Volume 38 • Number 5 • September 2026 www.co-rheumatology.com

Current Opinion in Rheumatology

Pediatric and heritable disorders
Edited by Polly Ferguson

Wolters Kluwer

Editorial introduction

Current Opinion in Rheumatology was launched in 1989. It is one of a successful series of review journals whose unique format is designed to provide a systematic and critical assessment of the literature as presented in the many primary journals. The field of Rheumatology is divided into 15 sections that are reviewed once a year. Each section is assigned a Section Editor, a leading authority in the area, who identifies the most important topics at that time. Here we are pleased to introduce the Journal's Section Editors for this issue.

SECTION EDITOR

Polly Ferguson

Dr Polly Ferguson received her B.S. and M.D. from the University of Iowa. She completed her Pediatric Residency and Pediatric Rheumatology & Immunology Fellowship and Post-Doctoral Research Fellowship at the University of Virginia. She is currently the Marjorie K. Lamb Professor of Pediatrics and Director of Pediatric Rheumatology at the University of Iowa Carver College of Medicine. She is an NIH funded investigator and her research program is focused on the etiology of autoinflammatory disorders including chronic recurrent multifocal osteomyelitis (CRMO) and neuroinflammation. She is an author on more than 100 peer reviewed publications, book chapters and reviews. Her work has been cited more than 5000 times.

Immune dysregulation in children with Down syndrome: clinical implications and emerging therapies

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Purpose of review
People with Down syndrome experience significant immune dysregulation, conferring elevated risk of autoimmune and inflammatory conditions. Despite the growing prevalence of adults living with Down syndrome, significant gaps remain in understanding and treating immune-mediated disease in this population. This review synthesizes current knowledge of immune dysregulation in Down syndrome, with focus on rheumatic manifestations and emerging therapeutic approaches.

Recent findings
Trisomy 21 drives constitutive, global immune remodeling characterized by mixed interferon hyperactivation, hypercytokinemia, and myeloid and lymphoid subset remodeling toward an autoimmunity-prone, pro-inflammatory state. Down syndrome associated arthritis is a distinct and aggressive entity warranting recognition separate from juvenile idiopathic and rheumatoid arthritis. People with Down syndrome face elevated risk of SJIA-associated lung disease and diffuse alveolar hemorrhage. Medication tolerance is a significant consideration, including intolerance to methotrexate and diminished response to TNF inhibitors. Early clinical trials of JAK inhibitors demonstrate promising results across multiple immune-mediated manifestations, including skin disease, arthritis, and Down syndrome regression disorder.

Summary
Immune dysregulation in Down syndrome is pervasive and mechanistically distinct, with interferon signaling as a central therapeutic target. Clinicians should be aware of Down syndrome specific diagnostic and management considerations, and future research should prioritize rigorous placebo-controlled trials and Down syndrome informed outcome measures.

Keywords
autoimmunity, Down syndrome, interferon, JAK inhibitors, trisomy 21

INTRODUCTION

Down syndrome is the most common chromosomal disorder worldwide, affecting approximately 1 in 700 infants [1]. It is caused by Trisomy 21 (T21), or the presence of three copies of chromosome 21. Life expectancy has increased from a mean of 26 years in 1950 to 53 in 2010 [2]. Despite their ability to thrive, many people with Down syndrome have multiple unmet needs, particularly regarding immune dysfunction and its management [3,4].

People with Down syndrome have a distinct clinical profile. This includes decreased risk of solid tumors, atherosclerosis, hypertension, and allergies and increased risk of Alzheimer's disease, childhood leukemia, lung infections, congenital heart defects, vision and hearing pathology, and autoimmunity. Individuals with Down syndrome are more susceptible to severe respiratory infections, a leading cause of death, and have a high risk of early-onset Alzheimer's disease, which contributes to morbidity and mortality [5–9].

This review examines the unique immunological landscape of people with Down syndrome and its management. We begin by highlighting distinct features of the immune system, including increased interferon signaling, before addressing specific autoimmune

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Curr Opin Rheumatol 2026, 38:305–313

DOI:10.1097/BOR.0000000000001174

KEY POINTS

- Trisomy 21 drives constitutive, global immune remodeling toward an autoimmunity-prone, pro-inflammatory state, with type I interferon hyperactivation as a central therapeutic target.
- Down syndrome associated arthritis is a distinct, aggressive entity separate from juvenile idiopathic arthritis and rheumatoid arthritis, complicated by diagnostic delay, methotrexate intolerance, and diminished TNF inhibitor response.
- People with Down syndrome are at elevated risk of immune-mediated lung complications, including SJIA-associated lung disease and diffuse alveolar hemorrhage, warranting a low threshold for evaluation.
- Early JAK inhibitor trials in Down syndrome show promising results, including normalization of interferon and cytokine levels, improvement in autoimmune skin conditions, and potential cognitive benefits.
- Down syndrome informed approaches to trial design, outcome measures, and shared decision-making are essential to advancing care for this population.

manifestations. We conclude with management challenges and emerging therapeutic approaches.

IMMUNE DYSREGULATION

Immune profiling in Down syndrome is characterized by hypercytokinemia, increased Type I (α/β) and Type II (γ) interferon signaling, B cell depletion, T cell activation and exhaustion, and accelerated immune senescence marked by a pronounced shift from naïve to memory and effector lymphocytes [10–13,14▪,15]. These changes are summarized in Fig. 1.

Innate immunity

Innate immune dysregulation from T21 encompasses reduced eosinophils in childhood and defective monocyte phagocytosis and chemotaxis, alongside altered dendritic and NK cell populations. The complement system is also dysregulated and elevated neopterin and cytokines, including IL-6 and TNF, demonstrate a chronic inflammatory state [16,17▪▪,18,19▪▪].

T21 causes persistently activated IFN transcriptional signaling, with enhanced sensitivity to IFN stimulation and hyperactivation of downstream JAK/STAT signaling, attributable to an extra copy of chromosome 21, which harbors four of six IFN-receptor genes (IFNAR1, IFNAR2, IFNGR2, IL10RB) (Fig. 2) [10,20▪,21,22]. T21-driven changes in the circulating proteome are indicative of chronic

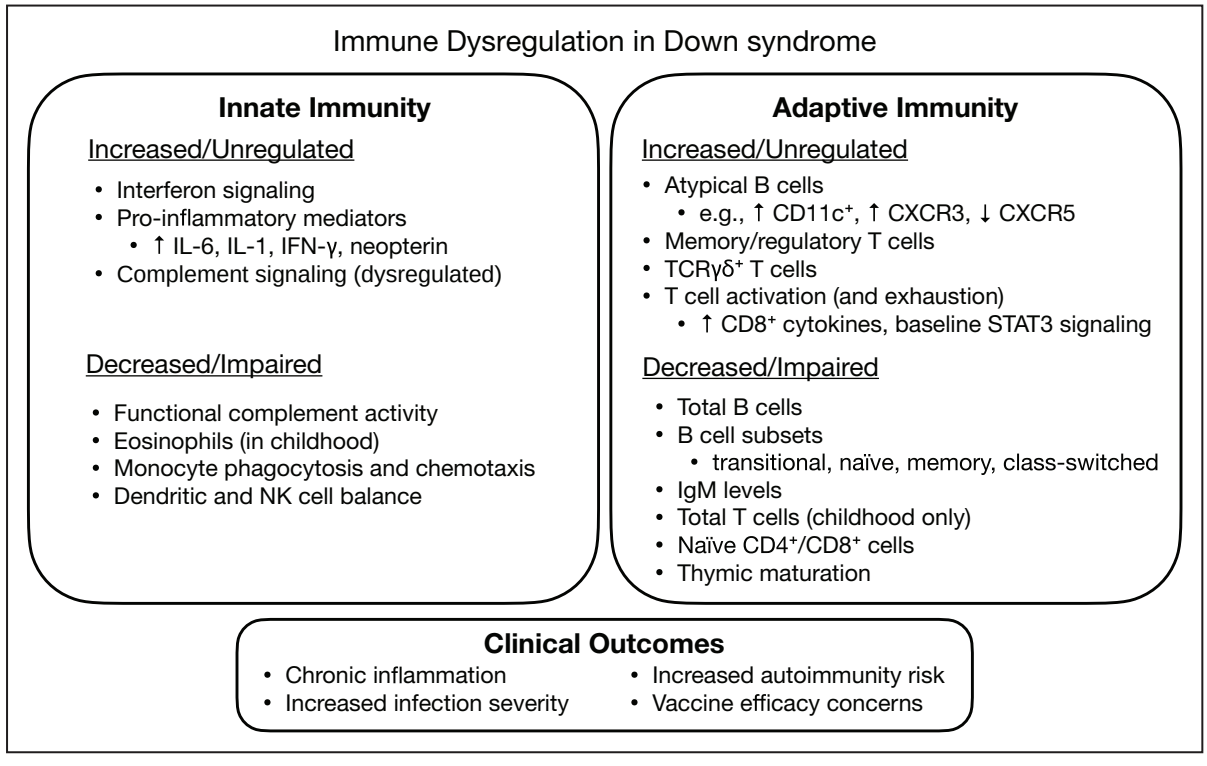

FIGURE 1. Overview of immune dysregulation in Down syndrome. Overview of the dysregulation noted in the innate and adaptive immune systems of people with Down syndrome, as well as resultant clinical outcomes.

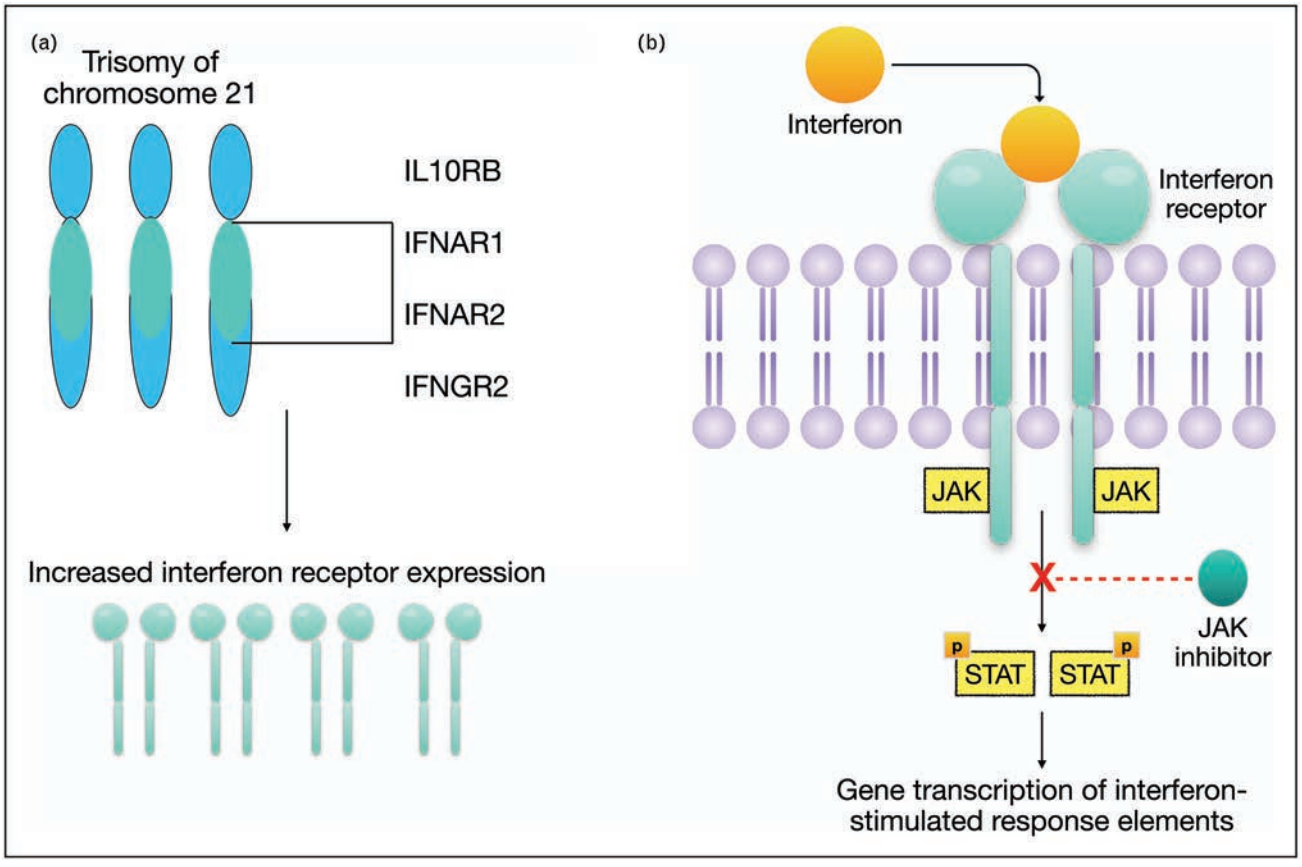

FIGURE 2. Increased interferon signaling in trisomy 21 and JAK inhibition. (a) Four of the six interferon receptors reside on chromosome 21, leading to increased interferon receptor expression in people with trisomy 21. (b) This leads to increased interferon signaling via the JAK-STAT pathway and ultimately increased gene transcription of interferon-stimulated response elements. JAK-inhibitors block the JAK-STAT pathway, therefore inhibiting interferon signaling

autoinflammation, and IFN transcriptional scores correlate with immune remodeling and hypercytokinemia [16,21]. Downstream consequences of increased IFN signaling include neurotoxic tryptophan catabolites via the kynurenine pathway and impaired cardiac differentiation through dysregulation of Wnt signaling in mice and in-vitro cell cultures [23,24]. Notably, restoring IFN signaling rescues cardiogenesis defects both *in vitro* (cell lines) and *in vivo* (mouse model) [23]. JAK inhibition in a mouse model improved cognition and rescued changes in neuroinflammatory and Alzheimer's disease-associated gene expression [20▪]. Correcting IFNR gene copy number in a mouse model normalized antiviral responses, prevented congenital heart defects, and improved cognition, craniofacial anomalies, and developmental delays, suggesting that T21 should classify as an interferonopathy [10].

Innate immune dysregulation from T21 contributes to increased viral infection severity and promotes the development of autoimmune disease. The former is driven in part by excessive negative feedback of the type I IFN pathway [25].

Adaptive immunity

T21 is associated with reduced B and T cell counts in childhood [14▪,26]. While T cell levels normalize by adulthood, B cell lymphopenia persists, particularly in transitional, naive mature, and memory B cell subsets. Atypical CD11c+ B cells are elevated, alongside low CXCR5 and high CXCR3 expression, mirroring B cell profiles seen in diseases such as lupus and rheumatoid arthritis [25,27]. Despite broadly normal IgG and IgA levels, IgM is reduced and autoantibody production, including rheumatoid factor, is markedly elevated [17▪▪,28,29]. Low levels of class-switched memory B cells further contribute to increased infection severity [30]. These B cell alterations have downstream implications for vaccine response and longevity, discussed further below [31–33].

People with T21 also have fewer total T cells in childhood and young adulthood, a higher proportion of peripheral TCR$\gamma\delta$+ cells, and altered thymic maturation [26,34–37]. Naive $CD4^+$ and $CD8^+$ compartments are reduced, with expansion of memory and regulatory T cells, likely secondary to chronic immune activation [34–36,38–41]. $CD8^+$ T cells produce

elevated cytokines, and naive, activated, and central memory CD4$^+$ T cells show baseline JAK-dependent STAT phosphorylation [25].

Abnormal expression of immune genes impacting adaptive immunity (such as *AIRE, ZAP70,* and *FCRL4*) is also noted [14▪].

Rachubinski *et al.*[17▪▪] suggest that immune remodeling in T21 toward an autoimmunity-prone, pro-inflammatory state begins early in life, as hypercytokinemia and myeloid and lymphoid subset changes were observed independent of clinical autoimmune disease or autoantibody positivity. The authors propose that this either reflects a prolonged preclinical inflammatory period preceding autoimmune disease, or that hypercytokinemia itself directly underlies many defining features of Down syndrome [17▪▪].

