables.
[b] Completed in 92 patients.
[c] $\chi^2 = 7.7653$.
[d] Completed in 43 patients.
[e] Completed in 68 patients.
[f] Completed in 113 patients.
[g] $\chi^2 = 5.605$.
[h] Completed in 98 patients.
[i] Completed in 81 patients.

groups. The child who received MMF as first-line therapy did not achieve disease remission with this treatment. Among children who achieved remission, there were no significant differences in frequency of relapse on therapy (12 of 41 vs 4 of 20; $\chi^2 = 0.597$; $P = 0.440$), but children receiving methotrexate alone relapsed significantly earlier compared with children on adalimumab (median 17 vs 23 months; Kruskal-Wallis $P = 0.155$; Mantel Cox $\chi^2 = 4.35$, $P = 0.043$, corrected for the duration of treatment; odds ratio [OR] 1.027; CI 1.001–1.0054; Figure 1B).

At the last available follow-up, children who were on adalimumab as first-line treatment (plus or minus methotrexate) were significantly more likely to have stopped the treatment for persistent remission than methotrexate alone (13 of 22 vs 23 of 93; $\chi^2 = 25.90$; $P < 0.001$) (Table 2). The number of relapses and the time to relapse after drug withdrawal were not significantly different between the two groups (Table 2).

Addressing second-line therapy, adalimumab was the most frequently administered drug given to 45 of 60 children (75%), in 39 with concomitant methotrexate and in 1 with mycophenolate, followed by mycophenolate administered to 14 of 60 children (23%) (Table 2). Children who received adalimumab (plus or minus methotrexate) as a second-line therapy were more likely to achieve remission on treatment compared with mycophenolate (40 of 45 vs 9 of 14; $\chi^2 = 14.6662$; $P = 0.005$), with no difference in time to achieve disease remission (Table 2; Figure 2A). We did not observe a significant difference in relapse on treatment (Table 2), time to relapse on treatment (Figure 2B), number of patients who stopped treatment, relapse after drug withdrawal, and time to relapse after drug withdrawal between the two groups. Additionally, we stratified the analyses of outcomes of the 116 patients with cCIU who received the first systemic therapy based on the different nature of anatomic subtype of uveitis and clustering by anterior involvement (61; 52%) versus posterior segment uveitis (55; 47%).

Children with posterior segment uveitis were more likely to achieve disease remission when receiving adalimumab (plus or minus methotrexate) as the first-line treatment compared with children who received methotrexate (12 of 13 vs 13 of 41; $\chi^2 = 32.3024$; $P < 0.001$); conversely, children with anterior uveitis did not show significant differences in disease remission when receiving adalimumab (plus or minus methotrexate) or methotrexate as first-line treatment (8 of 9 vs 28 of 52; $\chi^2 = 3.9558$; $P = 0.138$). Similarly, children with posterior segment uveitis were more likely to stop the first-line treatment for persistent remission when receiving adalimumab (plus or minus methotrexate) compared with methotrexate (9 of 13 vs 9 of 41; $\chi^2 = 18.5608$; $P = 0.001$); conversely, children with anterior uveitis did not show significant differences in treatment withdrawal for persistent remission when receiving adalimumab (plus or minus methotrexate) or methotrexate as first-line treatment (4 of 9 vs 14 of 37; $\chi^2 = 1.05$; $P = 0.305$).

In patients receiving methotrexate, the following factors did not affect the chance of achieving remission: biologic sex, ANA positivity, ESR at onset, the number of complications, and the type of complications at the disease onset. However, children with lower VA at onset were less likely to achieve disease remission with methotrexate (0.413 vs 0.023; $P = 0.001$).

Table 2. Treatment performed in a cohort of childhood chronic noninfectious uveitis*

	First course of systemic treatment					Second course of systemic treatment				
Treatment	Overall (n = 116)	MTX (n = 93; 80.2%)	MMF (n = 1, 0.9%)	ADA (n = 22, 19.0%)	*P* value	Overall (n = 60)	ADA (n = 45, 75%)	MMF (n = 14, 23.3%)	TCZ (n = 1, 1.7%)	*P* value
Concomitant therapy	5 MTX	–	–	5 MTX	–	40 MTX, 1 MMF	39 MTX, 1 MMF	–	1 MTX	–
Time of administration,[a] median (IQR)	6 (2–9)	5 (2–9)	4 (4–4)	7 (4–10)	0.1726	13 (7–24)	12 (7–19)	16 (8–31)	21 (21–21)	0.3211
Duration of therapy,[b] median (IQR)	25 (14–39)	24 (11–40)	5 (5–5)	33 (24–39)	0.1141	31 (12–41)	27 (15–40)	34 (7–49)	–	0.5011
Achievement of remission on therapy,[c] n (%)	61 (52.6)	41 (44.1)	–	20 (90.1)	<0.001[d]	49 (81.7)	40 (88.9)	9 (64.3)	–	0.005[e]
Time to achieve remission,[f] median (IQR)	6 (5–7)	6 (5–6.5)	–	6 (5–7.5)	0.9796	6 (5–9)	6 (5–9)	9 (5–11)	–	0.4195
Relapse on therapy in patients who achieved remission,[g] n (%)	16 (26.2)	12 (29.3)	–	4 (20.0)	0.440[h]	21 (42.9)	17 (42.5)	4 (44.4)	–	0.891[i]
Time to first relapse on treatment in patients who achieved remission,[j] median (IQR)	18 (10–25)	17 (10–23)	–	23 (16–28)	0.1555	18 (9–25)	18 (9–27)	18 (12–21)	–	0.7048
Pts stopping drug for persistent remission,[k] n (%)	36 (31.0)	23 (24.7)	–	13 (59.1)	<0.001[l]	26 (43.3)	22 (48.9)	4 (28.6)	–	0.077[m]
Uveitis relapse after stopping drug,[n] n (%)	20 (55.6)	12 (52.2)	–	8 (61.5)	0.587[o]	19 (76.0)	18 (81.8)	1 (33.3)	–	0.065[p]
Time free from relapse after stopping drug,[q] median (IQR)	5 (3–19)	6 (2–21)	–	4 (4–17)	0.6791	6 (5–12)	6 (5–12)	7 (4–25)	–	0.8815

* ADA, adalimumab; MMF, mycophenolate mofetil; MTX, methotrexate; IQR, interquartile range; TCZ, tocilizumab.
[a] n = 116 in first course; n = 60 in second course.
[b] n = 114 in first course; n = 58 in second course.
[c] n = 115 in first course; n = 59 in second course.
[d] $\chi^2 = 31.3591$.
[e] $\chi^2 = 14.6662$.
[f] n = 59 with achievement of remission in first course; n = 47 in second course.
[g] n = 61 in first course; n = 49 in second course.
[h] $\chi^2 = 0.5968$.
[i] $\chi^2 = 0.2319$.
[j] n = 61 in first course; n = 48 in second course.
[k] n = 115 in first course; n = 60 in second course.
[l] $\chi^2 = 25.9040$.
[m] $\chi^2 = 8.4322$.
[n] n = 36 in first course; n = 26 in second course.
[o] $\chi^2 = 0.2950$.
[p] $\chi^2 = 3.4024$.
[q] n = 36 in second course; n = 25 in second course.