AUTOIMMUNE DISEASES ASSOCIATED WITH TRISOMY 21

People with Down syndrome experience increased rates of autoimmune conditions, including Type 1 diabetes, celiac disease, Graves' disease, and autoimmune skin conditions, with at least 75% of adults affected by at least one diagnosis and 38% by at least two (Table 1) [17▪▪,25,42]. Thyroid disease affects approximately 50% of adults with Down syndrome, celiac disease 10%, and inflammatory arthritis 1% [17▪▪,43–45]. Data from the Crnic Institute's Human Trisome Project ($n=441$, ages 6 months to 57 years) found that 80% of thyroid, skin, and celiac diagnoses occurred by age 20, and 82.4% of adults had anti-TPO or ANA antibodies, with 41.2% having both. Twenty-five autoantibodies targeting tissues throughout the body were over-represented relative to age- and sex-matched controls, with two-thirds positive for six or more; notable associations included anti-MuSK with co-occurring neurologic conditions and anti-TPO with ear tube history. Elevated anti-SRP68, typically seen in necrotizing myopathies, were also noted [17▪▪]. Immunodeficiency also occurs in Down syndrome but is beyond the scope of this review.

Table 1. Prevalence of autoimmune conditions in people with Down syndrome

Body system	Specific condition	Prevalence in DS
Overall	≥1 autoimmune condition[a]	~75%
	≥2 autoimmune conditions	38.4%
	≥3 autoimmune conditions	13.6%
Endocrine	Autoimmune thyroid disease	50–53.1%
	Type 1 diabetes	2.2%
Gastrointestinal	Celiac disease[b]	5–9.6%
Musculoskeletal	Inflammatory arthritis	~1%
Skin	Any autoimmune skin disease	43%
	Atopic dermatitis	27.9%
	Hidradenitis suppurativa	20.6%
	Alopecia areata	7.7%
	Psoriasis	6.1%
	Vitiligo	1.9%

[a]Over 80% diagnosed in childhood.
[b]Often diagnosed before age 20 years.
Adapted from [17▪▪].

Down syndrome-associated arthritis

Down syndrome-associated arthritis (DAA) is an aggressive, immune-mediated arthritis affecting approximately 8.7 per 1000 children with Down syndrome [46]. Despite overlapping features with juvenile idiopathic arthritis (JIA) and rheumatoid arthritis, several distinct characteristics support its classification as a separate entity. DAA most commonly presents as polyarticular arthritis, with an average of fifteen joints affected at onset, though oligoarticular presentations with subsequent polyarticular progression are also seen. Onset typically occurs between ages 2 and 12, with equal sex distribution. DAA often follows a more aggressive and erosive course than JIA, compounded by a mean diagnostic delay of approximately two years, driven by provider unfamiliarity and the challenges of clinical assessment in individuals with developmental delay, altered pain expression, and joint hypermobility [45,47,48,49▪▪,50,51]. A multicenter study recently developed and evaluated a musculoskeletal screening tool to identify DAA during routine clinical care [49▪▪].

Systemic-onset juvenile idiopathic arthritis and associated lung disease

Systemic-onset juvenile idiopathic arthritis (SJIA) involves inflammatory arthritis with systemic features such as fever, rash, and serositis, and carries risk of severe complications, including macrophage activation syndrome and lung disease. SJIA-LD is a rare but potentially fatal complication characterized by lymphocytic interstitial inflammation and accumulation of lipoproteinaceous material and lipid-laden macrophages in the alveoli. T21 is one of five known risk factors for SJIA-LD, as 10% of the largest SJIA-LD cohort had T21 compared to 0.2% of the SJIA cohort without known lung disease. SJIA-LD is driven primarily by type II IFN (IFN-γ), evidenced by IFN-

driven pulmonary gene expression and elevated IL-18 and IFN-γ-driven chemokines in the lungs [52,53]. IFN hyperactivation characteristic of T21 may further potentiate lung disease development in these patients. Additional contributing factors include abnormal lung development in DS and elevated risk of IL-1 and IL-6 inhibitor intolerance in Down syndrome, an independent risk factor for SJIA-LD development [54].

Immune-mediated diffuse alveolar hemorrhage

Diffuse alveolar hemorrhage (DAH), or bleeding into the alveolar spaces due to alveolar-capillary basement membrane disruption, is a life-threatening condition occurring more frequently in children with Down syndrome. A 2018 French RespiRare Network study identified a 75-fold higher prevalence of idiopathic DAH in children with Down syndrome, with earlier onset and greater morbidity and mortality [55]. Bloom *et al.*[56] described five children with Down syndrome and DAH, all with autoimmune disease or autoantibodies of unknown significance and responded to glucocorticoids, IVIG, and/or rituximab. A literature review identified similar patterns, with drivers including congenital cardiopulmonary abnormalities, pulmonary arterial hypertension, infection, aspiration, and immune dysregulation [56–58]. A minority had hemoptysis. A low threshold for considering DAH should be maintained in children with Down syndrome presenting with anemia or presumed recurrent pneumonia, with or without hemoptysis, given the increased prevalence and potential for immune-mediated causes.

MANAGEMENT OF AUTOIMMUNITY IN PEOPLE WITH DOWN SYNDROME: UNIQUE CHALLENGES

Medication tolerance

Glucocorticoid side effects, including obesity, hyperglycemia, irritability, and poor sleep, are of particular concern given the increased prevalence of metabolic syndrome, behavioral and mood disorders, and obstructive sleep apnea [59,60] (Fig. 3). Methotrexate, a cornerstone of treatment for inflammatory arthritis, is frequently poorly tolerated in Down syndrome, with increased rates of mouth ulcers, gastrointestinal upset, and bone marrow suppression [61–63]. This is hypothesized to result from triplication of the reduced folate carrier gene (*SLC19A1*), increasing cellular methotrexate uptake across tissues, compounded by preexisting alterations in folate-dependent purine synthesis pathways [64]. People with

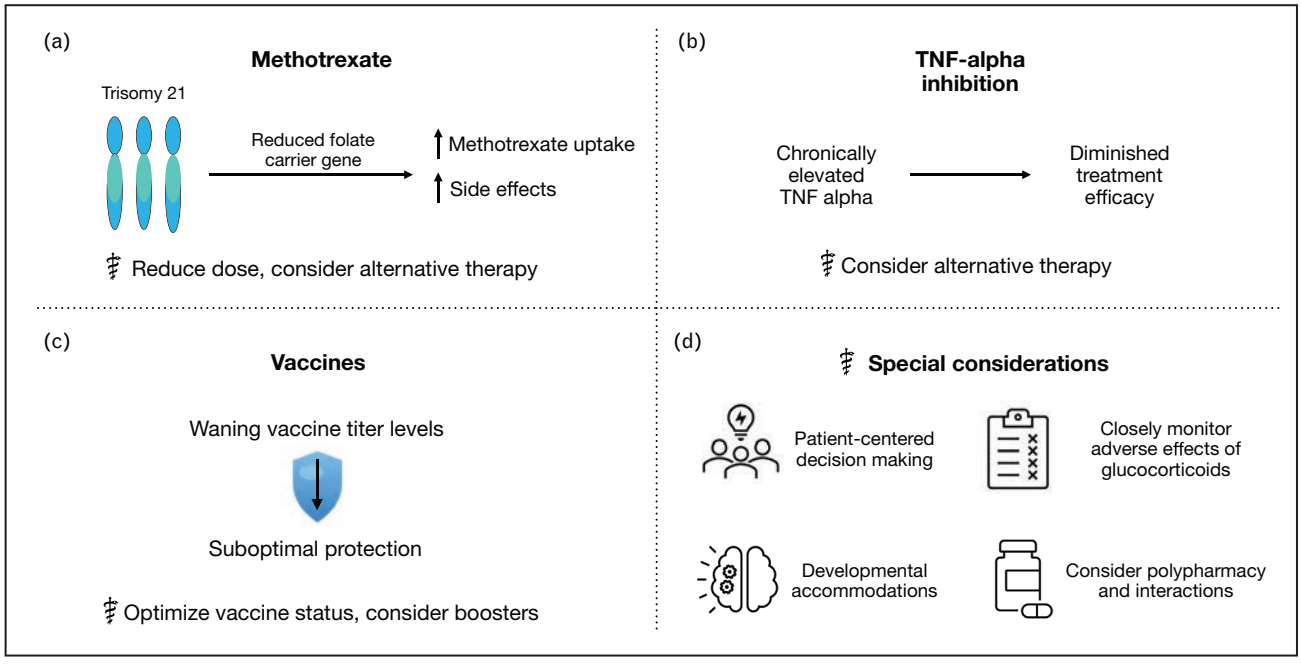

FIGURE 3. Considerations for the use of immune-modulating therapies in people with Down syndrome. The use of immunosuppressive medications in people with Down syndrome requires taking into account unique considerations. These include medication tolerance (a), medication efficacy (b), vaccine efficacy (c), polypharmacy (d), developmental accommodations (d), and more

Down syndrome may also demonstrate diminished response to TNF inhibitors. Data from the Childhood Arthritis and Rheumatology Research Alliance showed treatment failure with anti-TNF therapy in 60% of patients with Down syndrome compared to 17% in a JIA cohort without Down syndrome, likely reflecting the interferon-driven rather than TNF-driven nature of inflammation in Down syndrome associated arthritis, compounded by baseline TNF elevation reducing efficacy of standard dosing [48].

Vaccine response

Management of autoimmunity in people with Down syndrome is complicated by potential suboptimal and waning vaccine responses, leaving patients vulnerable to vaccine-preventable illness despite prior vaccination [33,65,66]. Vaccinations against pneumococcal infection, COVID-19, and influenza should be kept up to date, particularly in those on immunosuppressive therapy [67]. Certain immunosuppressive agents, such as JAK inhibitors, also warrant herpes zoster vaccination. Providers should review vaccine status prior to initiating immunosuppressive therapy, with particular attention before rituximab use.

Special considerations

Management plans must be developed through shared decision-making with patients and their families, with the individual patient's needs in mind. Many characteristics of Down syndrome influence medication and therapy selection, such as developmental delay, care coordination, swallowing difficulties, and/or aspiration risk [68,69]. Co-occurring conditions increase polypharmacy risk, while developmental delay may limit patients' ability to communicate side effects or tolerate blood draws. Lower thresholds for sedation during imaging or procedures, combined with cardiac and pulmonary comorbidities, present additional challenges during evaluation and management [70].

NEW FRONTIERS

As understanding of immune dysregulation in Down syndrome grows, the field is moving toward more targeted and personalized interventions. JAK inhibitors (JAKi) have emerged as a promising path forward as they suppress IFN-driven JAK/STAT signaling, reduce interferon-stimulated gene transcription, and dampen cytokine responses, and are already approved for conditions such as JIA, ulcerative colitis, alopecia areata, and monogenic interferonopathies [71]. In Down syndrome mouse models, JAKi prevented lethal immune hypersensitivity and normalized gene expression, and when administered to pregnant mice, prevented congenital heart defects [21,23,72]. In humans, case reports have documented successful treatment of alopecia areata, arthritis, and SJIA-LD with JAKi in people with Down syndrome [73–76].

The Crnic Human Trisome Project conducted a single-site, open-label phase II trial of tofacitinib – a JAK1/3 inhibitor, selected given JAK1's use by all four chromosome 21-encoded IFN receptors – in people with Down syndrome aged 12–50 with moderate-to-severe alopecia areata, hidradenitis suppurativa, psoriasis, atopic dermatitis, or vitiligo. Participants received tofacitinib 5 mg twice daily for 16 weeks, with an optional 40-week extension; primary endpoints were safety and reduction in whole-blood IFN transcriptional scores. An interim analysis of the first 10 completers demonstrated normalized IFN scores, decreased TNF and IL-6, reduced pathogenic autoantibodies, and improved skin disease and quality of life. Notably, cytokine levels normalized to non-Down syndrome population levels, rather than below, and remained stimulus-responsive, suggesting limited immunosuppression risk. Though lacking a placebo arm, improvements in spatial and episodic memory, visuomotor, and verbal tasks were noted after 16 weeks. No severe or definitively drug-attributable adverse events occurred, and no participants required dose modification or discontinuation [17▪▪].

Preliminary cognitive findings from the above tofacitinib trial contributed to the development of a trial targeting Down syndrome regression disorder (DSRD), an acute or subacute regression in cognition, self-care, and speech, often with psychosis, catatonia, or obsessive-compulsive disorder, typically resulting in significant impairment and often incomplete functional recovery [77]. A neuroinflammatory etiology is supported by inflammatory CSF, MRI, and EEG findings, impaired blood-brain barrier integrity, immune profiles resembling neuroinflammatory rather than healthy controls, and elevated autoantibodies including TPO and celiac-associated antibodies, with 45% having a personal autoimmune history [78,79▪▪,80]. A prospective observational study of 212 patients with DSRD found IVIG superior to lorazepam and both superior to no treatment across all five outcomes at 24 weeks [81▪▪]. A three-patient case series showed significant neurological improvement with tofacitinib, and a phase II trial evaluating lorazepam, IVIG, and tofacitinib is currently underway [82▪].

THE ROAD AHEAD

Significant efforts to advance Down syndrome research are underway, driven by organizations

including the NIH INCLUDE initiative, the Global Down Syndrome Foundation, the Trisomy 21 Research Society, and international Down Syndrome Medical Interest Groups. Recent work has addressed research priorities including community engagement, global funding, and policy reform, Down syndrome informed clinical trial design and syndrome-specific outcome measures, research representation, and family participation drivers [83▪,84–86].

While many questions remain, the work discussed here offers hope for future preventive and therapeutic strategies to improve outcomes for people with DS. In the near term, questions include whether JAKi should be initiated earlier for Down syndrome associated autoimmune conditions, such as DAA, rather than later as per standard treatment tiers. More broadly, whether blocking interferon signaling may be beneficial independent of a known autoimmune diagnosis remains an open question, with a phase II double-blind randomized trial underway to assess safety, neurodevelopmental effect, and global health impact of tofacitinib in people with Down syndrome ages 6–22 years without a required co-occurring condition. Future targets may include the JAK/STAT pathway, IFNs ligands, and mediator kinases driving IFN-dependent cytokine responses [17▪▪,87▪]. The benefits of JAKi may partly reflect effects on autoreactive B cells and B cell lineage remodeling, raising the potential for B cell-mediated therapies [88]. With continued focus on immune dysregulation in Down syndrome, there is great hope that the path forward will enhance the lives of this vibrant community.

Acknowledgements

The authors wish to thank Drs. Angela Rachubinski, Robert Fuhlbrigge, and Joaquin Espinosa for their thoughtful review of the manuscript. The authors used generative artificial intelligence tools to assist with shortening and editing portions of the manuscript text for clarity and word-count reduction, and to help generate selected minor components of figures. All artificial intelligence generated content was reviewed, edited, and verified by the authors, who take full responsibility for the final manuscript and figures.

Financial support and sponsorship

There were no sources of funding for this article.

The authors have no financial disclosures to report.

Conflicts of interest

Both authors partner with the Linda Crnic Institute for Down Syndrome at the University of Colorado on an investigator-initiated clinical trial.

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"Updates in chronic nonbacterial osteomyelitis: emerging insights across the age spectrum"

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Purpose of review
To review and highlight key research findings in children and adults with chronic nonbacterial osteomyelitis (CNO).