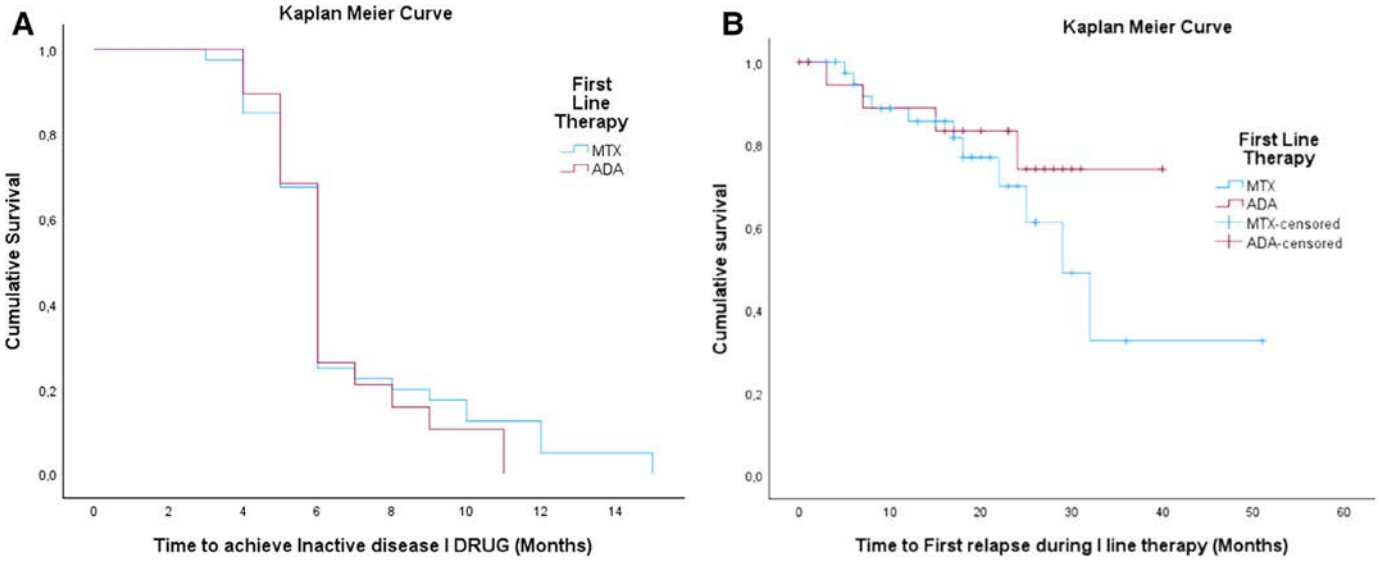

Figure 1. (A) Survival curve of the time to achieve remission on treatment with the first-line treatment (log-rank, $\chi^2 = 0.41$; $P = 0.522$). (B) Survival curve of the time to the first relapse on treatment after achieving remission with first-line treatment (log-rank, $\chi^2 = 4.35$; $P = 0.043$). ADA, adalimumab; MTX, methotrexate.

Additionally, treatment outcomes of patients receiving adalimumab (plus or minus methotrexate) as first-line immunosuppressive treatment were compared with patients receiving adalimumab (plus or minus methotrexate) after conventional DMARD failure. No significant differences were found between the two groups in ocular remission on treatment (20 of 22 vs 40 of 45), relapse on treatment (4 of 22 vs 16 of 39), stopping treatment due to persistent remission (12 of 22 vs 22 of 40), relapse after drug withdrawal (7 of 12 vs 18 of 22), time to achieve remission on treatment (median 6 vs 6 months), and time to flare after drug withdrawal for persistent remission (median 4 vs 6.5 months). However, children who received adalimumab (plus or minus methotrexate) as second-line treatment showed earlier relapse on treatment compared with children who received adalimumab (plus or minus methotrexate) as first-line treatment (log-rank $\chi^2 = 5.28$; $P = 0.021$; Supplementary Figure 2).

Results from the multivariate logistic regression models applied to the imputed datasets (Table 3) indicate that children

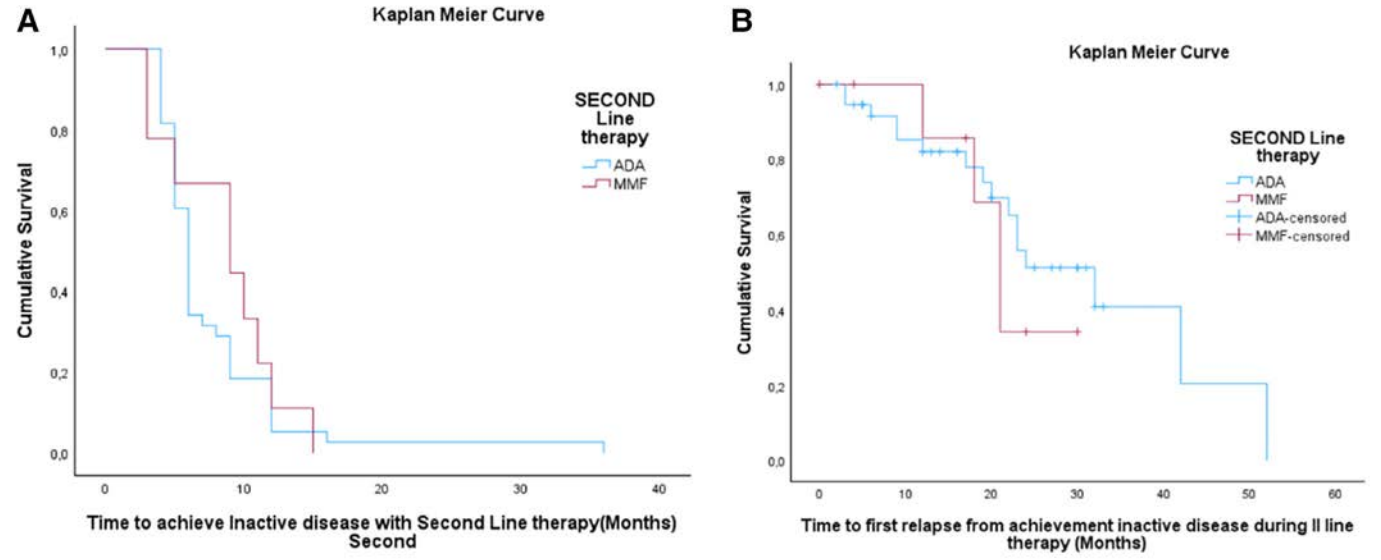

Figure 2. (A) Survival curve of the time to achieve remission on treatment with the second-line treatment (log-rank, $\chi^2 = 0.294$; $P = 0.587$). (B) Survival curve of the time to the first relapse on treatment after achieving remission with second-line treatment (log-rank, $\chi^2 = 2.90$; $P = 0.100$). ADA, adalimumab; MMF, mycophenolate mofetil. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/art.70090/abstract.

Table 3. Pooled results from the multivariable logistic regression models for achievement of remission, relapse on therapy, and stopping drug for persistent remission (among patients who achieved remission) and relapse out of therapy (among patients who stop drug) after multiple imputation (50 datasets)*

Variable	Achievement of remission	Relapse on therapy	Stop drug for persistent remission	Relapse out of therapy
Treatment, OR (95% CI)				
MTX	1	1	1	1
ADA	**17.87 (3.44–92.72)**	0.39 (0.07–2.26)	0.75 (0.14–4.14)	2.58 (0.34–19.68)
Duration of therapy, OR (95% CI)	1.00 (0.98–1.03)	**1.12 (1.03–1.22)**	**0.91 (0.85–0.97)**	1.01 (0.94–1.09)
Sex, OR (95% CI)				
Boys	1	1	1	1
Girls	0.67 (0.27–1.68)	1.51 (0.32–7.09)	0.22 (0.04–1.12)	0.39 (0.05–2.92)
Age, OR (95% CI)	1.01 (0.99–1.02)	1.00 (0.97–1.02)	1.01 (0.99–1.03)	0.97 (0.93–1.01)
Disease duration, OR (95% CI)	1.00 (0.98–1.02)	1.00 (0.97–1.03)	**1.09 (1.04–1.15)**	1.03 (0.98–1.08)
Anatomic location, OR (95% CI)				
Anterior	1	1	1	1
Nonanterior	**0.33 (0.12–0.88)**	0.42 (0.08–2.30)	**7.51 (1.24–45.4)**	0.73 (0.09–5.73)
ANA positivity, OR (95% CI)				
Yes	1	1	1	1
No	0.84 (0.25–2.79)	1.56 (0.23–10.77)	1.09 (0.16–7.21)	0.59 (0.06–5.88)
Complications, OR (95% CI)				
Yes	1	1	1	1
No	0.93 (0.25–3.48)	0.83 (0.08–8.87)	0.67 (0.09–4.95)	5.6 (0.63–49.48)
LogMAR onset, OR (95% CI)	0.67 (0.22–2.10)	0.97 (0.22–4.30)	0.59 (0.12–2.95)	1.06 (0.07–16.28)

* Bold indicates significant values. ADA, adalimumab; ANA, antinuclear antibody; CI, confidence interval; LogMAR, Logarithm of the Minimum Angle of Resolution; MTX, methotrexate; OR, odds ratio.

treated with adalimumab had significantly higher odds of achieving disease remission compared with those treated with methotrexate alone (OR 17.87; 95% CI 3.44–92.72), and children with nonanterior uveitis had significantly lower odds of achieving disease remission (OR 0.33; 95% CI 0.12–0.88). After adjusting for covariates, children receiving adalimumab are approximately 18 times more likely to achieve remission, whereas children with nonanterior uveitis are 0.3 times less likely to achieve disease remission. Moreover, the duration of therapy was significantly associated with relapse on therapy (OR 1.12; 95% CI 1.03–1.22) and with stopping drug for persistent remission (OR 0.91; 95% CI 0.85–0.97), whereas disease duration was significantly associated with stopping drug for persistent remission (OR 1.09; 95% CI 1.04–1.15) and nonanterior uveitis with stopping the drug (OR 7.51; 95 CI 1.24–45.4). The Cox proportional hazards models for time to achieve remission, time to relapse on treatment, and time to relapse out of therapy showed a significant association between relapse on treatment and duration of therapy (OR 1.04; 95% CI 1.00–1.08) (Table 4).

DISCUSSION

To the best of our knowledge, this is one of the largest cohorts reporting the therapeutic outcomes and course of cCIU in children. Adalimumab plus or minus methotrexate, a key drug for JIA-associated uveitis,[11,12] outperformed methotrexate as first-line treatment in achieving ocular remission in our cohort of children with idiopathic uveitis, particularly in posterior segment uveitis. Conversely, in anterior uveitis, there was no significant difference in disease remission between methotrexate and adalimumab, and methotrexate can be still considered as a valid treatment option. However, of those who achieved remission with first-line therapy, children who were treated with methotrexate alone relapsed more quickly than children treated with adalimumab. Additionally, a higher proportion of children on adalimumab were able to discontinue treatment due to persistent remission. These results echo clinical trial data in JIA-associated uveitis of Ramanan et al and Quartier et al, who demonstrated that adding adalimumab to methotrexate significantly suppressed uveitis activity, reduced the requirement for topical steroids, and delayed treatment failure compared with placebo.[11,12]

Furthermore, the beneficial effects of adalimumab on childhood uveitis demonstrated in our cohort are in line with previous case series and cohort studies with different subtypes of uveitis, including JIA-associated uveitis. They showed efficacy of adalimumab for childhood uveitis but did not compare it to methotrexate effect.[13–21] Indeed, in our cohort, methotrexate was still the most common first-line treatment used for the management of pediatric noninfectious uveitis, in keeping with national and international guidelines and the published literature.[6–9,15,19,20,22–24] However, methotrexate achieved uveitis remission in only 44% of our cases; this is in contrast with other studies reporting uveitis remission in around 73% of cases, possibly reflecting the more refractory nature of our cohort that included posterior segment as well as anterior uveitis.[24] When looking at the subcohorts, adalimumab (plus or minus methotrexate) appeared to show a

Table 4. Pooled results from the multivariable Cox proportional hazard regression model for time to achievement of remission, relapse on therapy, and relapse out of therapy after multiple imputation (50 datasets)*

Variable	Achievement of remission with first-line treatment	Relapse on treatment after remission with first line	Relapse out of therapy
Treatment, HR (95% CI)			
MTX	1	1	1
ADA	1.29 (0.70–2.36)	0.69 (0.18–2.67)	1.00 (0.34–2.92)
Duration of therapy, HR (95% CI)	0.99 (0.97–1.02)	**1.04 (1.00–1.08)**	1.02 (0.96–1.08)
Sex, HR (95% CI)			
Boys	1	1	1
Girls	1.24 (0.70–2.21)	1.72 (0.52–5.71)	0.54 (0.16–1.86)
Age, HR (95% CI)	1.00 (0.99–1.01)	1.00 (0.98–1.02)	0.98 (0.95–1.01)
Disease duration, HR (95% CI)	1.00 (0.99–1.01)	0.99 (0.97–1.01)	1.00 (0.98–1.03)
Anatomic location, HR (95% CI)			
Anterior	1	1	1
Nonanterior	0.80 (0.45–1.42)	0.43 (0.10–1.88)	1.20 (0.42–3.4)
ANA positivity, HR (95% CI)			
Yes	1	1	1
No	0.90 (0.44–1.82)	1.27 (0.31–5.27)	0.62 (0.14–2.85)
Complications, HR (95% CI)			
Yes	1	1	1
No	0.61 (0.29–1.32)	0.73 (0.13–4.07)	2.89 (0.64–13.1)
LogMAR onset, HR (95% CI)	0.85 (0.50–1.43)	1.35 (0.41–4.51)	0.68 (0.18–2.6)

* Bold indicates significant values. ADA, adalimumab; ANA, antinuclear antibody; CI, confidence interval; HR, hazard ratio; LogMAR, Logarithm of the Minimum Angle of Resolution; MTX, methotrexate.

significant benefit over methotrexate in posterior segment uveitis compared with anterior uveitis, but the number on adalimumab in the anterior uveitis group was smaller, which may have impacted the results.

Moreover, children in our cohort treated with methotrexate showed a significant earlier relapse of uveitis compared with those on adalimumab, which aligns with the work of Tirelli et al,[25] who showed that patients with JIA-associated uveitis have a low chance of maintaining long-lasting uveitis remission on methotrexate. Children treated with adalimumab as first-line treatment have a greater chance of discontinuing the therapy than those treated with methotrexate alone, which is likely to be due to better disease control with adalimumab.

Adalimumab is recommended as a second-line immunosuppressive agent for children with uveitis, including idiopathic uveitis.[4,6–8,11,12,16,17,22,26–28] In our cohort, comparing adalimumab used as a first-line versus using it as second-line agent, the ability to achieve remission and the proportion of patients who relapsed were similar. However, when adalimumab was used as a second-line agent, it was associated with an earlier relapse on therapy compared with use as a first-line therapy. Better performance of adalimumab when used as a first-line treatment has also been previously reported, although in a smaller and heterogenous cohort of 26 children with different subtypes of uveitis.[17]

There are several limitations with the study. The retrospective nature of the study, as well as the characteristics of the two recruiting centers, both of which are tertiary centers, will have introduced selection and referral bias. Some of the subcohorts of patients had small numbers of patients, hampering the chance to perform additional comparisons (ie, comparing the performance of adalimumab alone versus adalimumab with methotrexate). Adalimumab is only funded as a second-line immunosuppressive therapy in the United Kingdom; thus, adalimumab as a first-line approach mostly comes from the Florence, Italy center. Missing data and limited length of follow-up after treatment withdrawal will have affected the data analysis. Data on adalimumab failure secondary to antibody development were not available. Partial response was not assessed due to the limited number of patients.

Drug doses and subtherapeutic or tapering doses of drugs were not recorded. Multiple imputation was used to take into account for missing data uncertainty, leading to more accurate standard errors and unbiased results. However, this methodology involves increased complexity, computation time, and potential bias if imputation models are mis-specified, requiring careful implementation. It is superior to single imputation for robust inferences but demands more resources than simpler methods.

Treatment of cCIU is challenging with disease remission using the first-line treatment achieved in only 50% of patients. Adalimumab plus or minus methotrexate shows promise as a first-line treatment for cCIU, and it is possible that patients with posterior segment uveitis, who tend to have worse VA at presentation, would benefit from more aggressive treatment with biologics from the disease onset. Prospective, randomized trials comparing methotrexate and adalimumab as an initial systemic therapy in pediatric uveitis, in both anterior and posterior segment cCIU, would help define optimal treatment algorithms. Longevity of cCIU remission with adalimumab monotherapy also deserves

further study, including the risk of drug antibody formation. Effective treatment of cCIU is important not only for reducing ocular damage and improving visual outcomes for children but also for managing direct and indirect health care costs.

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AUTHOR CONTRIBUTIONS

All authors contributed to at least one of the following manuscript preparation roles: conceptualization AND/OR methodology, software, investigation, formal analysis, data curation, visualization, and validation AND drafting or reviewing/editing the final draft. As corresponding author, Dr Maccora confirms that all authors have provided the final approval of the version to be published and takes responsibility for the affirmations regarding article submission (eg, not under consideration by another journal), the integrity of the data presented, and the statements regarding compliance with institutional review board/Declaration of Helsinki requirements.