Recent findings
Recent studies highlight substantial progress in CNO. Emerging data supports the existence of distinct phenotypic clusters in children and adults, along with recognition of extraosseous manifestations associated with greater disease severity and biologic use. New EULAR/ACR classification criteria and expert consensus recommendations represent important progress toward improving patient care. Administrative data is promising for cohort building and epidemiologic research in CNO. Recent work has identified key health domains impacting patients, highlighting the multidimensional nature, and reduced quality of life in CNO. Genetic and biomarker studies provide insight into inflammatory pathways. Advances in imaging and disease activity assessment emphasize the limitations of clinical measures alone, with composite measures providing improved performance. Reports of sarcopenia, and bone microarchitecture abnormalities suggest additional information may be gleaned from imaging. Finally, expanded therapeutic options are being used in recalcitrant cases suggesting that targeting interleukin (IL)-17/IL-23/Janus kinase pathways need to be tested in controlled studies to determine their place in treatment of CNO.

Summary
There is encouraging progress in CNO, with research efforts expanding our understanding of this disease across the age spectrum, with the ultimate goal of improving patient care.

Keywords
autoinflammatory disease, chronic recurrent multifocal osteomyelitis, chronic nonbacterial osteomyelitis, Synovitis, Acne, Pustulosis, Hyperostosis, Osteitis (SAPHO) syndrome

INTRODUCTION

Chronic nonbacterial osteomyelitis (CNO) is a rare autoinflammatory bone disease affecting children and adults, characterized by sterile bone inflammation, and accompanying extraosseous manifestations [1,2]. Despite their shared pathogenesis involving dysregulation of innate immune pathways, the clinical presentation and disease course vary across the age spectrum [3]. Additionally, the diagnosis of CNO remains challenging due to lack of validated biomarkers, and the need to exclude mimickers, infection and malignancy. Treatment is largely expert-based and involves the use of nonsteroidal anti-inflammatory drugs (NSAIDs), biologic or targeted synthetic disease-modifying antirheumatic drug (DMARDs), and bisphosphonates [4–7]. In this review, we highlight recent research findings in children and adults with CNO, including advances in understanding clinical manifestations, disease nomenclature, genetics, biomarkers, and treatment. We performed a literature search of PubMed-indexed English articles over the last 18 months (January 9, 2024–March 31, 2026) and identified a total of 267 potential articles; after screening abstracts and full-length articles, we included 36 original articles to highlight key emerging themes in CNO.

Defining phenotypic clusters in chronic nonbacterial osteomyelitis

Investigators have searched for clinically meaningful disease clusters to guide treatment and prognosis. Yue *et al*. studied 44 children with CNO and defined

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Curr Opin Rheumatol 2026, 38:314–319

DOI:10.1097/BOR.0000000000001176

KEY POINTS

- The adoption of chronic nonbacterial osteomyelitis (or osteitis) as the preferred term in children and adults emphasizes the central disease feature of sterile bone inflammation, and improves communication amongst clinicians, patients, and researchers towards advancing the field in chronic nonbacterial osteomyelitis (CNO).
- The identification and refinement of phenotypic clusters in CNO could help stratify treatment, identify refractory disease, and predict outcomes for our patients.
- Findings from collaborative work identifying key health domains and reduced quality of life in CNO highlight the importance of the multidimensional nature of this disease, and towards improving outcomes for our patients.
- Epidemiologic research of rare autoinflammatory diseases, such as CNO, is possible using validated administrative codes for accurate cohort building.
- Bone lesion, and potentially muscle, assessments by MRI are essential to guide treatment decisions, and combined with patient and clinician assessments play a role in comprehensively measuring disease activity and treatment response in our patients.

two groups, one with chronic bone pain (group 1) and another with acute systemic inflammation (group 2) that could be identified by cluster analysis of clinical variables without imaging [8]. Group 2 had shorter disease course, more fever, higher C-reactive protein (CRP)/interleukin-6 (IL-6)/tumor necrosis factor (TNF) and disease activity. Treatments were comparable, and both groups had favorable treatment response. In another cohort, four clusters were identified using imaging-reported bone sites in 334 CNO children: pelvic-dominant, axial-thoracic, lower-extremity, and upper-extremity [9].

Similar work is ongoing in adult CNO. Three distinct clusters (typical/anterior chest wall with skin, axial, peripheral) were found by hierarchical clustering on bone lesion and skin features in 135 Chinese adults with CNO [10]. Spine involvement was common in both typical and axial, while peripheral had asymmetric single site involvement. Mean disease activity decreased over 6 months in all three groups. Two phenotypic clusters were identified in 102 adults with CNO using demographic, cutaneous and osteoarticular data [11]. Cluster 1 was female, older, and had palmoplantar pustulosis (PPP); cluster 2 was characterized by acne, hidradenitis suppurativa (HS), and sacroiliac involvement. Despite equal spine disease, more bisphosphonates were used in cluster 1; refractory disease was similar in both. Further work is needed to test whether phenotypic clusters can be used to stratify treatment, identify refractory disease, and predict outcomes.

Characterizing new extraosseous manifestations in chronic nonbacterial osteomyelitis

Extraosseous manifestations in CNO occur in more than half of patients. New reports suggest that pulmonary involvement may be associated with CNO. Hospach *et al.* reported 22 pediatric German CNO patients with pulmonary involvement [12▪]. Pulmonary lesions were identified by WB-MRI, with an estimated prevalence of 2.8%. These patients were more likely female, older, and had multifocal lesions. Lung lesions were in lower lobes, mainly as consolidations, pleural involvement, and nodules (median 2 lesions, median size < 2 cm). Lung biopsies showed granulomatous inflammation with lymphocyte infiltrates. In practice, the authors suggest careful observation, as 80% achieved partial or complete remission of lung lesions during follow-up.

Recent studies highlight differences in CNO disease severity and use of biologics between extraosseous+ and extraosseous- groups. Extraosseous+ CNO in children (commonly skin) had more active disease, more bone lesions on MRI, and required more frequent use of biologics [13]. Notably, bisphosphonate use was similar in both groups. In a pediatric study from Turkey, extraosseous+ CNO had a high proportion of clinical Familial Mediterranean Fever (22.5%), more bone sites involved, and required more biologics, suggesting a more severe CNO phenotype [14].

Promising use of administrative data for research in chronic nonbacterial osteomyelitis

To shed light on the occurrence of CNO in inflammatory bowel disease (IBD), a nationwide population-based cohort study in Sweden found that children with IBD had a sixfold increased risk of developing CNO [adjusted hazard ratio (HR) of 5.87, 95% confidence interval 2.95–11.66] [15▪]. Incidence rates of CNO were higher for IBD patients compared to non-IBD individuals; the overall prevalence of CNO was 0.3% in IBD, compared to 0.06% in non-IBD. IBD-CNO patients had more extra-gastrointestinal (GI) manifestations, required more biologics, and had higher healthcare utilization, than IBD without CNO. Importantly, Malmquist *et al.* validated ICD-10 codes against chart review in a small subset of children with CNO, and their findings were in line with our group's work which found that a combination of ICD-10-CM codes for identifying adults with

SAPHO-CNO had an estimated sensitivity of 0.80 and PPV of 0.80 [16]. Thus, these early studies show promising use of ICD-10-CM codes for cohort building across the age spectrum in CNO.

Disease classification and nomenclature in chronic nonbacterial osteomyelitis

Significant progress was made towards a unified approach to classifying patients with pediatric CNO. Zhao *et al.* developed and validated the new EULAR/ACR classification criteria for pediatric CNO [17▪▪]. This international group developed a score across 9 factors with a score of ≥55 consistent with CNO; the new criteria performed very well in their validation cohort [sensitivity (Sn) = 82%, specificity (Sp) = 98%]. Further, the criteria had excellent performance against clinician diagnosis in another study (Sn = 93%, Sp = 98%, accuracy 0.957). The new EULAR/ACR criteria are robust and accurate for classifying pediatric CNO in clinical practice, and research.

Towards improving care of adults with CNO, the first European expert consensus recommendations on disease definition, diagnosis and treatment were published [18▪]. Chronic nonbacterial osteitis is now considered the preferred disease term, given the core disease manifestation of sterile bone inflammation. Although high-quality evidence for decision making is lacking, these recommendations will serve as a foundation for future collaborative research studies.

Knowledge gaps and disease awareness in chronic nonbacterial osteomyelitis

A survey of 244 Turkish orthopedists and pediatricians reported relative inexperience with CNO [19]. Insufficient knowledge about CNO was common, and only 50% of clinicians correctly answered questions on CNO, with an increasing trend with more experience in practice. Reassuringly, most clinicians (>85%) desired more formal training in CNO.

Similarly, a survey study amongst Chinese rheumatologists found limited confidence in the diagnosis and management of adult CNO [20]. Bone scans and CTs were commonly used, while MRI was underutilized, and second line treatment choices varied, with bisphosphonates infrequently prescribed.

Finally, in a survey study of CNO patients and physical therapists, Leerling *et al.* found that both groups wanted more specific information and guidance on physical therapy (PT) use in CNO [21]. Clearly, more work is needed to increase knowledge of CNO.

Key domains and reduced quality of life in chronic nonbacterial osteomyelitis

In an important study by Oliver *et al.*, a collaborative international group identified key health domains in children and adults with CNO [22▪]. Through a process of binning and winnowing, 25 domains were identified and mapped to OMERACT core areas. In addition to pain intensity, MSK and skin symptoms, impactful domains on a person's life were health-related quality of life (QOL) (HRQOL), mental health, and social participation. Further work is needed to identify domain measures in prospective cohorts.

Given the importance of HRQOL, a recent large study used the EQ-5D instrument to measure the perceived health status and wellbeing in 138 adults with CNO [23▪]. In this U.S.-based prospective cohort, Lenert *et al.* showed that QOL is significantly reduced in adults, with more than a third of individuals reporting problems across all measured domains, including mobility, self-care, activities, pain, and anxiety/depression. Importantly, adults with CNO had a similar reduction in QOL as reported in other chronic rheumatic diseases. These findings highlight the importance of the multidimensional nature of this disease, and of targeting reduced QOL as a major outcome in adult CNO.

Genetics of chronic nonbacterial osteomyelitis

There have been new publications implicating new genes in disease pathogenesis either in a single patient or small cohort [24,25]. Here, we limited our discussion to those reports with more than one patient or in a single patient with supportive functional studies. TBXAS1 mutations, previously shown to cause Ghosal hematodiaphyseal dysplasia, were identified in three Turkish children (including 2 siblings) with NSAID responsive multifocal CNO [24]. The unrelated patients had biallelic variants in TBXAS1 (index patient IVS8 + 1 G>A and p.Gly473Trp; siblings genotypes were IVS3 + 5 G>C and p.Pro448Leu), with the index case's variants reported as likely pathogenic. TBXAS1 encodes the enzyme thromboxane synthase (TXAS), and they postulate that reduced TXAS function increases pro-inflammatory prostaglandin E2 (PGE2) production, which could lead to manifestations of CNO. All 3 children improved significantly on NSAIDs. In another study, Xiong *et al.* reported a homozygous truncating mutation in OGFRL1 in a 7-year-old Chinese girl with multifocal CNO and intermittent fevers [25]. Functional studies showed increased inflammation (high serum CXCL8/TNF/IL-6/IL-8), through activation of MAPK and NK-kB signaling in myeloid cells, culminating in bone

inflammation. Further studies are needed to determine the extent that genetic variants contribute to the heritability of CNO.

Potential biomarkers in chronic nonbacterial osteomyelitis

To study the effects of bisphosphonate treatment on immune pathways, Watson *et al.* identified decreased expression of *TRDV2* and *TRGV9* (encoding subunits of the $\gamma\delta$ T-cell receptor) in the peripheral blood of 6 children with CNO before and after pamidronate treatment [26]. Gene set enrichment analysis revealed suppressed Th17 and osteoclast differentiation pathways. However, it lacked a non-CNO pamidronate control group. Kawada *et al.* performed proteomic profiling to identify differentially expressed proteins in 11 children with CNO [27]. Pathway analyses in active CNO ($n = 5$) revealed enriched clusters in axon guidance, neutrophil degranulation, and regulation of MAPK cascade (vs. controls), and enrichment in the intermediate filament organization compared to inactive CNO ($n = 6$). Bui *et al.* studied osteoclastogenesis from PBMCs and/or serum in 69 children, which included active ($n = 19$, 22) and inactive ($n = 18$, 20) CNO patients. None of these children were treated with bisphosphonates. They found that neither PBMCs nor serum from patients with active CNO consistently altered osteoclastogenesis [28].

Zhang *et al.* identified 45 differentially expressed micro RNAs (miRNAs) in six adults with CNO, and four miRNAs potentially helpful to differentiate from controls [29]. Enrichment analyses on 34 miRNAs in KEGG and GO databases revealed multiple involved pathways including immune system, endocrine, infectious disease and cancers. Finally, monocyte pSTAT1 levels may serve as immunological markers in pediatric CNO, as its expression was elevated in interferon stimulated PBMCs from active CNO ($n = 9$) and decreased in those patients achieving clinical remission [30▪]. Four of the nine patients had persistently elevated pSTAT1 levels that responded to treatment with various JAK inhibitors (JAKi). These findings implicate the STAT1 pathway in CNO and suggest that pSTAT1 levels may be useful in determining disease activity.

MRI scoring tool, and bone and muscle assessments in chronic nonbacterial osteomyelitis

Nuruzzaman *et al.* used a qualitative user-centered design approach to validate the web-based version of the ChRonic nonbacterial Osteomyelitis Magnetic Resonance Imaging Scoring (CROMRIS) tool in children with CNO [31]. The web-based CROMRIS had high usability, with at least moderate reliability amongst radiologists. This important study lays the groundwork for additional reader calibration, and use of CROMRIS in future clinical trials. Vogele *et al.* showed that sarcopenia detected on WB-MRI could play a role in prognostication [32▪]. Sarcopenic children with CNO, measured by the total psoas muscle index, had larger mean bone lesion area at baseline, and lower reduction in bone lesion size over time.

Zhang *et al.* found lower trabecular bone scores (TBS), reflective of bone microarchitecture, in adults with CNO [33]. Lower TBS was associated with increased odds of vertebral fracture, with better discrimination than BMD. About a third of patients had low BMD or osteoporosis, raising the importance of performing DXA in adults. Subsequently, Zhang *et al.* showed higher proportion of bone loss, bone microstructure damage, and lower muscle amongst women with CNO [34]. Lumbar spine BMD and skeletal muscle gauge, but not TBS, were significantly associated with increased odds of vertebral fractures. Further research is needed to determine the generalizability of these findings, to elucidate sex-differences in bone and muscle measures, and to identify factors associated with incident vertebral fractures in adult CNO.

Disease activity assessments in chronic nonbacterial osteomyelitis

Validated assessments of CNO disease activity (DA) are lacking. However, progress has been made, including the development and validation of a clinical disease activity measure in children (CNO CDAS) using an international registry [35]. The CNO CDAS sums the score of 3 variables: patient pain, patient global assessment, and clinical CNO lesion count.

More recently, in a longitudinal treat-to-target (T2T) study aiming at MRI disease-free state, multiple DA measures were assessed in biologic-naïve children with CNO ($n = 37$) [36]. Although patient and physician-reported DA measures indicated inactive disease, MRI continued to show active bone lesions, and disease progression. Subsequently, a study in 400 children with CNO by Reiser *et al.* showed that composite scores combining clinical data and MRI lesion counts performed better than single measures, with MRI-inclusive scores demonstrating more consistent and meaningful changes over time [37]. Thus, a multidimensional measure with patient, physician, and MRI data may be needed.

Treatment advances in chronic nonbacterial osteomyelitis

In practice, predicting which CNO patients may require second-line treatment after oral NSAIDs

remains difficult. Nowicki *et al.* found that children with symmetric bone lesions (odds ratio, OR = 6.9), and higher number of regions affected (OR = 1.9) were significantly more likely to be treated with second-line medications [38▪▪]. In a study by Cam *et al.*, the number of bones involved at baseline was significantly associated with relapse (OR = 1.2, P = 0.017) [39]. These important studies could guide clinicians in counseling their pediatric patients regarding the need for more aggressive treatment.