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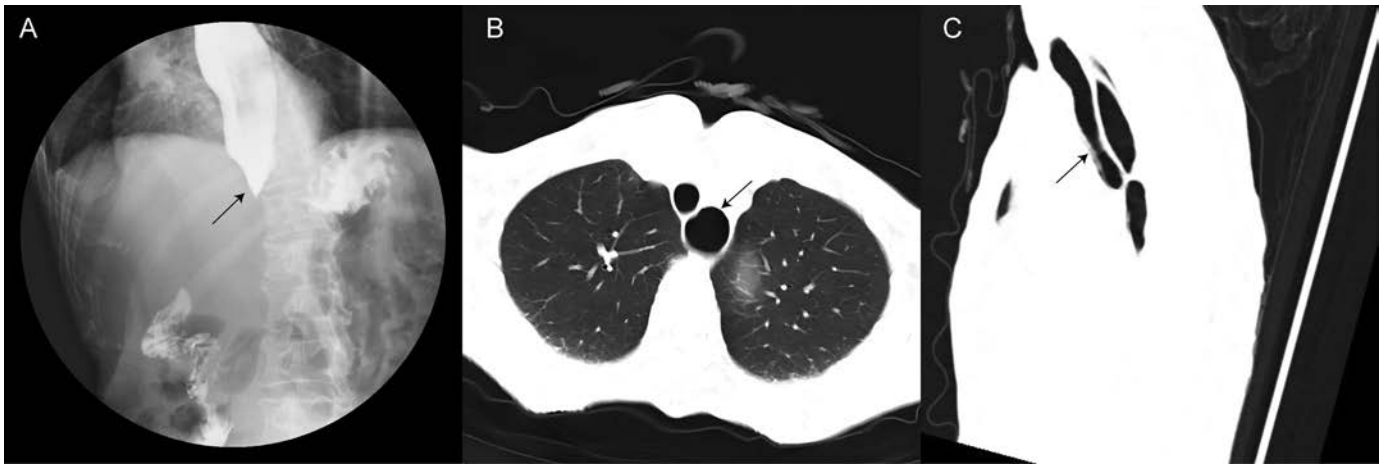
Clinical Image: Esophageal dilation and stenosis in systemic sclerosis



The patient, a 59-year-old woman, presented to the emergency department with progressively worsening dyspnea and upper abdominal distension over the past 12 days. For five years, she had been experiencing progressive skin tightening, burning substernal pain, and shortness of breath due to systemic sclerosis (SSc). On physical examination, the skin was significantly thickened and hardened, and the "salt-and-pepper" sign was evident on her upper chest. She weighed 34 kg (75 lb) and had grade 3 muscle strength. (A) Iodine–water esophagography demonstrated esophageal lumen dilation and high-grade stenosis, likened to a bird's beak between the lower end of the esophagus and the stomach. Chest high-resolution computed tomography scan revealed a markedly dilated esophagus. (B) On axial images, the esophageal diameter was greater than that of the trachea, (C) whereas the sagittal view showed signs of tracheal compression. A diagnosis of SSc with esophageal dilation and stenosis was established. Esophageal involvement is a severe manifestation of SSc and is associated with anti-Topo1 antibodies, possibly resulting from esophageal smooth muscle fibrosis and nerve injury.[1,2] Severe esophageal disorders often indicate a poor prognosis and higher mortality risk.[1,2] Unfortunately, this patient succumbed to malnutrition and respiratory failure caused by her esophageal involvement and respiratory muscle weakness related to SSc.

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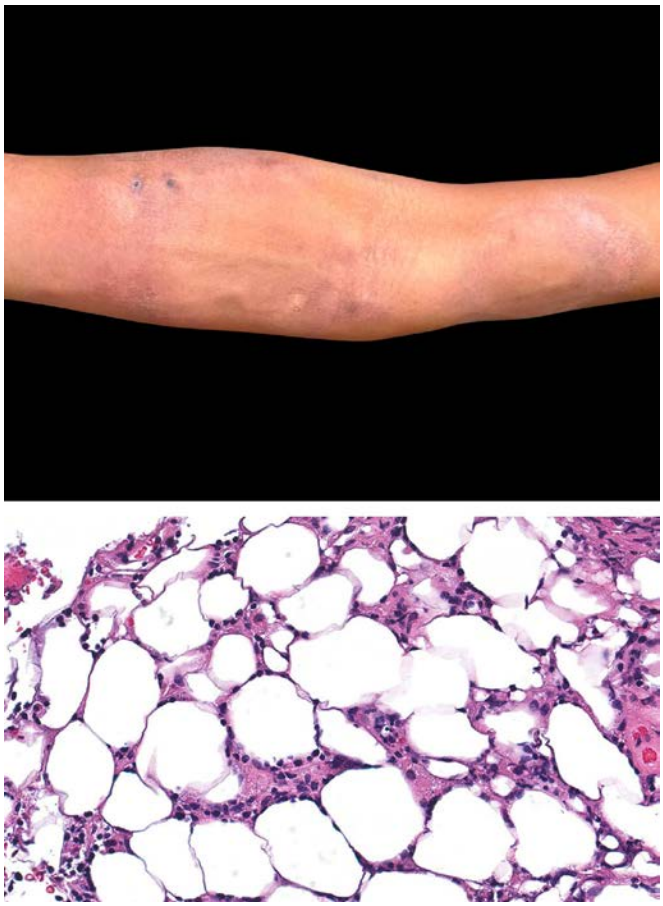
Clinical Images: Subcutaneous panniculitis-like T cell lymphoma



The patient, a 40-year-old woman, with a medical history of systemic lupus erythematosus, presented with a six-year history of leg discoloration. Biopsies performed since disease onset showed findings suggestive of tumid lupus erythematosus, discoid lupus erythematosus (DLE), and lupus erythematosus panniculitis (LEP). However, her hyperpigmented plaques continued to progress despite treatment. One year after the most recent biopsy showing DLE and LEP, she presented with new indurated plaques on her arms and legs, darkening of old lesions, and new-onset fatigue. Her medications included hydroxychloroquine at 400 mg daily, methotrexate at 20 mg weekly, prednisone at 10 mg taper, topical clobetasol, tacrolimus, and triamcinolone. She had received monthly anifrolumab infusions for a few months with no improvement of lesions. Examination showed hyperpigmented indurated plaques with erythematous borders on the anterior bilateral thighs, forearms, and lower back. Hyperpigmented nodules were present on the left leg and right forearm (Panel 1). Right forearm punch biopsy showed atypical lymphocytes rimming adipocytes in the subcutaneous tissue (Panel 2). The majority of atypical lymphocytes were CD8+ with positive Granzyme B, T cell intracellular antigen 1, Ki-67, and Beta F1 immunostaining. These findings were consistent with subcutaneous panniculitis-like T cell lymphoma (SPTCL), and the patient was referred to our cutaneous lymphoma team. SPTCL is a rare primary cutaneous lymphoma that mimics panniculitis. Autoimmune disease is present in approximately 20% of cases, and clinicopathologic presentation is often mistaken for LEP, making diagnosis challenging.[1,2] This case highlights that SPTCL should be in the differential of lupus panniculitis that transforms clinically or continues to worsen despite appropriate treatment.

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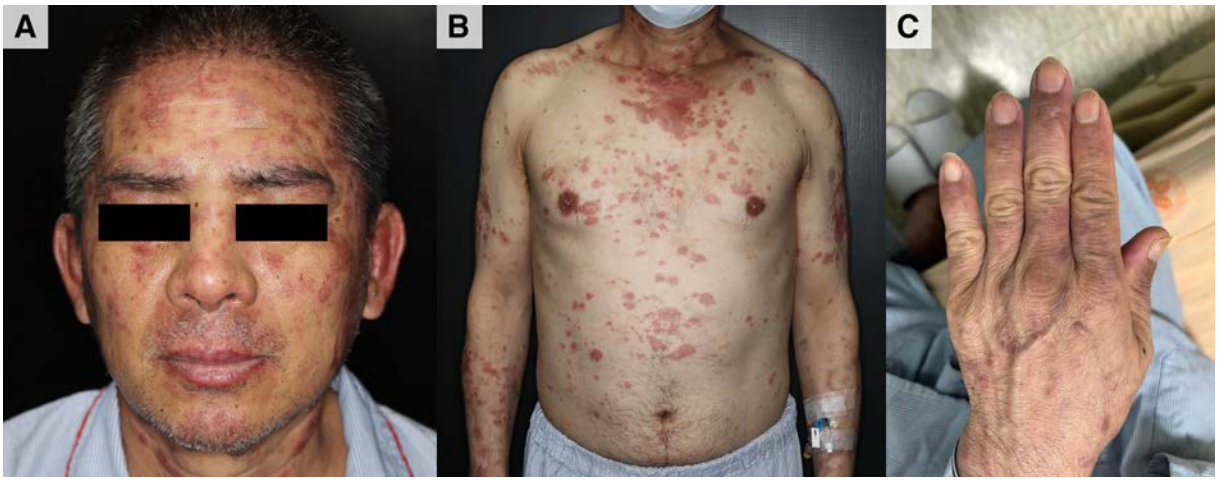
Clinical Images: Targeting Rowell syndrome in systemic lupus erythematosus



Rowell syndrome was originally proposed as a unique clinical pattern by Rowell et al in 1963.[1] It describes the development of erythema multiforme (EM)–like eruptions in individuals with underlying lupus erythematosus (LE), representing an uncommon but characteristic overlap of these two conditions. Over the decades, several diagnostic criteria have been proposed to better characterize this association between lupus and EM-like eruptions. Although its definition remains debated, the revised criteria proposed by Zeitouni et al are commonly referenced.[2] These criteria require the presence of all three major components (LE, EM-like lesions, and a speckled antinuclear antibody pattern) together with at least one minor criterion, including anti-Ro/SSA or anti-La/SSB positivity, rheumatoid factor, or chilblain-like lesions. A previously healthy 60-year-old man developed a two-week generalized, pruritic, painful skin rash. Physical examination revealed well-demarcated, edematous, and erythematous macules, papules, and plaques, with typical/atypical targetoid lesions over the face (A), trunk (B), and limbs, along with acral violaceous papules (C). Palms, soles, and mucosa were spared. The presence of targetoid lesions was highly suggestive of EM, prompting an investigation into its common triggers. However, a thorough investigation for its common triggers proved unrevealing. A comprehensive review excluded typical infectious etiologies, particularly recent herpes simplex virus or *Mycoplasma pneumoniae* infection. Furthermore, there was no history of exposure to culprit medications, such as nonsteroidal anti-inflammatory drugs, antibiotics, or anticonvulsants. With no identifiable cause, the possibility of an autoimmune etiology was raised. Evaluation for a systemic autoimmune disease revealed speckled antinuclear antibody (1:1,280), anti–double-stranded DNA antibody, anti-Ro-52, and rheumatoid factor positivity; low complement levels; and low-level proteinuria. Histopathologic analysis of skin from the upper back demonstrated vacuolar interface dermatitis with dyskeratosis and subepidermal separation. CD123 immunohistochemical staining revealed plasmacytoid dendritic cell infiltration in the dermal, intraepidermal, and perieccrine regions.[3,4] A diagnosis of systemic LE presenting with features of Rowell syndrome was established.[5] This rare entity is defined by the development of EM-like lesions in patients with lupus. The acral violaceous papules were identified as chilblain lupus (perniosis), a cutaneous finding frequently associated with this syndrome. Treatment with hydroxychloroquine (400 mg/day, approximately 5 mg/kg/day), methotrexate (15 mg/wk), and prednisolone (initiated at 0.5 mg/kg/day and subsequently tapered to a maintenance dose of 5 mg/day) led to complete clinical resolution of the cutaneous lesions within four months. Given its rarity, Rowell syndrome carries important clinical significance, as EM-like eruptions in lupus may be misinterpreted as infectious or drug-induced EM. Awareness of this association helps prevent diagnostic delay and underscores the educational value of this case.

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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LETTER

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Endometriosis as a comorbidity in pregnant patients with systemic lupus erythematosus: comment on the article by Nguyen et al

To the Editor:

We read with great interest the article by Nguyen et al[1] in *Arthritis & Rheumatology* focusing on the investigation of the temporal trends in the proportions of adverse pregnancy outcomes (APOs) and treatment in a nationwide cohort of pregnant patients with systemic lupus erythematosus (SLE) in Sweden over two decades. Aiming to estimate the burden of SLE in pregnancy, the authors conducted a descriptive analysis of over 1,400 pregnant patients with SLE, and they found that APOs (preeclampsia, preterm delivery, and small for gestational age birth) and cesarean delivery have decreased over the last two decades in Sweden, with these findings potentially reflecting improved treatment strategies over the years.[1]

Pregnant patients with SLE have elevated risks of APOs, such as fetal loss, preterm delivery, fetal growth restriction, and hypertensive disorders of pregnancy compared to those without SLE.[1,2] Although the putative role of a coexisted endometriosis in pregnancy outcome was not discussed in the context of the study of Nguyen et al,[1] we wish to point out that patients with SLE have a significantly higher risk of endometriosis compared with those without SLE.[3] Endometriosis is a disease characterized by both inflammatory responses and immune system dysregulation, thus resembling autoimmune diseases.[4] Moreover, recent investigations highlighted the partially shared genetic factors associated with both SLE and endometriosis, thus emphasizing the role of various gene polymorphisms related to inflammation, autoimmunity, tissue remodeling and neoangiogenesis, interferon pathways and signaling, cytokines function, tumor growth or suppression, NF-κB pathway, hormonal function, and metabolism in the observed associations.[4,5] Although SLE is not generally considered an absolute obstacle to pregnancy,[6] endometriosis predisposes patients to an increased risk of early pregnancy loss and later pregnancy complications, including fetal growth restriction, gestational diabetes, placenta previa, antepartum and postpartum hemorrhage, and cesarean hysterectomy.[7] Therefore, we suggest that the role of endometriosis in pregnant patients with SLE cannot be underestimated and clinicians should always be alerted for the possible co-occurrence of these diseases, considering that an increased awareness and vigilance is needed. Moreover, repurposing therapies across these conditions may decrease further the observed APOs.

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Reply

To the Editor:

We thank the authors for their interest in our recent article[1] and for highlighting the potential role of endometriosis in pregnancies among patients with systemic lupus erythematosus (SLE). We agree that endometriosis is an important clinical condition

characterized by immune dysregulation and inflammatory pathways that may overlap with autoimmune diseases, including SLE. The possibility that coexisting endometriosis could influence pregnancy outcomes in this population is a clinically relevant consideration.

As noted by the authors, prior research has suggested that endometriosis may be associated with SLE[2,3] and with adverse pregnancy outcomes (APOs),[4] and emerging literature indicates shared biologic mechanisms between endometriosis and SLE.[5] Increased awareness of coexisting conditions is important for clinicians caring for pregnant patients with SLE, particularly given the complexity of managing risks in this high-risk population.

Our study was designed as a nationwide descriptive analysis aimed at characterizing temporal trends in APOs and treatment patterns among pregnant patients with SLE in Sweden over two decades, rather than evaluating etiologic contributions of specific comorbidities.[1] The primary objective was to assess whether the burden of APOs has changed over time at the population level and to contextualize these trends alongside evolving treatment practices. We focused on the overall population and several selected clinical subgroups with established and well-documented associations with APO risk in SLE, such as antiphospholipid syndrome and lupus nephritis. Evaluation of additional coexisting gynecologic conditions, including endometriosis, was beyond the scope of the present analyses. In response to the authors' interest in endometriosis, we searched for a history of endometriosis before pregnancy in our cohort and observed a low prevalence; 17 of 1,417 (1.2%) SLE pregnancies in which the woman had a history of endometriosis before pregnancy. Given these small numbers, particularly when further stratified across calendar periods, meaningful temporal trend analyses of the subgroup with endometriosis would not have been statistically reliable. In addition, because our study population was restricted to pregnancies that led to delivery, it was not designed to evaluate the broader reproductive implications of endometriosis in SLE, such as fertility challenges or the need for assisted reproductive treatments.