When a patient with CNO fails NSAIDs, bisphosphonate use is one of the standard second line choices with pamidronate used more often than zoledronic acid (ZA) [40]. Patel *et al.* report on their experience using zoledronic acid for treatment of 17 pediatric CNO patients [41]. They found that ZA was well tolerated, improved pain, and reduced adjunctive medication use. BMD increased gradually over time without complications, and spine remodeling was observed but vertebra plana lesions did not improve. The authors suggested serial DXAs during ZA treatment.

Building on expert consensus recommendations in adult CNO, recent publications highlight benefits of PT [18▪]. Leerling *et al.* found that PT was most beneficial for range of motion and pain [21]. PT modalities included active exercises, manual treatment, and counseling, while interventional modalities (i.e., dry needling) were rarely used. About one third of adults never used PT, while recent PT users were more likely female, younger, and had higher education.

There is limited data about treatment strategies when standard second line therapies (csDMARD, bisphosphonate or TNFi) do not adequately control disease. Hou *et al.* performed a systematic review of treatments with IL-23 inhibitors (n = 6), IL-17 inhibitors (n = 9), and JAKi (n = 11) in adults with SAPHO that showed favorable responses of 40–50% [42▪]. Additionally, Yamamoto *et al.* described the effectiveness of IL-23 inhibitors in five adult patients with refractory CNO with axial lesions and PPP, with skin lesions, pain, DA scores, and MRI improved in all patients [43].

Fazeli *et al.* reported a favorable response to JAKi (75% were on tofacitinib) in a systematic analysis of 72 adults with CNO [44▪]. Additionally, in seven patients with paradoxical psoriasis from IL-17A inhibitors, switching to JAKi led to favorable bone and skin responses [45]. These early findings suggest that these agents may be helpful in those that fail standard treatment, but larger controlled trials are needed.

CONCLUSION

There is encouraging progress in CNO, including characterizing new extraosseous manifestations, potential of novel biomarkers, and effectiveness of treatments. Additional basic and clinical research efforts are needed to further expand our understanding of CNO across the age spectrum and lead to improved outcomes for our patients.

Acknowledgements

None.

Financial support and sponsorship

A.L. is funded by the National Institutes of Health (K23-AR082966) and P.J.F. by the generous support of the Marjorie K. Lamb Family through the Marjorie K. Lamb Professorship.

Conflicts of interest

A.L. and P.J.F. do not have any conflicts of interest.

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- ▪ of special interest
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Type I interferonopathies: 15 years after the concept–news and views

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Purpose of review
Genetic autoinflammatory conditions constitute an increasing field. Among them, type I interferonopathies (IFNp-I) were conceptualized 15 years ago as inborn errors of immunity due to chronic activation of the type I interferon (IFN-I) signalling pathway. Here, we provide recent insights in genetic mechanisms, clinical phenotypes and therapeutic options for these severe and rare disorders.

Recent findings
We will cover the novel findings into disease mechanisms, particularly the role of PTP1B in STING and IFNAR signalling, as well as the contribution of endosomal TLR pathways. We will also discuss the expanding phenotypic spectrum highlighted by recent case reports and cohort studies, together with the topic of clinical expressivity, including clinical non-penetrance, and possible mechanistic explanations such as monoallelic expression, the STING HAQ haplotype, and innovative approaches to characterise disease variability. Finally, we discuss current targeted therapeutic approaches for these disabling conditions, as well as potential new treatments for the future.

Summary
Overall, these findings highlight the need to consider these rare diseases across a wide range of clinical phenotypes. Advances in next-generation sequencing have enabled a genetic diagnosis in suspected cases and the implementation of targeted treatments, thereby reducing diagnostic uncertainty and providing the possibility of genetic counselling.

Keywords
Aicardi–Goutières syndrome, autoinflammation, clinical non-penetrance, genetic disease, type 1 interferon

INTRODUCTION

Type I interferonopathies (IFNp-I) represent an expanding group of rare monogenic autoinflammatory diseases characterized by inappropriate and sustained activation of the type I interferon (IFN-I) pathway signalling, resulting in tissue inflammation and progressive organ damage. The concept IFNp-I was introduced and formalised 15 years ago by Yanick J. Crow [1]. The first clinically described case was Aicardi–Goutières syndrome (AGS), reported as a severe early-onset encephalopathy in 1984 by Jean Aicardi and Françoise Goutières, and remains the most common genetic form of IFNp-I [2]. IFNp-I are caused by pathogenic variants in genes involved in intracellular nucleic acid metabolism and clearance, sensing and downstream IFN-I signalling [3▪].

Over the past decade, advances in clinical phenotyping, screening strategies, and next-generation sequencing (NGS) have expanded the spectrum of IFNp-I to more than 40 distinct genotypes, revealing substantial phenotypic diversity and overlap [3▪,4▪▪]. Since the initial description of AGS, larger cohorts

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Curr Opin Rheumatol 2026, 38:320–327
DOI:10.1097/BOR.0000000000001179

KEY POINTS

- Mutations in PTPN1, TLR7, and UNC93B1 reveal novel regulatory and dysregulated mechanisms of IFN-I signalling.
- Adult-onset presentation and expanded phenotypic variability with atypical involvement in SAVI and Coatomer subunit alpha (COPA) have been reported.
- Clinical non-penetrance likely extends beyond protective/aggravating allele, reflecting a complex interplay of genetic, immune, and environmental factors.
- Advanced understanding of IFN-I pathophysiology drives future targeted therapies (cGAS, STING, TLR inhibitors), though challenges remain in delivery, patient stratification, timing and safety.

and case reports have progressively revealed a much broader phenotypic spectrum, with highly variable clinical severity, spanning neonatal, paediatric and adult-onset disease, including organ-restricted and atypical phenotypes [5–7▪].

Beyond canonical defects in nucleic acid sensing, recent studies have uncovered new regulatory mechanisms that play a crucial role in modulating IFN-I signalling, thereby expanding the pathogenic framework of IFNp-I. These include newly identified regulatory nodes, such as PTP1B (encoded by *PTPN1*), which acts as negative regulators at multiple levels of cytokine and IFN-I receptor signalling to maintain immune homeostasis [8▪▪]. While genetic defects were initially linked to cytoplasmic nucleic acid sensing, in the past 4 years, gain-of-function (GOF) mutations in TLR7 [9,10,11▪▪,12▪] or its chaperone UNC93B1 have been identified [13,14], highlighting the pathogenic consequences of aberrant endosomal RNA sensing via TLRs leading to excessive IFN-I production and early-onset systemic lupus erythematosus (SLE) within the spectrum of IFNp-I.

The identification and functional characterisation of the genetic determinants underlying IFNp-I have provided a strong rationale for mechanism-based targeted therapies aimed at modulating dysregulated IFN-I signalling. However, despite major advances, significant challenges remain. Highly penetrant variants coexist with hypomorphic alleles, as well as common risk haplotypes, contributing to marked clinical heterogeneity [15,16▪,17▪]. Consequently, diagnostic delays remain frequent, particularly in patients with atypical, late-onset, or organ-restricted presentations, often leading to misclassification as idiopathic inflammatory or immune-mediated disease. Meanwhile, the rapidly expanding therapeutic landscape from JAK inhibition and interferon receptor (IFNAR) blockade to emerging upstream and gene-based strategies raises new questions regarding patient selection, timing of intervention, and long-term safety.

Here, we review recent insights into IFNp-I and to address these challenges requiring an integrated understanding of disease mechanisms, clinical heterogeneity and treatment strategies.

NOVEL MECHANISTIC INSIGHTS

IFNp-I result from chronic activation of IFN-I signalling driven either by IFN-I overproduction or by defective regulation. Since their initial description in 2006, several mechanisms have been identified [3▪,4▪▪]: defects in nucleic acid metabolism and sensing (AGS) i.e 'intracellular oligonucleotidopathies'; constitutive activation of STING signalling [including STING-associated vasculopathy with onset in infancy (SAVI) and COPA syndrome]; proteasome dysfunction Proteasome-associated autoinflammatory syndrom (PRAAS) and defective regulation of IFNAR signalling [4▪▪]. Additional genetic defects have also been reported, although their underlying mechanisms remain less well characterised, such as *ACP5* mutations causing spondyloenchondrodysplasia characterized by TRAP deficiency and increased IFN-I signalling.

Recent advances in immunogenetics have uncovered novel molecular mechanisms linking IFN-I regulation to systemic autoimmunity, notably through the PTP1B and TLR7 pathways. In particular, Zhu *et al.* [8▪▪] reported a case series of 12 patients identifying haploinsufficiency of *PTPN1* (encoding PTP1B), as a novel cause of IFN-mediated autoinflammatory encephalopathy. Mechanistically, PTP1B functions as a key negative regulator of IFN-I signalling by promoting STING proteasomal degradation, and dephosphorylating TYK2, a component of the IFNAR complex. Loss of PTP1B results in STING accumulation and enhanced signalling, and increased sensitivity to IFNAR activation [8▪▪].

Recent reports have identified GOF mutations in *TLR7* as a significant cause of monogenic SLE and early-onset IFNp-I. *TLR7*, encoded on the X chromosome, recognises single-stranded RNA (ssRNA) derived from microbial and self-origin [18]. Since 2022, heterozygous variants have been shown to enhance TLR7 signalling, leading to activation of the NF-κB and IRF7 pathways and subsequent overproduction of IFN-I [11▪▪,18]. Clinically, *TLR7* GOF mutations are associated with a broad phenotypic spectrum ranging from classical SLE to autoimmune cytopenias (including thrombocytopenia and haemolytic anaemia), and cardiovascular involvement [9,10,11,12,18,19–23▪]. Strikingly, neuropsychiatric

involvement reminiscent of AGS was reported, including anti-NMDA (N-méthyl-d-aspartate) encephalitis, AQP4-positive neuromyelitis optica and other AGS-like neuroinflammatory features [12,18,19–20,22▪]. At the molecular level, *TLR7* GOF variants are located across key structural domains, leading to enhanced signalling through distinct mechanisms depending on variant specific location. Most mutations are found within the homodimerisation domain (F506S, F507L, F507S, L528I) [18,19,22], while others are located in the ligand-binding domain (Y264H, L267P) [18,20], the juxtamembrane region (G818V) [21], and more recently in the transmembrane domain (L840R) [20]. This distribution suggests that TLR7 hyperactivation may arise from several mechanisms. Variants within the homodimerisation domain are proposed to enhance receptor signalling [18,19,22]. In contrast, variants affecting the ligand-binding domain increase ligand affinity [18,20] and lower activation threshold for ligand (guanosine and cGMP) [18]. G818V promotes ligand-independent activation [21], while L840R located in the transmembrane domain may strengthen TLR7 interaction with UNC93B1 resulting in NF-κB overactivation [20]. Together, these findings underscore the mechanistic diversity of TLR7-driven disease. However, the precise molecular mechanisms remain to be fully elucidated.

UNC93B1 is a chaperone protein essential for the stability and endosomal trafficking of TLRs (including TLR7 and TLR8) from the endoplasmic reticulum to the endolysosome for TLR signalling. GOF variations in *UNC93B1* have been associated with a range of autoimmune and autoinflammatory diseases [13,24▪,25▪]. Variants that enhance TLR7 signalling (V117L, G325C, I317M, E92G, Glu49dup) are linked to SLE-like phenotypes with elevated IFN-I signatures, whereas those affecting TLR8 signalling (L330R, R466S, R525P) are associated with chilblain lupus [24▪,26]. Further variants such as R336C are associated with atypical phenotypes within the IFNp-I spectrum [13,27]. Mechanistically, *UNC93B1* GOF variants promote aberrant TLR signalling through different mechanisms. The Glu49dup variant impairs TLR7 degradation and endosomal sorting, leading to its accumulation within endosomal compartments and sustained activation [28]. In parallel, variants located at the dimer interface (such as R336C, R336L) may facilitate TIR domain dimerisation and downstream signalling of the TLR7 [25▪,26,29]. Variants such as L330R, R466S and G325C seem to enhance interaction with TLR8 and receptor responsiveness [24▪]. Notably, certain *UNC93B1* variants, like V117L [14], albeit rare, are present in the general population and may act as risk factors rather than strictly monogenic causes. Overall, UNC93B1-driven TLR dysregulation, highlights complex and still incompletely understood regulatory pathways that warrant further investigation.

EXTENDED PHENOTYPES

Although IFNp-I can be associated with multiorgan involvement (Fig. 1), main clinical features include central nervous system (CNS) inflammation and skin vasculopathy. The prototypical IFNp-I, that is, AGS was initially described as a severe encephalopathy occurring after a normal period of development followed by an encephalitic period with neurological regression with possible skin vasculopathy at a later age. However, milder phenotypes and adult-onset can also be observed with AGS-related genes. As described above, PTPN1 haploinsufficiency is associated with autoinflammatory encephalopathy – distinct from AGS – with subacute onset, loss of motor and language skills without seizures [8▪▪]. Neuroimaging shows variable cerebral atrophy (sometimes initially unilateral) and white-matter abnormalities associated with enhanced IFN-I signalling reflected by elevated IFN-I score, and cerebrospinal fluid (CSF) neopterin levels. Despite the severe neurological presentation, clinical stabilisation and/or neuroradiological improvement have been observed with high-dose of steroids and without treatment. More recently, Calame *et al.*[30] reported 13 cases with ultra-rare heterozygous predicted loss-of-function (pLOF) variants in *PTPN1*, also presenting with neurological involvement and systemic inflammation.

Over the last years, alongside with the discovery of novel underlying IFNp-I mechanisms as well as description of patients' series and cohorts, IFNp-I phenotype extended to include, lung inflammation with profibrotic interstitial lung disease (ILD) and/or alveolar haemorrhage is the core feature of two IFNp-I driven by chronic STING signalling (SAVI and COPA syndrome), and has been described in limited number of other IFNp-1 patients [31] and other organ manifestations. Biological and/or clinical autoimmunity is often observed in IFNp-I, including SLE. Further noncanonical clinical features have been reported such as hepatic involvement beyond TORCH-like presentation in AGS (hepatic steatosis, chronic transaminitis) [5,32–34▪] and pulmonary hypertension [5▪,35].