Importantly, the observed decline in APO proportions over time in our study is unlikely to be explained solely by unmeasured comorbidities unless their prevalence changed substantially during the study period. Future research starting from patients with SLE and coexisting endometriosis, rather than pregnancies alone, may provide additional insight into reproductive trajectories, including fertility treatment use and pregnancy outcomes. Such studies could help refine risk stratification and guide multidisciplinary management strategies.

We appreciate the authors' emphasis on increased clinical vigilance and the need for continued investigation into factors that may contribute to pregnancy risk in patients with SLE. Their comments highlight an important area for future research, and we hope that our findings contribute to ongoing efforts to improve care and outcomes for this population.

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Interstitial lung disease in ANCA-associated vasculitis: comment on the article by Chalkia et al

To the Editor:

We read with great interest the study by Chalkia et al on interstitial lung disease (ILD) in antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis, which represents an important contribution to understanding this challenging clinical entity.[1] Their European multicenter cohort included 162 patients with ILD in ANCA-associated vasculitis (AAV-ILD), of whom 39 had ANCA-ILD without systemic vasculitis (SV). We recently reported our experience with 101 patients from a pneumology center with a diagnosis of idiopathic interstitial pneumonia or interstitial pneumonia with autoimmune features (IPAF).[2] We retested the autoimmunity serology in all these patients, and 21 (20.8%) of them were found to have perinuclear ANCA (p-ANCA) positivity, whereas 27 were diagnosed as having IPAF p-ANCA negativity. Our study focused on the natural history of patients with p-ANCA–positive ILD, documenting that 43%

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Pregnant patients with SLE have elevated risks of APOs, such as fetal loss, preterm delivery, fetal growth restriction, and hypertensive disorders of pregnancy compared to those without SLE.[1,2] Although the putative role of a coexisted endometriosis in pregnancy outcome was not discussed in the context of the study of Nguyen et al,[1] we wish to point out that patients with SLE have a significantly higher risk of endometriosis compared with those without SLE.[3] Endometriosis is a disease characterized by both inflammatory responses and immune system dysregulation, thus resembling autoimmune diseases.[4] Moreover, recent investigations highlighted the partially shared genetic factors associated with both SLE and endometriosis, thus emphasizing the role of various gene polymorphisms related to inflammation, autoimmunity, tissue remodeling and neoangiogenesis, interferon pathways and signaling, cytokines function, tumor growth or suppression, NF-κB pathway, hormonal function, and metabolism in the observed associations.[4,5] Although SLE is not generally considered an absolute obstacle to pregnancy,[6] endometriosis predisposes patients to an increased risk of early pregnancy loss and later pregnancy complications, including fetal growth restriction, gestational diabetes, placenta previa, antepartum and postpartum hemorrhage, and cesarean hysterectomy.[7] Therefore, we suggest that the role of endometriosis in pregnant patients with SLE cannot be underestimated and clinicians should always be alerted for the possible co-occurrence of these diseases, considering that an increased awareness and vigilance is needed. Moreover, repurposing therapies across these conditions may decrease further the observed APOs.

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Reply

To the Editor:

We thank the authors for their interest in our recent article[1] and for highlighting the potential role of endometriosis in pregnancies among patients with systemic lupus erythematosus (SLE). We agree that endometriosis is an important clinical condition

progressed to overt AAV within 12 months. We identified p-ANCA positivity as a strong predictor of progression to vasculitis (odds ratio 26.3); however, 12 patients with p-ANCA positivity never developed SV. We also compared patients with p-ANCA–positive ILD and p-ANCA–negative IPAF, according to the current definition.[3] p-ANCA–positive ILD had more significantly nonspecific interstitial pneumonia pattern and bronchiectasis at chest high-resolution computed tomography. These intriguing findings raise the question whether p-ANCA–positive ILD is a distinct entity that differs from IPAF.

Chalkia et al provide important complementary insights from a different clinical perspective. Although our cohort captured patients earlier in their disease course at the stage of isolated lung involvement with positive ANCA, their study examined patients with established AAV-ILD (76%) or ANCA-ILD without vasculitis (24%) over a median 4.2-year follow-up. Interestingly, they observed no progression from ANCA-ILD to AAV-ILD during their extended observation period, which may reflect a more stable phenotype in patients with longer-standing ANCA-positive lung disease.

Several convergent findings strengthen the evidence base for clinical management. Both studies identified usual interstitial pneumonia as the predominant pattern (57% in both cohorts), challenging earlier assumptions that nonspecific interstitial pneumonia would predominate in immune-mediated ILD. The novel application of standardized fibrosis scoring by Chalkia et al represents an important methodologic advance, demonstrating that higher baseline fibrosis grade independently predicted both mortality and respiratory failure. This reinforces our observation that patients with p-ANCA positivity with more severe baseline fibrosis never progressed to SV, perhaps reflecting a distinct fibrotic rather than inflammatory endotype.

The divergent findings regarding progression from ANCA-ILD to AAV-ILD likely reflect different clinical populations and observation windows. Our cohort, enriched for newly diagnosed patients, captured the critical early period when progression risk appears highest, whereas the cohort in the study by Chalkia et al with longer disease duration may represent a more stable, lung-limited phenotype. This suggests routine ANCA testing in new ILD diagnoses should be considered, with vigilant monitoring during the first year.

We commend the authors for their rigorous multicenter collaboration and standardized radiologic assessment. Future prospective studies would benefit from systematic ANCA testing at initial ILD diagnosis, inclusion of control groups with ANCA negativity, and randomized comparisons of immunosuppressive versus antifibrotic strategies. Together, our studies highlight both the heterogeneity and poor prognosis of ANCA-associated lung disease, underscoring the urgent need for such trials in this vulnerable population. All data used in this research are already included in the article.

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Reply

To the Editor:

We thank Dr Iannone and colleagues for their comments on our article, "Interstitial lung disease in ANCA-associated vasculitis: a European multicentre study."[1] Our European multicenter cohort included 162 patients with interstitial lung disease (ILD) associated with antineutrophil cytoplasmic antibody–associated vasculitis (AAV) or ILD associated with antineutrophil cytoplasmic antibody (ANCA) positivity in the absence of systemic vasculitis.[1] We identified relevant clinical, radiologic, and prognostic features that help define this disease spectrum. In comparison, Dr Iannone et al analyzed 101 patients with idiopathic interstitial pneumonia, among whom 21 were ANCA positive.[2] Despite differences in cohort composition and study design, both studies highlight the association between myeloperoxidase (MPO)-ANCA and ILD, supporting the concept of ANCA-associated ILD (ANCA-ILD) as a clinically meaningful phenotype.

In the cohort reported by Dr Iannone et al, 43% of patients with ANCA-positive ILD progressed to overt AAV, a rate higher than previously reported.[3] In contrast, no such progression occurred in our cohort during follow-up. Conversely, 19% of patients with ILD associated with AAV (AAV-ILD) in our study had a history of ILD, suggesting that ILD may precede systemic vasculitis in a substantial proportion of cases, and the absence of earlier ANCA testing may represent an important diagnostic pitfall. Taken together, these observations suggest that ANCA-positive ILD can evolve into AAV-ILD, and the reported frequency of this progression depends on the timing of ANCA testing in patients with ILD. Nevertheless, both studies underscore the importance of ANCA testing in patients presenting with ILD, despite the lack of evidence-based treatment strategies for this subgroup.

In our cohort, when comparing patients with ANCA-ILD and AAV-ILD, baseline pulmonary function was similar, with a predominance of the usual interstitial pneumonia (UIP) pattern in both groups. Radiologic fibrosis appeared more extensive in the group with ANCA-ILD, possibly reflecting earlier onset or longer disease duration before diagnosis. Long-term outcomes were comparable, with forced vital capacity percentage and the severity of radiologic fibrosis, which were assessed using our novel systemic fibrosis score, emerging as independent predictors of mortality. Overall mortality was substantial, with lung disease progression and respiratory failure as leading causes of death. Radiologic progression was observed in 53% of patients and occurred more frequently among younger patients and those presenting with a UIP pattern. Similarly, Dr Iannone et al reported radiologic progression in approximately 50% of their cohort. Taken together, these observations suggest that MPO-ANCA–positive ILD represents a distinct clinical entity that requires further characterization of pathophysiology and management.

Author Chalkia's work was supported by the European Renal Association Long-Term Fellowship for Young Greek Nephrologists at the University of Cambridge in collaboration with the Hellenic Society of Nephrology and Stavros Niarchos Foundation. Author Jayne's work was supported by the NIHR Cambridge Biomedical Research Centre.

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Immunometabolic and translational considerations of dipyridamole in experimental rheumatoid arthritis: comment on the article by Marco-Bonilla et al

To the Editor:

We read with great interest the article by Marco-Bonilla et al, "Dual action of dipyridamole in experimental rheumatoid arthritis," which presents compelling evidence that dipyridamole alleviates joint inflammation while preserving skeletal muscle mass in experimental arthritis.[1] The work highlights purinergic signaling as a potential therapeutic axis linking immune regulation and musculoskeletal outcomes in rheumatoid arthritis (RA), and we commend the authors for their valuable contribution to this important area of research.

Although the study offers meaningful insights, several aspects related to mechanistic depth and translational applicability warrant further consideration and could help strengthen the interpretation of the findings. The authors attribute the beneficial effects of dipyridamole to activation of adenosine/A2BR and AMPK/cAMP signaling pathways,[2] supported primarily by pharmacologic modulation of adenosine receptors. However, the study does not distinguish between extracellular and intracellular adenosine or AMP concentrations in skeletal muscle, an important consideration for clarifying the precise molecular cascade underlying the observed effects. In addition, although potential cross-talk between A2AR and A2BR heterodimers is proposed,[3] this interaction is not directly explored, nor is the downstream interplay between AMPK activation and other muscle metabolic pathways comprehensively delineated. Although the current data are informative, more targeted mechanistic approaches—such as the use of AMPK inhibitors or A2BR overexpression systems—could help to solidify the causal relationship between adenosine signaling, AMPK activation, and myostatin downregulation.

An additional point of interest concerns the timing-dependent efficacy of dipyridamole. The study shows that restoration of creatine kinase levels and attenuation of muscle fibrosis are evident with preventive administration starting at disease induction but not with therapeutic treatment initiated after disease establishment. Although this observation is intriguing, the underlying mechanisms remain unclear. It is not known

whether this reflects irreversible muscle structural damage, impaired satellite cell function, or loss of myogenic potential in established RA.[4,5] Moreover, the potential clinical implications of this timing dependence—such as whether dipyridamole may be more effective in early stage disease—are not explicitly discussed. Further exploration of these issues could enhance the translational relevance of the preclinical findings and inform future clinical trial design.

Finally, as a US Food and Drug Administration–approved antiplatelet agent, dipyridamole has well-characterized pharmacokinetic properties and known off-target effects, including vasodilation and bleeding risk. The use of a single dose in the current study provides clear and consistent results; however, a dose–response analysis could offer valuable insight into the optimal therapeutic window for balancing anti-inflammatory and muscle-protective effects. In addition, exploring potential interactions between dipyridamole and standard RA therapies, such as methotrexate or anti–tumor necrosis factor agents, would further contextualize its applicability as a potential adjunct treatment.

In conclusion, this study provides strong phenotypic evidence supporting the therapeutic potential of dipyridamole in experimental RA. Addressing the considerations outlined above may help to further clarify its mechanism of action and strengthen its translational relevance, thereby building on the authors' important and timely work.

Zhu and Wei contributed equally to this work.

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Reply

To the Editor:

In response to Yichun Zhu et al, we appreciate their interest in the implications of our findings in "Dual action of dipyridamole in experimental rheumatoid arthritis"[1] and welcome the opportunity to clarify several aspects. We agree that our nucleotide extraction protocol from frozen tissue does not directly demonstrate whether dipyridamole modulates muscular intracellular or extracellular nucleotide levels, and this limitation was acknowledged in the manuscript. However, intracellular and extracellular nucleotide changes have been previously described in C2C12 cells, and dipyridamole increases intracellular AMP levels and the AMP/ATP ratio, promoting AMPK activation.[2] Our three-dimensional myobundle model under interleukin-6 stimulation recapitulates rheumatoid arthritis (RA)–associated muscle atrophy together with a modulation in extracellular adenosine induced by dipyridamole.[1] These findings should be interpreted as supportive rather than definitive but reflect nucleotide changes that perfectly correlate with those described in our manuscript and with the hypothesis outlined. Interpretations regarding compartment-specific nucleotide changes must be made cautiously.

Regarding A2AR-A2BR cross-talk, we propose, but do not confirm, a cross-talk between receptors based on our results and previous data. The formation and interdependence of this heterodimer had previously been described in C2C12 cells. Although A2AR is not the predominant receptor in muscle, its suppression impaired the protective effects mediated by A2BR.[3] In our RA model, we assessed this interdependence using the A2AR antagonist SCH58261 and the A2BR antagonist PSB603 (supplementary data).[1] Both antagonists reversed the anti-inflammatory joint effects and the antiatrophic muscle effects of dipyridamole, reducing fiber size and myostatin (MSTN) expression. They also abolished dipyridamole-induced AMPK expression.[1] Although we did not directly demonstrate heterodimer formation in situ, these data support functional dependence on both receptors.

Consistently, small interfering RNA–mediated suppression of A2BR in C2C12 cells reduced AMPK activation and increased MSTN expression across differentiation stages, reinforcing the link between A2BR, AMPK, and MSTN regulation.[1] The more preventive effects on fibrosis reflect the absence of established collagen deposition at early stages. Preventing fibrosis and reversing pre-existing collagen accumulation are distinct processes, the latter potentially more dependent on A2AR expression, which has been linked to fibrosis in other tissues.[4,5] The relationship between creatine kinase and adenosine signaling requires further investigation.

Timing-dependent efficacy of dipyridamole is an outstanding question. According to our results, both preventive and

therapeutic strategies are effective for inflammation and muscle decline. Early interventions could feasibly delay the point in which dysregulation is so severe that cachexia has no clinical return. However, it is unknown how early we can act because patients usually arrive in a flare and may have underlying muscle damage.

In this study or in previous studies,[6–8] adverse effects of dipyridamole (such as bleeding) have not been reported. When translating into human trials, this should be considered, as well as dose response and combination with disease-modifying antirheumatic drugs.

Drs Marco-Bonilla and Fresnadillo are co-first authors and contributed equally to this work. Supported by grants from Instituto de Salud Carlos III (ISCIII) through research grants PI22/00347 and co-funded by the European Union and RD21/0002/0025 and RD24/0007/0031 Health Outcomes-Oriented Cooperative Research Networks, granted by ISCIII and funded by the European Union—NextGenerationEU via Mecanismo de Recuperación, Transformación y Resiliencia. Authors have filed a patent (907642) on the use of dipyridamole as a novel therapy for muscular myogenesis disorders and inflammatory arthritis.

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HAVCR2 in subcutaneous panniculitis-like T cell lymphoma: comment on the article by Chambers et al

To the Editor:

Chambers et al provide striking clinical images of a 40-year-old woman with subcutaneous panniculitis-like T cell lymphoma (SPTCL).[1] The clinical images highlight the teaching point that SPTCL can mimic lupus erythematous panniculitis (LEP) and discoid lupus erythematosus both clinically and on skin biopsy. A number of other key teaching points should also be made around this case.

First, germline testing for hepatitis A virus cellular receptor 2 (*HAVCR2*) pathogenic variants (PVs) is strongly recommended in patients with suspected or confirmed SPTCL. Discovered in 2018, *HAVCR2* PVs are found in over half of patients with SPTCL, and testing is available in standard commercial immunodeficiency and cytopenia panels.[2,3] *HAVCR2* encodes the checkpoint protein T cell Ig and mucin domain containing protein 3 (TIM-3). Founder variants are seen in East Asian and European populations. The p.Tyr82Cys PV occurs with a minor allele frequency (MAF) of 1.64% in East Asians and the p.Ile97Met PV occurs in Europeans with a MAF of 0.45%. These missense variants cause protein misfolding with loss of the TIM-3 immune check point conferred by autosomal recessive inheritance, with incomplete penetrance. Patients with SPTCL are enriched in genes involving interleukin-16 (IL-6)–JAK-STAT3 and tumor necrosis factor (TNF) signaling; those who have $HAVCR2^{WT}$ frequently have mutations in *UNC13D*, *PIAS3*, and *KMT2D*.[4] Genetic testing has implications both for individual diagnosis and family planning for patients with SPTCL.