Last year, David *et al.* reported the largest cohort of patients with COPA syndrome. This European multicentric study of 38 patients highlighted the core involvement of the lungs, joints and kidneys, while significantly expanding the initially described phenotype to include cutaneous (reminiscent of SAVI skin vasculopathy), cardiac and gastrointestinal manifestations [5▪]. Interestingly, while clinical non-penetrance is a known characteristic of COPA syndrome,

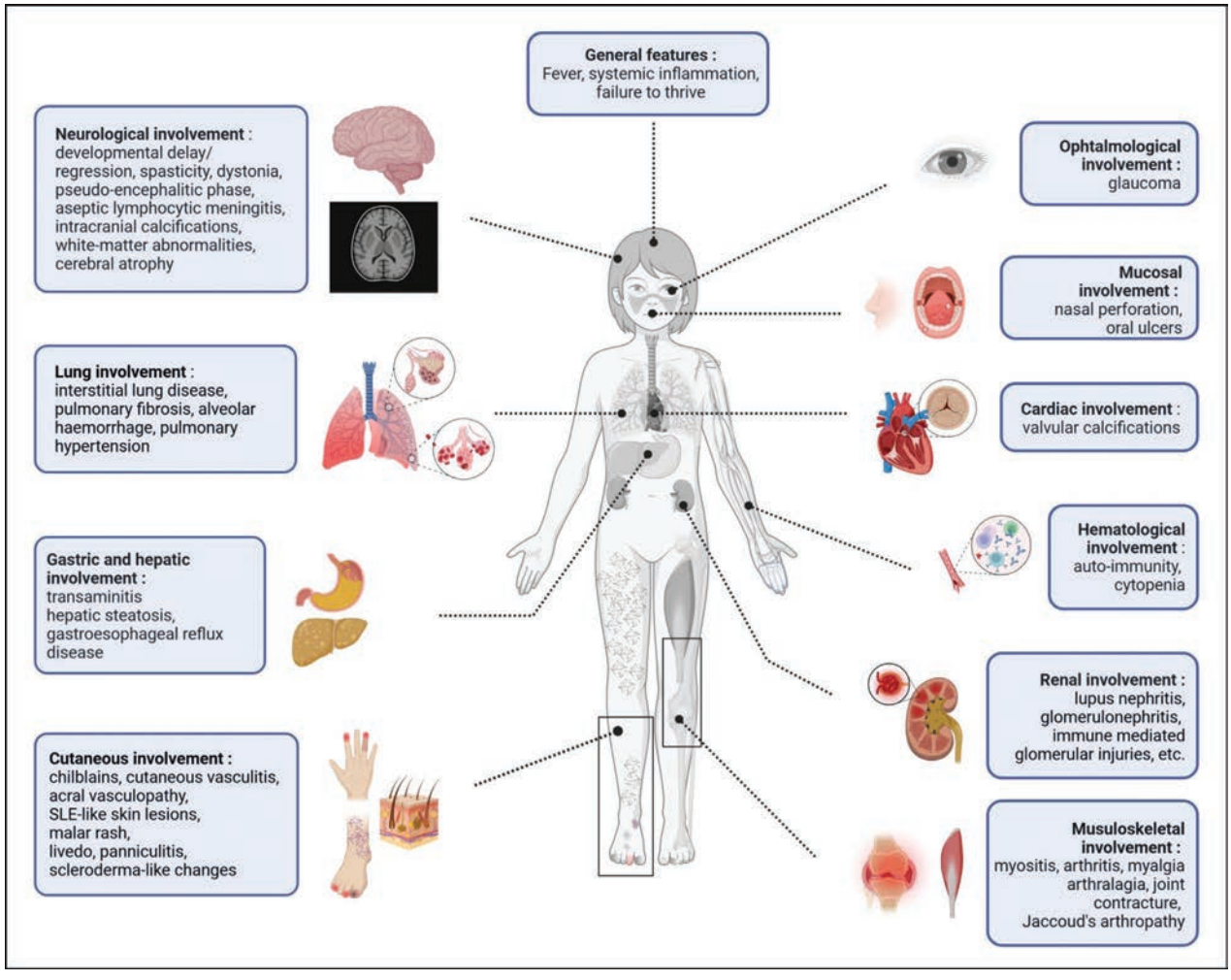

FIGURE 1. Broad phenotypic spectrum of type I interferonopathies, highlighting the diversity of clinical manifestations.

adult-onset and variable clinical expressivity have also been reported also in SAVI [5▪,6▪].

Data from a cohort of 71 PRAAS patients gathered by Goldbach-Mansky's team (National Institutes of Health, USA) refined the clinical spectrum of this heterogeneous and severe IFNp-I [4▪▪]. Patients in this cohort harboured biallelic, dominant-negative or digenic proteasome-related mutations, with dominant-negative and constitutive proteasome defects associated with earlier onset and more severe haematological and immunological manifestations.

CLINICAL EXPRESSIVITY

Although driven by underlying genetic mechanisms, variable clinical expressivity is observed across inborn errors of immunity (IEI), including IFNp-I. For example, clinical non-penetrance is observed in some individuals with GOF mutations in *IFIH1*, with isolated positive IFN signature and intracranial calcifications without developing clinical features [36]. Similarly, COPA syndrome is associated with a high frequency of clinical non-penetrance estimated (20–25%) [5▪,37], with normal or mildly elevated IFN score and no clinical signs, including normal kidney and lung explorations [i.e. normal lung CT scan, normal pulmonary function tests (PFT) and kidney function]. Several hypotheses may explain clinical non-penetrance in IEIs [15], encompassing genetic, epigenetic and environmental factors. Interestingly, the Bogunovic lab has highlighted monoallelic expression as an explanation to nonpenetrance in at least 4% of IEI-associated genes in a clonally expanded T-cell model [16▪]. So far, no similar data have been reported on *COPA* and other IFNp-I-associated genes, nor on other potential explanations, such as mutation reversion.

While mosaicism has been associated with non-attenuated phenotypes in SAVI and COPA syndrome [7▪,38], tissue or cell specificity may account to phenotype variability. Interestingly most of the proteins

mutated in IFNp-I are broadly expressed across cell types and tissues. However, possible expression intensity may account for differential inflammatory damage to the organs (CNS, lung, skin). One approach to investigate this phenomenon is to study peripheral mononuclear blood cells (PBMCs) and tissues using transcriptomic analysis. Indeed, single-cell RNAseq analysis of PBMCs have provided insights into IFNp-I pathogenesis [39,40], and spatial transcriptomics of tissues such as lungs in polyfactorial autoimmune diseases [41]. Relevant murine models, can also help to explore the human phenotype to understand human disease. Of note, SAVI murine models do not fully recapitulate the human phenotype, and not all AGS murine models present with CNS inflammation [42]. Interestingly, Nemec *et al.*[42] reported microglia replacement model using conditionally immortalised ER-Hoxb8 macrophages, which can engraft into a microglia-depleted brain and acquire microglia-like features *in vivo*. Using this system, they generated *Adar1*-mutant cell lines to investigate the intrinsic microglia contribution to AGS pathophysiology, showing that *Adar1* mutations, including D1113H variant, drive IFN production *in vivo*, supporting a central role for microglia in AGS-associated neuroinflammation.

In addition, it has been proposed that a common *STING1* allele (HAQ STING) may contribute to the marked clinical non-penetrance observed in individuals carrying pathogenic COPA variants [43▪]. However, a second report described five asymptomatic mutation carriers lacking this HAQ allele, suggesting that STING haplotype status alone is insufficient to explain disease expression in COPA syndrome [17▪]. Beyond HAQ STING allele, no other common polymorphisms or second genetic hit have been reported in the context of IFNp-I. Notably, digenism is possible in PRAAS and may also contribute in other IFNp-I. Additionally, recent work on *UNC93B1*[14,24▪,26,29] and *P2RY8*[44–46] variants have highlighted the continuum between genetic susceptibility to lupus and monogenic conditions.

Finally, environmental factors may also explain clinical variability and clinical nonpenetrance. Particularly, exposure to antigens during acute or chronic viral infections or to antibiotics, might participate, although supporting data remain limited. Prospective natural history studies are needed to tackle the potential contribution of environmental factors (NCT07040774; NCT02974595).

KEY BOX: DIAGNOSIS

IFNp-I require an integrated diagnostic approach. Diagnosis relies on the combination of clinical phenotype, biological evidence of IFN-I pathway activation (e.g. ISG signature), and genetic testing; no single element is sufficient, and the absence of a molecular diagnosis does not exclude the condition (Fig. 2).

IFNp-I should be suspected in specific clinical settings. These disorders should be considered in

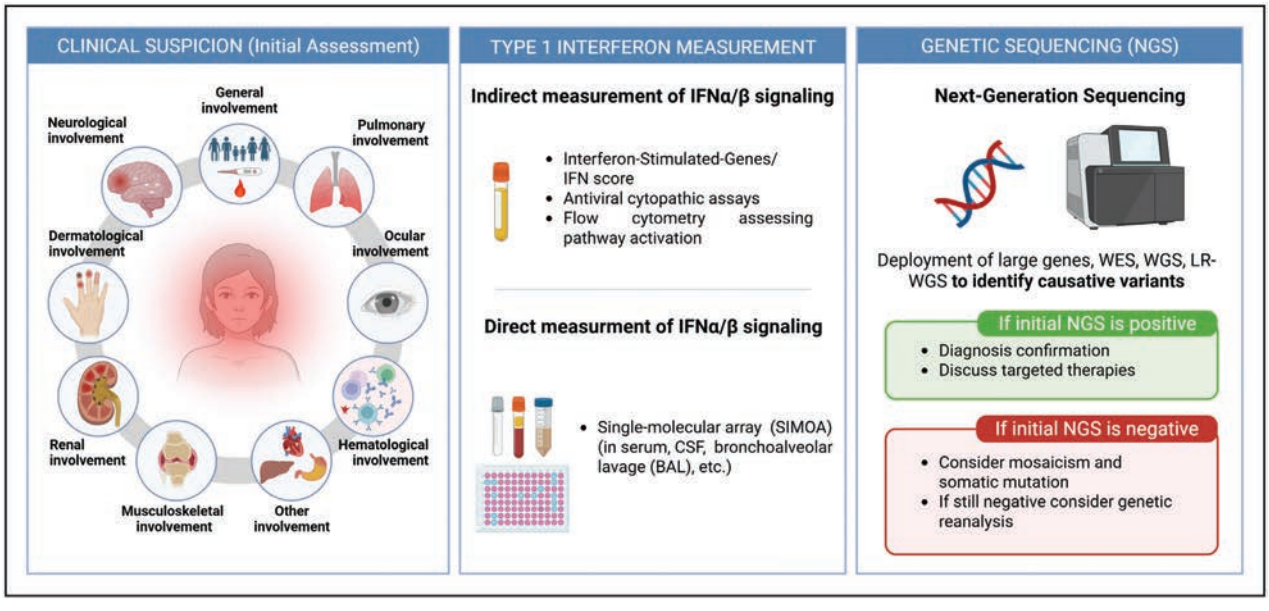

FIGURE 2. Key factors to consider for the diagnosis of type 1 interferonopathies. Type 1 interferonopathies diagnosis relies on integrated approach combining clinical features, biological evidence of type 1 interferon measurement (IFN score or IFN concentration) and definitive confirmation by genetic testing. IFN, interferon.

patients with early-onset, atypical, or treatment-refractory inflammatory disease, particularly when overlapping with SLE, autoinflammatory disorders, or immune dysregulation, even in case of negative C-reactive protein (CRP) levels.

Although the brain and the skin are the two most affected organs, the clinical phenotype can be multisystemic and heterogeneous. Key features may include neurological involvement (developmental delay or regression, spasticity, aseptic lymphocytic meningitis, pseudo-encephalitic phase, spasticity, microcephaly), characteristic neuroimaging findings (intracranial calcifications, white-matter abnormalities, cerebral atrophy), dermatological manifestations (chilblains, vasculitis, SLE-like skin lesions, livedo, panniculitis), as well as systemic (fevers, failure to thrive), musculoskeletal (myalgia, myositis, joint deformity with calcification, joint subluxation), pulmonary (ILD, pulmonary fibrosis, alveolar haemorrhage), autoimmune (biological and/or organ-driven autoimmunity including SLE and autoimmune thyroiditis), renal (lupus nephritis), ocular involvement (early-onset glaucoma), hepatogastric involvement [hepatic steatosis, transaminitis, gastroesophageal reflux disease (GERD)] and others (dental abnormalities).

Penetrance

Clinical expressivity can be observed even in the same family in cases of both autosomal dominant and autosomal recessive mutations. Additionally, clinical non-penetrance is described in IFHI1-related IFNp-I and COPA syndrome.

Biological findings support, but do not solely define, the diagnosis. Common laboratory features include lymphopenia, elevated erythrocyte sedimentation rate (ESR) with normal CRP level, and autoantibody positivity with anti-DNA antibodies being less common, while sustained activation of the IFN-I pathway (most often assessed by ISG signature) represents a key biological hallmark.

Absence of an IFN signature does not exclude disease. ISG expression may be absent, especially in around 22% of RNASEH2B patients. ISG elevation can also be attenuated in late-onset, organ-restricted, or treated patients with anifrolumab, highlighting the importance of integrating clinical, biological and genetic data.

TREATMENTS: NEW INSIGHTS AND FUTURE DIRECTIONS

The management of autoinflammatory diseases focuses on controlling inflammation, limiting organ damage and reducing glucocorticoid exposure. JAK inhibitors (JAKi), small-molecule targeting the JAK–STAT pathway, have been the most widely used in IFNp-I for over a decade and have revolutionised conventional IFNp-I therapeutics, replacing previously inefficient therapies. Indeed, their efficacy has been documented across studies in SAVI, AGS, PRAAS and COPA syndrome, showing consistent improvement in cutaneous, articular and systemic manifestations, [27,47–51]. However, their impact on pulmonary fibrosis and neurological involvement remains limited, likely due to preexisting irreversible organ damage, and restricted CNS penetration. Clinical response may wane over time; however, dose escalation is constrained by safety concerns (pleiotropic cytokine effects, anaemia, lymphopenia, thrombosis and infections), requiring close monitoring [52,53].

Anifrolumab, an anti-IFNAR1 monoclonal antibody blocking IFN-I signalling, is approved for adult SLE [54–56] and emerged as a promising option in IFNp-I. Indeed, recent cohort studies and case reports in JAKi-refractory IFNp-I (including SAVI, PRAAS, TREX1 and DNASE2 deficiency) showed effective normalization of IFN signature, improvement in skin manifestations and steroid tapering [57–62]. IFN signature normalisation has also been reported in three AGS patients treated with anifrolumab but showed variable neurological benefit, likely limited by preexisting CNS damage [63]. IFNAR1 blockade improves cutaneous disease, particularly after JAKi failure or intolerance, though its effect on lung, brain and kidney inflammation, as well as its long-term impact on organ damage remain to be established.

In parallel, alternative approaches such as reverse transcriptase inhibitors (RTi) showed limited efficacy in reducing IFN-I signalling and clinical effect, suggesting additional interferogenic triggers contributing to disease pathogenesis [64,65] Allogeneic hematopoietic stem cell transplantation (HSCT) may represent an alternative for severe, treatment refractory cases of PRAAS, with reported clinical benefit but variable outcomes [66–68]. Limited data in TLR7-related disease and SAVI [69] suggest inconsistent efficacy of HSCT, particularly on neurological involvement. Advances in IFNp-I pathophysiology enable the development of targeted therapies such as cGAS, STING and TLR inhibitors, with molecule such as enpatoran showing promising efficacy in a phase II clinical trial in adult SLE patients [70]. Other innovative approaches include antisense oligonucleotides and gene-based therapies. However, key challenges remain, particularly, efficient delivery across the blood brain barrier (BBB), as well as unresolved patient stratification based on genetic mechanism (GOF, LOF and mosaicism), optimal timing of intervention, the potential benefit of combination therapies, and long-term safety.

CONCLUSION

Over the past 15 years, since the conceptualisation of IFNp-I, both clinical and pathophysiological spectrum has expanded significantly and now encompasses diseases affecting nearly all organs. Although most cases begin in childhood, diagnoses and disease onsets can also occur in adulthood. We have also witnessed a major therapeutic shift, with nearly a decade of experience using JAKi that has substantially improved patient management, despite persistent significant unmet needs. More recently, anifrolumab has shown promising efficacy, although important questions remain regarding its long-term use and optimal positioning in treatment strategies. The development of additional targeted therapies is expected in the coming years. Finally, issues of clinical nonpenetrance and variable expressivity continue to represent key challenges and important avenues for future research.

Acknowledgements

We thank the patients and their families for their constant trust.

Financial support and sponsorship

This work was supported as part of the national plan for rare diseases by the French Ministry of Health, as well as by CRMR RAISE.

Conflicts of interest

There are no conflicts of interest.

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Polyarticular juvenile idiopathic arthritis: insights from genetic studies on disease risk and pathogenesis

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Purpose of review
Genetic and multiomics studies are reshaping our understanding of polyarticular juvenile idiopathic arthritis (JIA) and shifting the field from symptom- and phenotype-based categories toward biologically informed disease definitions. We summarize recent findings on disease risk and pathogenesis while focusing on genetic contributions to disease susceptibility and pathogenic mechanisms.