Second, although the patient in the clinical images was diagnosed with a repeat skin punch biopsy, many patients require a deep tissue biopsy for diagnosis. SPTCL often presents with a prolonged inflammatory prodrome with nonspecific skin lesions, and patients are often presumed to have LEP. Ironically, lymph node biopsies may only show reactive or dermatopathic lymphadenopathy in this type of lymphoma. Because the lymphoma resides primarily in the subcutaneous soft tissue rather than the lymph node or skin, positron emission tomography computed tomography and surgical consultation may be required to obtain adequate diagnostic specimens.[5,6]

Third, dysregulation in TIM-3 leads not only to overt lupus and lupus-like manifestations in a subset of patients but also other autoimmune, autoinflammatory, and lymphoproliferative manifestations such as hemophagocytic lymphohistiocytosis (HLH),[7] dermatomyositis,[8] and anasarca (Figure 1).[6] Although TIM-3 does

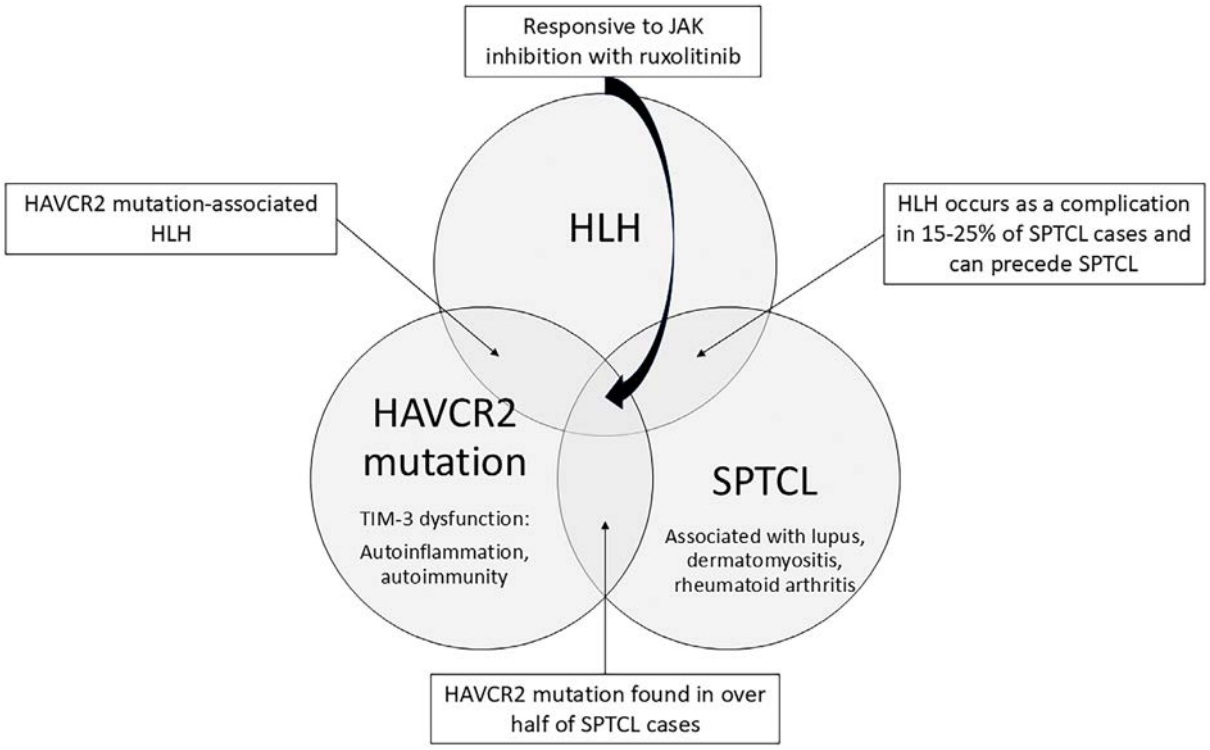

Figure 1. Relationships across HAVCR2, HLH, and SPTCL. TIM-3 is an inhibitor of immune response, promoting T cell exhaustion and preventing immune cell overactivation. HAVCR2 mutation leading to TIM-3 dysregulation results in autoinflammation and autoimmunity manifesting as HLH and/or SPTCL. HAVCR2, hepatitis A virus cellular receptor 2; HLH, hemophagocytic lymphohistiocytosis; SPTCL, subcutaneous panniculitis-like T cell lymphoma; TIM-3, T cell Ig and mucin domain containing protein 3.

not contain a clear inhibitory signaling motif, it functionally inhibits immune response by promoting T cell exhaustion and preventing immune system overactivation. TIM-3 dysregulation results in excessive production of pro-inflammatory cytokines and chemokines including CXCL10, IL-1β, IL-18, and sCD25. Macrophage activation causes excess serum IL-1 and TNF, promoting the development of systemic lupus erythematosus, SPTCL, and HLH.[9] Whereas TIM-3 dysregulation drives the alpha/beta positive CD8 positive T cells in subcutaneous tissue, another important mimic of SPTCL is primary cutaneous gamma/delta T cell lymphoma, which behaves more aggressively than SPTCL.

Finally, the inflammatory syndromes associated with the germline PV in *HAVCR2* are highly responsive to immunosuppressives, particularly cyclosporine and JAK inhibition with ruxolitinib.[10] Thus, SPTCL can often be treated with immunosuppression rather than cytotoxic chemotherapy. In summary, we thank Chambers et al for raising awareness of this challenging entity among the rheumatology community, and we hope these further teaching points are beneficial.

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Reply

To the Editor:

We thank Dr Chen and colleagues for their thoughtful commentary on our recent clinical image case highlighting subcutaneous panniculitis-like T cell lymphoma (SPTCL) and appreciate the opportunity to further discuss several important teaching points raised by the authors. We agree that germline testing for hepatitis A virus cellular receptor 2 (*HAVCR2*) pathogenic variants is an important and evolving consideration in patients with SPTCL, particularly given its association with immune dysregulation and hyperinflammatory syndromes, such as hemophagocytic lymphohistiocytosis.[1] Since the identification of *HAVCR2* mutations in SPTCL in 2018, there has been increasing recognition of its role in disease pathogenesis and potential implications for prognosis and family counseling.[1,2] However, in many locations, this testing is not yet universally incorporated into routine diagnostic evaluation, which is often supported by clinicopathologic and immunophenotypic findings. Our report highlights the often protracted and diagnostically challenging course of SPTCL, particularly in the setting of prior misdiagnosis. We thank the authors for highlighting the potential benefit of adopting more routine germline testing for *HAVCR2* pathogenic variants, both for individual diagnosis and longer-term considerations.

We agree that it is paramount to obtain adequate tissue for SPTCL diagnosis. Although deeper incisional or excisional biopsies may be necessary in some cases, we have found that deep punch biopsy, depending on anatomic location, can provide sufficient subcutaneous tissue to demonstrate classic features of SPTCL including adipocyte rimming by atypical CD8+ cytotoxic T cells with positive Granzyme B, TIA-1, and Beta F1 immunostaining.[3] Telescoping punch biopsies may also be used to reach subcutis. Appropriately performed punch biopsies can be diagnostically adequate when sufficient subcutis is obtained.[3]

We further acknowledge the expanding understanding of T cell Ig and mucin domain containing protein 3 (TIM-3) dysregulation in contributing to a range of autoimmune, autoinflammatory, and lymphoproliferative manifestations.[4] These insights continue to refine our understanding of the relationship between autoimmunity and lymphoproliferative disorders and highlight that immunosuppressive therapies, including cyclosporine and JAK inhibitors such as ruxolitinib, are increasingly recognized as effective treatment options for SPTCL, particularly in patients with underlying immune dysregulation. Management decisions remain individualized based on disease severity and extent of systemic involvement.[5]

We hope that through our clinical case image, readers will consider SPTCL in patients with presumed lupus panniculitis who demonstrate clinical progression or fail to respond to appropriate therapy. We again thank the authors for their valuable contributions, which further highlight the complexity and evolving understanding of this condition.

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