Recent findings
Classical HLA and non-HLA studies established the polygenic immune-mediated pathogenesis of JIA with distinct, partially overlapping, genetic architectures across the International League of Associations for Rheumatology categories. Rheumatoid factor (RF)-positive polyarticular JIA is increasingly considered a childhood-onset seropositive rheumatoid arthritis, whereas oligoarticular and RF-negative polyarticular JIA, although nonidentical, share substantial immunogenetic features. Recent subtype-integrative genome-wide association studies and transcriptomic and chromatin-interaction analyses prioritized candidate genes mediating lymphocyte activation, cytokine signaling, and immune regulation. Synovial atlas and spatial transcriptomic studies have further connected genetic susceptibility to immune-cell states and organized inflammatory niches, linking inherited risk to the chronic arthritis-sustaining tissue environment.

Summary
Genetic and multiomic studies support a shift toward biologically informed disease classification, evinced in the proposed Pediatric Rheumatology International Trials Organization framework, and provide a foundation for subtype-aware risk stratification and therapeutic target discovery in JIA. The association of genetic variations with prognosis warrants future investigation.

Keywords
disease classification, genetics, juvenile idiopathic arthritis, multiomics, polyarticular juvenile idiopathic arthritis

INTRODUCTION

Juvenile idiopathic arthritis (JIA) is a heterogeneous group of pediatric inflammatory arthritis cases, rather than a single disease entity [1▪]. Under the International League of Associations for Rheumatology (ILAR) classification, JIA has traditionally been divided into mutually exclusive clinical categories to provide a practical framework for clinical descriptions, cohort assembly, and clinical trials [2]. Since most of the genetic and integrative studies have been conducted within this framework, we followed the ILAR classification in this review and focused on rheumatoid factor (RF)-positive polyarticular, RF-negative polyarticular, and oligoarticular JIAs subtypes. These categories have been most extensively characterized in large-scale genetic and integrative studies and therefore provide the most robust foundation for examining genetic contributions to disease risk and pathogenesis.

Over the past two decades, genetic studies have shown that inherited susceptibility is not uniformly distributed across these categories [3]. These prior findings provide insight into disease risk and biological relationships among JIA categories, while also

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Curr Opin Rheumatol 2026, 38:328–335

DOI:10.1097/BOR.0000000000001172

KEY POINTS

- Genetic studies have shown that International League of Associations for Rheumatology-defined polyarticular and oligoarticular juvenile idiopathic arthritis (JIA) categories are not genetically interchangeable, which supports a shift toward a biologically informed classification.
- Rheumatoid factor (RF)-positive polyarticular JIA is increasingly regarded as a childhood-onset form of seropositive rheumatoid arthritis.
- Oligoarticular and RF-negative polyarticular JIA share a substantial immunogenetic architecture; however, HLA effect sizes, age-at-onset effects, and subtype-limited loci reveal important biological differences.
- Multiomic studies have linked inherited susceptibility to lymphocyte activation, gene regulatory programs, and spatially organized synovial inflammatory niches.
- These findings provide a mechanistic basis for subtype-aware risk stratification and therapeutic target discovery for juvenile-onset inflammatory arthritis.

highlighting the limitations of classification based solely on clinical phenotypes. Together with emerging genetic and molecular evidence, they support a shift toward a biologically informed classification, as reflected in the proposed Pediatric Rheumatology International Trials Organization (PRINTO) classification criteria and broader efforts to develop a molecular nomenclature for childhood arthritis [4,5].

This review discusses how genetic and integrative studies have advanced our understanding of disease risk and pathogenesis in polyarticular JIA, with a selective comparison to oligoarticular JIA. The scope of this review was limited to the genetic contributions to disease susceptibility and pathogenic mechanisms. The relationships between genetic variations and treatment response or disease prognosis remain an area of active investigation outside the scope of this review.

CLASSICAL GENETIC ARCHITECTURE OF NON-SYSTEMIC JUVENILE IDIOPATHIC ARTHRITIS

RF-positive polyarticular, RF-negative polyarticular, and oligoarticular JIAs are polygenic immune-mediated diseases with a substantial heritable component, although precise estimates vary according to subtype and method [3]. The strongest genetic risk factors are the major histocompatibility complex (MHC) proteins, particularly the human leukocyte antigen (HLA) class II loci. Susceptibility also extends beyond the HLA region to a broad network of non-HLA immune-regulatory genes. This multilocus architecture indicates that JIA pathogenesis involves multiple immune pathways rather than a single genetic determinant [3].

Oligoarticular and RF-negative polyarticular JIA share a well characterized HLA architecture, with strong susceptibility conferred by HLA-DRB1*11:03/04, HLA-DRB1*08:01, and HLA-DPB1*02:01. Conversely, HLA-DRB1*15:01 appears to confer protection in these categories. Meta-analytical evidence has further reinforced the central role of HLA-DRB1 variation across JIA subtypes, supporting the view that variations in antigen presentation are primary determinants of disease risk [3,6]. The HLA associations across the JIA categories are summarized in Table 1.

In contrast, RF-positive polyarticular JIA shows a distinct HLA profile characterized by strong associations with shared epitope-encoding HLA-DRB1 alleles, specifically HLA-DRB1*01:01, *04:01, *04:04, *04:05, *04:08, and *10:01 [3]. Structurally, this susceptibility is defined by the risk-conferring histidine at HLA-DRB1 position 13, shared with adult seropositive RA, a finding discussed further in Section 2 [7]. Subsequent MHC fine mapping further

Table 1. HLA associations across JIA categories

JIA category	HLA risk alleles	HLA protective alleles	HLA-DRB1 amino acid position 13
Oligoarticular JIA	HLA-DRB1*11:03/04 HLA-DRB1*08:01 HLA-DPB1*02:01	HLA-DRB1*15:01	Glycine
RF-negative polyarticular JIA	HLA-DRB1*11:03/04 HLA-DRB1*08:01 HLA-DPB1*02:01	HLA-DRB1*15:01	Glycine
RF-positive polyarticular JIA	HLA-DRB1*01:01 HLA-DRB1*04:01 HLA-DRB1*04:04 HLA-DRB1*04:05 HLA-DRB1*04:08 HLA-DRB1*10:01 (shared epitope alleles)	Not well characterized	Histidine

HLA, human leukocyte antigen; JIA, juvenile idiopathic arthritis; RF, rheumatoid factor.
HLA-DRB1 position 13 amino acid refers to the structurally defined risk determinant identified by MHC fine-mapping (Hinks *et al.*, Ann Rheum Dis, 2017)[7].

Table 2. Key non-HLA susceptibility loci in nonsystemic JIA

Gene/locus	Associated JIA category	Functional type	Immune pathway	Key reference(s)
PTPN22	oJIA, RF-negative pJIA, RF-positive pJIA	Coding variant (R620W)	Lymphocyte activation; negative regulation of TCR signaling	Hersh & Prahalad, 2015 Hinks *et al.*, 2013
STAT4	oJIA, RF-negative pJIA, RF-positive pJIA	Noncoding; possible regulatory	Cytokine signaling (IL-12/IL-23/IFN pathway)	Hersh & Prahalad, 2015
PTPN2	oJIA, RF-negative pJIA	Noncoding; *cis*-eQTL	T-cell activation; cytokine signaling	McIntosh *et al.*, 2017
JAK1	oJIA, RF-negative pJIA	Noncoding; *cis*-eQTL	JAK-STAT signaling; cytokine receptor signaling	McIntosh *et al.*, 2017
IL2 / IL2RA / IL2RB	oJIA, RF-negative pJIA	Noncoding; regulatory	IL-2 signaling; T regulatory cell homeostasis	Hersh & Prahalad, 2015 Hinks *et al.*, 2013
IL6 / IL6R	oJIA, RF-negative pJIA	Noncoding; regulatory	IL-6 cytokine signaling; inflammatory response	Hersh & Prahalad, 2015
CD86 (ILDR1_CD86 locus)	oJIA, RF-negative pJIA	Noncoding; *cis*-eQTL	T-cell costimulation; antigen presentation	McIntosh *et al.*, 2017
IRF8	oJIA, RF-negative pJIA	Noncoding; regulatory	Innate immune signaling; myeloid cell differentiation	Kim *et al.*, 2024
TNFAIP3	RF-positive pJIA	Coding/noncoding; regulatory	NF-κB signaling; negative regulation of inflammation	Hersh & Prahalad, 2015
C5orf56 / IRF1	oJIA	Noncoding; regulatory	Interferon signaling; immune regulation	Hinks *et al.*, 2013

eQTL, expression quantitative trait locus; IFN, interferon; IL, interleukin; JIA, juvenile idiopathic arthritis; oJIA, oligoarticular JIA; pJIA, polyarticular JIA; RF, rheumatoid factor; TCR, T-cell receptor.
Functional type refers to the predominant mechanism through which the risk allele is thought to act. *cis*-eQTL indicates that the variant is associated with altered expression of the gene in cis. All loci listed have reached genome-wide significance in at least one published study.

confirmed that genetic susceptibility was structured and category-specific rather than generic across clinically defined JIA categories [7]. These divergent HLA profiles underscore that ILAR-defined categories are not genetically interchangeable and may represent biologically distinct disease entities that differ in their antigen and T-cell repertoires [3].

Non-HLA studies have expanded the framework of JIA pathogenesis beyond antigen presentation. Dense genotyping using the ImmunoChip platform has identified 14 new susceptibility regions that reached genome-wide significance in oligoarticular and RF-negative polyarticular JIA [8]. A complementary genome-wide association meta-analysis identified nine additional regions, several of which contained *cis*-expression quantitative trait loci (*cis*-eQTL), suggesting that inherited risk may occur through altered gene regulation [9]. In oligoarticular and RF-negative polyarticular JIA, susceptibility variants have been identified in immune regulatory genes, including PTPN22, STAT4, PTPN2, interleukin (IL)2, IL2RA, IL2RB, IL6, and IL6R, implicating lymphocyte activation, cytokine signaling, and immune regulation in inherited susceptibility. RF-positive polyarticular JIA also shares risk genes such as PTPN22 and STAT4, and TNFAIP3 variants have been specifically associated with this category [3]. The key non-HLA susceptibility loci are summarized in Table 2. Together, these studies establish an immunogenetic foundation for nonsystemic JIA and provide a basis for linking inherited risk to pathogenic mechanisms and biological classifications.

WHAT GENETICS TAUGHT US ABOUT DISEASE BOUNDARIES

Genetic research has increasingly demonstrated that the clinical phenotype-based boundaries in JIA do not fully capture the underlying biological relationships. MHC fine-mapping has established that RF-positive polyarticular JIA is genetically distinct from other JIA categories and is increasingly being recognized as the childhood-onset form of the same disease entity as adult seropositive rheumatoid arthritis (RA) [7,10,11▪▪], specifically sharing the risk-conferring histidine at HLA-DRB1 amino acid position 13 [7]. By contrast, oligoarticular and RF-negative polyarticular JIA share a substantial immunogenetic foundation, including a common association with glycine at the same HLA-DRB1 position [7]. This

structural divergence-histidine for RF-positive polyarticular JIA and seropositive RA, and glycine for oligoarticular and RF-negative polyarticular JIA-implies that these categories present fundamentally different antigens and engage in distinct T-cell repertoires, providing a molecular basis for their biological distinction. Nevertheless, large-scale meta-analyses have revealed quantitative differences in association strength, with alleles such as HLA-DRB1*08 and HLA-DRB1*11 showing stronger associations in oligoarticular JIA than in RF-negative polyarticular JIA [6], and specific loci such as C5orf56/IRF1 appearing to be subtype-limited [8]. These findings support a model in which oligoarticular and RF-negative polyarticular JIA are closely related but not genetically identical.

The age of onset further refined this relationship. HLA-DRB1*11:03/04 confers risk to both oligoarticular and younger-onset RF-negative polyarticular JIA but not to older-onset polyarticular disease, whereas HLA-DRB1*08:01 appears to contribute to risk across age groups [3]. These age-dependent HLA effects provide direct genetic support for the proposed PRINTO classification criteria, which define early-onset antinuclear antibody (ANA)-positive JIA as a distinct disorder irrespective of joint count, as the shared HLA-DRB1*11 risk signal suggests that joint count may be a less reliable discriminator than age at onset and ANA status [4]. Recent subtype-integrative studies have further reinforced the idea that substantial components of susceptibility are shared across ILAR categories, with López-Isac *et al.*[12] and Li *et al.* [13] identifying cross-subtype loci implicating immune regulatory pathways and T-cell activation beyond the HLA region. Together, these findings suggest that traditional clinical labels capture only part of the underlying biological architecture of childhood arthritis.

MULTIOMIC INSIGHTS INTO PATHOGENIC MECHANISMS: FROM GENETIC VARIANTS TO CELLULAR NICHES

Recent genomic and multiomic studies have begun to connect the genetic susceptibility of JIA to specific immune pathways, cellular states, and tissue niches (Table 3). Most large-scale genetic studies have been enriched for, or focused on, the common ILAR categories of oligoarticular and RF-negative polyarticular JIA. These studies support a substantial heritable

Table 3. Key findings and translational implications from recent multiomic studies in nonsystemic JIA

Study	Approach	Primary JIA category studied	Key finding	Translational implication
Kim *et al.* 2024	Integrative GWAS + immune repertoire profiling	oJIA, RF-negative pJIA	SNP-based heritability approximately 73%; reduced TCR diversity linked to genetic risk regions and clonally expanded CXCL13+BHLHE40+ T helper cells	Links inherited risk to T-cell repertoire alterations
Fan *et al.* 2024	Multiomics + genome editing	Not subtype-specific	Novel JIA genes identified; first genetic link to bone mineral density traits	Supports genomics-guided drug repurposing and links inflammatory susceptibility to musculoskeletal comorbidity
Tarbell & Jarvis 2025	Integrative GWAS + transcriptomics + chromatin data	Not subtype-specific	HIPK1 prioritized at PTPN22 locus; reduced HIPK1 in CD4+ T cells impairs inflammatory feedback	HIPK1 as candidate target for immune modulation in T cells
Bolton *et al.* 2025	Synovial tissue atlas; scRNA-seq + spatial transcriptomics + GWAS risk gene localization	oJIA, RF-negative pJIA, psoriatic arthritis	SPP1+ macrophages enriched in polyarticular and extended disease; organized inflammatory niches identified	SPP1+ macrophage niche as target for preventing oligoarticular extension
Inamo *et al.*2026	Spatial immune-stromal mapping; subcellular-resolution spatial transcriptomics + cell–cell interaction analysis + GWAS signal enrichment	oJIA, RF-negative pJIA	NOTCH3+ endothelial–fibroblast crosstalk and CXCL9/CXCR3 macrophage-T cell axis identified	Stromal–immune crosstalk as therapeutic target in chronic synovitis

GWAS, genome-wide association study; JIA, juvenile idiopathic arthritis; oJIA, oligoarticular JIA; pJIA, polyarticular JIA; RF, rheumatoid factor; scRNA-seq, single-cell RNA sequencing; SNP, single-nucleotide polymorphism; TCR, T-cell receptor.

contribution to disease susceptibility, although the estimates vary according to subtype composition, ancestry, and analytical methods [14▪].

Integrative genome-wide association studies (GWAS) and transcriptome-wide association studies (TWAS) have prioritized susceptibility genes involved in lymphocyte activation, costimulation, and cytokine signaling, including JAK1, CD86, PTPN2, STAT4, CD247, IRF8, and RHOH [15▪]. Several associated variants act as *cis*-eQTLs, particularly in $CD4^+$ T cells, suggesting that inherited risk may operate through altered gene regulation rather than protein-coding changes alone [9,14▪], which is consistent with the predominance of JIA-associated loci in noncoding regions. Functional integration with immune repertoire profiling has further implicated altered T-cell biology, including reduced T-cell receptor alpha diversity and the expansion of $CXCL13^+$ $BHLHE40^+$ T helper cell populations [14▪]. Notably, these $CD4^+$ T-cell eQTL signals converged with synovial transcriptomic data showing prominent T-cell infiltration in inflamed JIA tissues [16▪▪], suggesting that inherited regulatory variants in T cells may shape the downstream tissue inflammatory environment. Together, these findings suggest that inherited risk in common nonsystemic JIA is expressed not simply as generalized inflammation, but through specific regulatory programs in lymphocyte activation and antigen-experienced immune cell states.

Familial JIA studies have provided complementary evidence using shared genomic segment analyses in high-risk pedigree patients. These analyses identified signals in the MHC class I and III regions, including HLA-A*02:01, suggesting that inherited susceptibility in JIA may extend beyond the classical HLA class II framework [17▪].

Synovial tissue studies have added a spatial dimension to the genetic and immune cell findings. Spatial transcriptomic and synovial atlas studies of the JIA synovium have identified stromal, endothelial, myeloid, and lymphoid compartments associated with inflammation and disease severity [16▪▪,18▪▪]. These studies are particularly important because they place inherited risk signals and disease-associated transcriptional programs within tissues that sustain chronic arthritis. Rather than viewing the synovium as a passive target of systemic autoimmunity, these data support a model in which local tissue-resident cells, vascular structures, infiltrating immune cells, and stromal programs form organized inflammatory niches. NOTCH3-related endothelial-fibroblast communication and CXCL9/CXCR3-mediated macrophage-T-cell interactions suggest that immune-stromal crosstalk contributes to the maintenance of synovial inflammation [18▪▪]. This is relevant to polyarticular disease because progression from limited to more extensive joint involvement may depend not only on systemic immune predisposition but also on whether local synovial niches can sustain and amplify inflammatory circuits. $SPP1^+$ macrophages, enriched in the inflamed synovial tissue and associated with disease severity, were specifically identified in the joints of children with polyarticular JIA and in those whose oligoarticular disease extended to polyarthritis [16▪▪]. This links the synovial cellular composition to joint extension, suggesting that $SPP1^+$ macrophage programs within local niches may help determine whether oligoarticular disease progresses to polyarticular involvement. Thus, the synovial atlas and spatial transcriptomic studies provide a mechanistic bridge between inherited susceptibility, cell-state dysregulation, and the clinical evolution of arthritis.

Environmental exposure enrichment analyses integrating TWAS and mRNA expression profiles suggested possible interactions between JIA-associated genetic signals and external exposure to air pollutants and heavy metals [19]. However, these findings remain exploratory and require validation through subtype-aware epidemiological and mechanistic studies.

RECENT ADVANCES IN TARGET PRIORITIZATION, RISK STRATIFICATION, AND CLINICAL TRANSLATION

By linking genetic risk to immune-cell states and synovial inflammatory niches, recent multiomic studies have created a foundation for translational research in JIA. Recent integrative studies have translated JIA susceptibility loci into candidate genes, molecular targets, and risk stratification tools. In oligoarticular and RF-negative polyarticular JIA, the integration of GWAS, transcriptomic, and chromatin interaction data has helped to prioritize candidate genes at established risk loci. Using open target genetics, RNA-seq, and 3D chromatin data, integrative analyses prioritized HIPK1 at the PTPN22 locus and suggested that reduced HIPK1 expression in $CD4^+$ T cells might weaken the negative feedback control of GATA4- and TP53-associated inflammatory programs [20▪▪]. Although mechanistically informative, these findings require validation using primary patient samples and in vivo models. Magnetic resonance-based plasma proteomic analysis has also identified GP1BA and TNFSF11 as candidate proteins associated with JIA susceptibility, although these findings remain hypothesis-generating and require validation in subtype-aware cohorts [21▪].

Polygenic risk score (PRS) analysis showed nonlinear and sex-dependent performance in JIA, with

stronger discrimination reported in females than in males, suggesting that future genetic risk models may require sex-aware calibration rather than uniform application across patients [22▪]. The current JIA PRS remains a research tool rather than a clinical instrument.

JIA-associated uveitis is a complication-specific example of genetic risk stratification across nonsystemic JIA categories. The integration of HLA markers, including HLA-DRB1, HLA-DPB1, and HLA-A, with ANA status and age at onset improved the uveitis risk classification beyond clinical factors alone [23▪], although further validation is needed. HLA associations in ANA-positive JIA further suggest that uveitis risk reflects the immunogenetic background shared across oligoarticular and RF-negative polyarticular JIA [24▪]. Mechanistic profiling has additionally implicated antigen-driven B-cell activation, including expansion of $CD19^{+}IgD^{-}CD27^{-}$ double-negative type 1 B cells and increased somatic hypermutation in the B-cell receptor repertoire [25▪]. These findings are relevant to polyarticular JIA, primarily because they illustrate how complication-specific risk can be cut across the ILAR categories.

Cross-disease genetic analyses have placed JIA within a broader network of immune-mediated rheumatic diseases. JIA datasets show genetic overlap with seropositive RA, SLE, and systemic sclerosis, with shared pathways, including JAK–STAT signaling [11▪▪]. Additional analyses have linked JIA risk to bone-related traits and candidate genes, such as COLEC10 and TNFRSF11B [15▪], and network-based approaches have connected JIA-associated genes with multiple GWAS traits, providing a framework for understanding shared molecular pathways and comorbidity patterns [26▪]. These findings are not yet clinically actionable but provide a foundation for target prioritization and biologically informed stratification in pediatric rheumatology.

LESSONS FROM ADULT SEROPOSITIVE RA: IMPLICATIONS FOR JUVENILE-ONSET DISEASE

RF-positive polyarticular JIA is increasingly regarded as a childhood-onset form of seropositive RA, rather than as a biologically separate JIA category. This is supported by its close genetic resemblance to adult seropositive RA, including shared HLA-DRB1 risk architecture and cross-disease genetic overlap [10,11▪▪]. Accordingly, the concepts developed for adult seropositive RA provide a useful framework for understanding juvenile-onset seropositive arthritis, particularly in terms of early disease development and risk stratification.

In adults seropositive RA, disease development is increasingly conceptualized as a multistep process that begins before clinically apparent arthritis. The European Alliance of Associations for Rheumatology (EULAR) Study Group proposed a terminology for individuals at risk of RA, including stages defined by genetic risk factors, environmental risk factors, systemic autoimmunity associated with RA, symptoms without clinical arthritis, and unclassified arthritis, thereby forming the concept that RA evolves through identifiable preclinical and early clinical phases [27]. Within this framework, the mucosal origins hypothesis proposes that anticitrullinated protein antibody (ACPA) generation may begin at mucosal surfaces before clinically apparent arthritis develops [28,29▪]. Formalized risk-stratification approaches have also been developed, including the EULAR definition of arthralgia suspicious for progression to RA and, more recently, the EULAR/American College of Rheumatology (ACR) risk stratification criteria for the arthralgia risk stage [30,31▪]. Analogous preclinical stages of childhood-onset seropositive RA have not yet been identified. ACPA are detectable in a subset of children with RF-positive polyarticular JIA; however, presymptomatic population-level data and systematic screening programs analogous to those used in adult at-risk cohorts are lacking. A key question is whether, preclinical phases, mucosal immune signatures, or early risk states comparable to those in adult RA can be identified before persistent synovitis is established and adult risk stratification frameworks can be meaningfully adapted to the pediatric context [29▪,31▪].

CONCLUSION

Genetic and multiomic studies have transformed our understanding of nonsystemic JIA and demonstrated that the ILAR-defined categories are not genetically interchangeable. RF-positive polyarticular JIA is best regarded as the childhood-onset form of seropositive RA, whereas oligoarticular and RF-negative polyarticular JIA share a substantial, but distinct, immunogenetic foundation. These advances connect inherited risks to immune pathways and synovial niches, and provide a basis for biologically informed classification, risk stratification, and therapeutic target discovery. Future studies with well phenotyped, subtype-aware, and ancestry-diverse cohorts are warranted to elucidate these relationships.

Acknowledgements

None.

Financial support and sponsorship

This work was supported by the JSPS KAKENHI Grant Number 23K07911 and 26K11351, Takeda Science Foundation Research Grant , the MEXT Project for

Developing Innovation Systems for the Formation of Hubs for Medical Human Resource Development , and the Advanced Medical Human Resource Development Program.

Conflicts of interest

There are no conflicts of interest.

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Update on IgA nephropathy: implications for treatment in IgA vasculitis: a guide for rheumatologists

Julia A. Ford and Ora Gewurz-Singer

Purpose of review
IgA vasculitis (IgAV) and IgA nephropathy (IgAN) have historically been treated as distinct disease entities in clinical practice and in drug development, despite growing evidence speaking to a shared pathogenesis. Recent years have seen an explosion in therapeutic trials in the IgAN space, with multiple approvals of targeted therapies and a shifting paradigm of care; meanwhile, IgAV has lagged behind with a paucity of randomized trials. What can rheumatologists learn from IgAN, and can IgAV patients benefit from therapeutic advances in IgAN?

Recent findings
In this article, we will compare and contrast the epidemiology and clinical presentations of IgAV and IgAN, and explore the evidence supporting a shared pathogenesis including the 'four hit hypothesis'. We will review emerging therapies in IgAN and their biologic basis for the rheumatology audience, and discuss how lessons learned in IgAN might be applied to IgAV.

Summary
Rheumatologists should be aware of the therapeutic advances in IgAN, which may inform future management of IgAV patients, particularly those with renal involvement.

Keywords
complement, IgA, IgA nephropathy, IgA vasculitis

INTRODUCTION

IgA vasculitis, also known as Henoch–Schoenlein purpura, is a systemic immune-mediated small vessel vasculitis characterized by a clinical tetrad of palpable purpura, arthralgias/arthritis (often affecting the lower extremities), gastrointestinal involvement (ranging from abdominal pain, to gastrointestinal hemorrhage or intussusception), and renal involvement. Kidney disease in IgAV is an immune complex-mediated glomerulonephritis and can range from microscopic hematuria with minimal proteinuria to nephrotic range proteinuria, elevated creatinine and hypertension. Urologic, neurologic, and respiratory manifestations (such as alveolar hemorrhage) are reported in IgAV, though are rare [1]. IgAV is the most common systemic vasculitis in children, who tend to have a milder, self-limited course compared to adults, who comprise the minority (10–30%) of IgAV cases but tend to have a more aggressive course with more severe renal involvement [2]; in fact, in a French cohort of 260 adult IgAV patients, 30% had renal failure at presentation [3]. Various triggers of IgAV have been identified (particularly respiratory infections including COVID-19 [4], medications, or malignancy) but the precise cause of IgAV is unclear. Estimated incidence of IgAV varies according to geography.

While pediatric IgAV usually requires only supportive care, more severe presentations of IgAV particularly in adults are managed with glucocorticoids with limited data to support the use of steroid-sparing disease-modifying antirheumatic drugs, as has been reviewed in detail by others [5,6]. Rituximab [7] and mycophenolate mofetil [8] have demonstrated efficacy in small studies, while cyclophosphamide

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Curr Opin Rheumatol 2026, 38:336–342

DOI:10.1097/BOR.0000000000001171

KEY POINTS

- IgAV and IgAN have overlapping genetics and pathogenesis including the 'four-hit hypothesis'.
- New treatment paradigms for IgAN should be considered for IgAV.
- Recent studies have shown poor renal outcomes in IgAN even with limited proteinuria, making the case for more aggressive treatment.
- New targeted treatments recently approved for IgAN, though excluded from trials, might be reasonable to consider in IgAV.

has not shown convincing benefit [3]. As of this writing, the phase III RIGA trial comparing rituximab and glucocorticoids to glucocorticoids alone in adult IgA is active (NCT05329090); however, there are no current Food and Drug Administration (FDA)-approved therapies for IgAV.

IgA nephropathy (IgAN) is the most commonly diagnosed glomerular disease in the United States with an estimated incidence of 1 per 100 000 persons and a leading cause of end-stage renal disease (ESRD) in young adults [9]. In contrast to IgAV, which has a bimodal age distribution (with peaks in childhood at 7–9 years, and adulthood in the 50 s), IgAN incidence peaks at ages 20–30 s. Patients with IgAN may present with one or more episodes of gross hematuria (particularly in setting of upper respiratory infection); with microscopic hematuria with or without proteinuria; with progressive renal dysfunction; or less commonly with nephrotic syndrome or rapidly progressive glomerulonephritis. Naturally, extrarenal symptoms are absent in IgAN, which may result in delayed recognition of the disease compared to IgAV. Differences and similarities between IgAV and IgAN are summarized in Fig. 1. In contrast to IgAV, there have been numerous controlled trials of targeted therapies in IgAN leading to multiple drug approvals in the past several years to be discussed later in this article.

IGA VASCULITIS AND IGA NEPHROPATHY: SAME OR DIFFERENT DISEASES?

Though IgAN and IgAV (even when it involves the kidneys) are treated as distinct clinical entities, studies have shown tremendous overlap in their pathogenesis and genetics [10,11]. Genome-wide association studies (GWAS) have found shared HLA susceptibility in IgAN and IgAV, involving the HLA-DRB1 region [12▪,13], and a recent cross-phenotype GWAS analysis identified 21 shared-risk loci between IgAN and IgAV [12▪]. Renal involvement in IgAV, also known as IgAV with nephritis (IgAVN), is histopathologically indistinguishable from that seen in IgAN [14▪▪]. IgA deposition in the mesangium was described in both entities as early as 1969 [15]. The range of histopathology in IgAN and IgAVN spans from mesangial proliferation, to focal and segmental proliferation, to severe crescentic glomerulonephritis. The Oxford MEST-C scoring system (M = mesangial hypercellularity; E = endocapillary hypercellularity; S = segmental glomerulosclerosis; T = tubular atrophy/interstitial fibrosis; C = crescents) correlates with kidney outcomes in IgAN, and has been evaluated in IgAVN cohorts as well [16]. IgAVN patients tend to exhibit

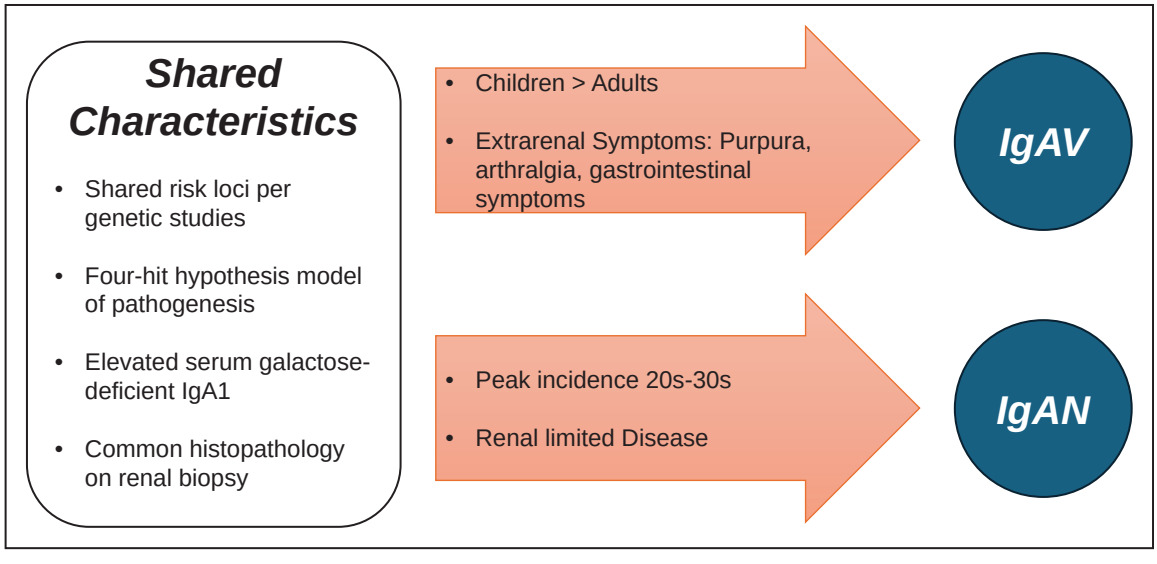

FIGURE 1. Comparing and contrasting IgA vasculitis and IgA nephropathy.

more acute changes on biopsy (such as E and C lesions), whereas IgAN patients exhibit more signs of chronicity (S and T) [17]; perhaps this is due to delayed recognition of IgAN compared to IgAVN, as the latter presents with more overt and easily detectable extrarenal symptoms.

Emerging evidence suggests that the four-hit hypothesis, widely accepted amongst nephrologists to explain the pathogenesis of IgAN [18,19▪▪], also applies to IgAVN. Given shared mechanisms of pathogenesis, it is reasonable to ask whether lessons learned for the management of IgAN can be extrapolated to IgAVN and perhaps even to extrarenal manifestations of IgAV. A detailed description of the four-hit hypothesis is beyond the scope of this article; however, a basic understanding is necessary to recognize potential therapeutic targets that might be shared between IgAN and IgAV. The four-hit hypothesis includes the following (Fig. 2):

(1) Hit 1: the overproduction of an aberrantly glycosylated IgA, galactose-deficient IgA1 (Gd-IgA1), in Mucosal Associated Lymphoid Tissues (MALT) of the gastrointestinal or upper respiratory tracts [20]. Serum Gd-IgA1 levels have been shown to be significantly higher in IgAN and in IgAVN compared to healthy controls [21,22]. In patients with a genetic predisposition, an environmental stimulus (such as infectious pathogens) at the mucosal lining results in upregulation of the B-cell modulators B-cell Activating Factor (BAFF) and A Proliferation Inducing Ligand (APRIL), promoting B-cell class switching from naive B cells to a Gd-IgA1-producing B cells [23].
(2) Hit 2: antibodies to the Gd-IgA1 are formed. Serum levels of anti-Gd-IgA1 antibodies correlate to disease activity in patients with IgAVN [24].
(3) Hit 3: the formation of anti-Gd-IgA1-containing circulating immune complexes mediated by complement factors. Markers of the lectin and alternative complement pathways are increased in IgAVN [25]. Biopsies of skin and kidney have shown deposition of complement components C3 and C5–C9 [26–28].
(4) Hit 4: deposition of circulating immune complexes into the blood vessel walls and renal mesangium activating the mesangial cells, which in turn activates the inflammatory and fibrotic pathways resulting in kidney injury.

It is not yet understood why in IgAN Gd-IgA1 immune complexes have a tropism for renal

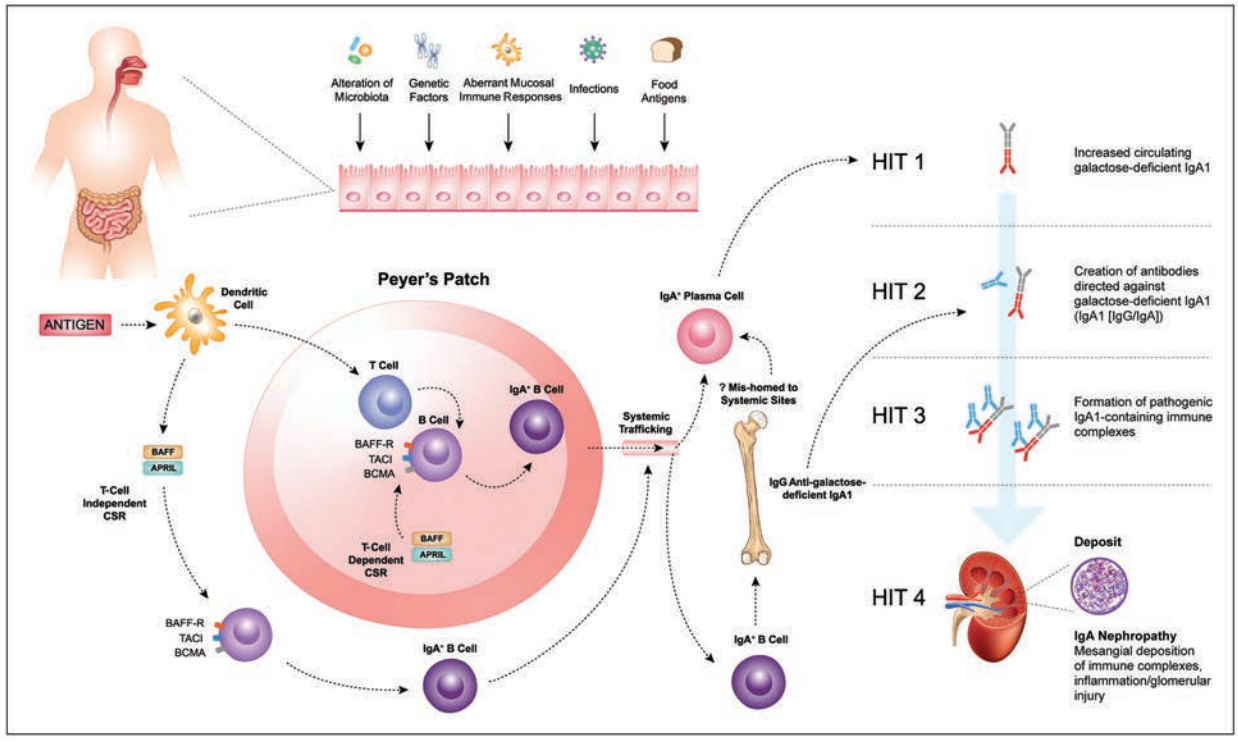

FIGURE 2. Four-hit hypothesis of IgA nephropathy pathogenesis. Obtained with permission from Chee Kay Cheung. Source: Cheung CK, Barratt J, Liew A, *et al.* The role of BAFF and APRIL in IgA nephropathy: pathogenic mechanisms and targeted therapies. *Frontiers in Nephrology* 2024;3: 1346769.

mesangial tissue while in IgAV, immune complexes deposit less selectively in several organs such as the joints, skin, and gastrointestinal tract. Some have wondered whether patients with IgAN may have had unrecognized vasculitis in the past [29▪▪].

Drugs targeting the various steps of the four-hit hypothesis are either approved for use by the FDA in the United States or under discovery in IgAN. Unfortunately, IgAV patients have been excluded from the IgAN trials. It is reasonable, however, to hypothesize these drugs might also be effective in IgAV, due to shared pathogenesis.

A NEW PARADIGM FOR TREATING IGA NEPHROPATHY

Major shifts in the treatment approach to IgAN have been driven by two key findings: patients with low-grade proteinuria (defined as urine protein of <1 g/day), who previously had been categorized as low risk of progression and monitored off therapy, were shown to have poor long-term outcomes [30–32], and patients with low-grade proteinuria were shown to have improved renal outcomes when treated with immunosuppressive therapies, such as glucocorticoids [33]. In the United Kingdom National Registry of Rare Kidney Diseases cohort of 2299 adults and 140 children with IgAN, patients with proteinuria of less than 1 g/day had a 30% chance of kidney failure at 10 years and a 50% chance at 15 years [30]. Similarly, in a Chinese cohort of 1530 patients, any level of proteinuria above normal (defined as >0.3 g/day) imbued a worse renal prognosis [32]. The Therapeutic Evaluation of Steroids in IgA Nephropathy Global [33] Trial showed that glucocorticoids used in patients with proteinuria (<1 g/day) had improved renal outcomes compared to patients treated without glucocorticoids [33]. These findings have led to the changes in the 2025 KDIGO Practice Guidelines for IgAN and IgAVN, lowering the threshold for acceptable levels of proteinuria and defining those at risk for progressive kidney failure and in need of treatment as patients with proteinuria more than 0.5 g/day [14▪▪].

Furthermore, a two-pronged approach was recommended in the KDIGO Guidelines for management of both IgAN and IgAVN: use of renal protective strategies to reduce nephron loss including lifestyle modifications and use of agents such as renin–angiotensin–aldosterone system (RAAS) blockers, sodium glucose co-transporter 2 (SGLT2) inhibitors, and endothelin-1 receptor antagonists (ERA); and use of immunomodulatory agents to target mechanisms of inflammation in IgAN/IgAVN and prevent or reduce IgA-IC formation and mesangial IC deposition and inflammation. Prong one, the use of renal protective strategies, is already considered the standard of care in patients with IgAVN and largely is initiated by our colleagues in nephrology who co-manage these patients alongside rheumatology. Of note, there have also been recent advances in this arena. Atrasentan (brand name Vanrafia), a selective ERA and sparsentan (brand name Filspari), a first-of-its-class dual ERA and angiotensin II receptor blocker, were recently approved and are available for use in IgAN due to their significant impact on reducing proteinuria in IgAN trials [34,35,36▪].

Prong 2, using immunomodulatory agents to target mechanisms of inflammation, is particularly compelling for consideration in IgAV with and without nephritis. Though there is mechanistic plausibility that the various immunomodulatory drugs recently approved in IgAN might be effective in IgAV, as mentioned previously, this population was excluded from the clinical trials.

IMMUNOMODULATORY DRUG ADVANCEMENTS IN IGA NEPHROPATHY

The recent significant advancements in our understanding of the pathogenesis of IgAN have facilitated the development of novel therapies that target the various steps of the four-hit hypothesis (Table 1).

Drugs targeting Gd-IgA-1 production (hit 1)

Targeted release budesonide (also known as Nefecon; brand name Tarpeyo), is a slow-release oral glucocorticoid, which targets hit 1 by working locally at the MALTs to reduce production of Gd-IgA1. Nefecon received accelerated FDA approval in December 2021 and full approval 2 years later in 2023 after the release of the results of the Phase III NEFecon in IgAN trial (NeflgArd) [37]. In the NefIgArd trial, 364 patients with primary IgAN, all of whom were optimized on RAAS blockade, were randomized to treatment with Nefecon 16 mg/day or placebo for 9 months and followed for 12 months. The primary outcome, the time-weighted average of estimated glomerular filtration rate (eGFR) over 2 years, showed a statistically significant treatment benefit with Nefecon versus placebo (difference 5.05 ml/min./1.73 m^2). Furthermore, there was a 27% reduction in proteinuria versus placebo at month 9 and 48% reduction 3 months after stopping budesonide at month 12 [37]. The most common adverse events reported with Nefecon were peripheral edema and muscle spasms.

Agents that block the B-cell stimulators APRIL and BAFF also target hit 1 and reduce GD-IgA1 production. Sibeprenlimab (brand name Voyxact), a monoclonal antibody to APRIL, was newly FDA-

Table 1. New targeted therapies approved for use in IgA nephropathy in the United States

Drug name (brand name)	Mechanism of action	Target of the four-hit hypothesis	Dosing/formulation
Atrasentan (Vanrafia)	Endothelin-receptor antagonist	N/A	0.75 mg daily orally
Sparsentan (Filspari)	Dual endothelin and angiotensin receptor antagonist	N/A	200–400 mg daily orally
Targeted-release budesonide (Tarpeyo)	Glucocorticoid targeted to the gut	1	16 mg daily orally
Sibeprenlimab (Voyxact)	Monoclonal antibody to APRIL	1	400 mg every 4 weeks subcutaneously
Iptacopan (Fabhalta)	Complement factor B inhibitor	3	200 mg twice daily orally

approved in November 2025. In the interim analysis of the first 320 patients in the phase III ENVISION trial, sibeprenlimab given at 400 mg subcutaneously every 4 weeks resulted in a significant reduction in proteinuria (–50.2%) compared to an increase (of 21. %) with placebo at 9 months [38,39▪]. The safety profile was similar in the two groups.

Several other anti-APRIL and anti-BAFF agents are under development. In the phase II ORIGIN trial atacicept, a dual anti APRIL/BAFF inhibitor, reduced proteinuria compared to placebo by 35% at 9 months [40]. In the open-label extension to 96 weeks atacicept showed an acceptable safety profile [41]. The phase III ORIGIN III trial of atacicept has completed recruitment (NCT04716231).

Preliminary data suggests targeting APRIL and BAFF might also be effective in IgAVN. A small, single armed study of another anti-APRIL/BAFF drug called telitacicept in 13 IgAVN patients showed significant improvement in proteinuria [42]. A phase II trial is underway. Additionally, several retrospective studies have shown efficacy of the anti-APRIL and BAFF agents in IgAVN [43–45]. In a pediatric retrospective observational study, 24 children with IgAV or IgAVN were treated with telitacicept compared to 30 matched-control IgAVN patients treated with conventional therapy. Proteinuria was significantly reduced in the treatment arm at 36 weeks [43]. Of significance, five patients with only extrarenal IgAV reported improvement in gastrointestinal, skin, and joint symptoms, prompting the question could blocking APRIL and BAFF play a role in treatment of nonrenal IgAV?

Targeting the complement lechtin, alternative and terminal pathways (hit 3)

As described above, there is growing evidence to suggest that the complement system plays a significant role in hit 3 of the four-hit model of pathogenesis of IgAN and IgAVN, particularly through the lectin and alternative pathways, which both culminate in the terminal complement pathway [28,46]. Multiple agents that target complement are being investigated in IgAN, with some already approved and others still on the horizon.

Iptacopan, an oral factor B inhibitor which blocks the alternative complement pathway, received accelerated FDA approval in August 2024 for use in IgAN. The pivotal APPLAUSE trial compared iptacopan 200 mg orally twice a day to placebo in 222 patients with IgAN and a UPCR (urine protein to creatinine ratio) of more than 1 g/day [47▪]. At month 9, the UPCR was 38% lower in the iptacopan group compared to the placebo group ($P < 0.001$) with a tolerable side effect profile, no unexpected safety findings and no increase in infection risk.

Several agents targeting the terminal complement pathway are under early investigation. In a phase II trial of 43 IgAN patients, ravulizumab, a long acting monoclonal antibody to complement C5, showed a statistically significant reduction in proteinuria of –41.9% compared to a –16.8% change with placebo (30.1% treatment effect; $P = 0.005$) [48]. A phase III trial is enrolling (NCT04201262). Cemdisiran, another agent targeting complement 5, is a small-interfering RNA that works by suppressing hepatic C5 production and is administered subcutaneously; a phase II trial of 31 patients showed improvement in proteinuria over placebo [49]. Repurposing from anti-neutrophilic antibody-associated vasculitis, the C5a-receptor inhibitor avacopan (brand name Tavneos) has shown modest efficacy in a small, open-label pilot study of 10 patients with IgAN [50].

CONCLUSION AND FUTURE DIRECTIONS

IgAV and IgAN are siloed in our clinics and drug trials (patients with IgAV have been excluded from clinical trials of IgAN therapies), despite evidence demonstrating a shared pathogenesis and genetic overlap.

Indeed, the renal biopsies of IgAV and IgAN are indistinguishable. As the treatment arsenal for IgAN has grown rapidly in recent years with targeted therapies, it is important for the rheumatologist to stay up to date with this evolving field, and for future clinical trials to examine efficacy of these therapies in the IgAV space.

Acknowledgements

None.

Financial support and sponsorship

None.

Conflicts of interest

There are no conflicts of interest.

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Difficult-to-treat, complex-to-manage, treatment-refractory spondyloarthritis: semantics or substance?

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Purpose of review
The concept of difficult-to-treat (D2T) disease is increasingly recognized across immune-mediated inflammatory diseases, and was recently introduced in spondyloarthritis (SpA). Several terms, including difficult-to-manage (D2M), complex-to-manage (C2M), and treatment-refractory (TR) describe disease states characterized by persistent symptoms and inadequate response to targeted therapies. This review aims to clarify the emerging constructs of D2M and TR disease in axial spondyloarthritis (axSpA) and psoriatic arthritis (PsA), and their implications for emerging research in this area.

Recent findings
Recent initiatives from ASAS, EULAR, and GRAPPA have proposed definitions to frame D2T clinical scenarios in axSpA and PsA. These converge on distinguishing treatment-refractory disease, characterized by persistent objective inflammation despite multiple targeted therapies, from broader D2M/C2M states driven by multifactorial contributors including non-inflammatory factors. Emerging data suggest that clinical and biological heterogeneity across disease domains may contribute to these phenotypes. Challenging phenotypic presentations often display overlapping features between axSpA and PsA, supporting the concept of a continuum across the SpA spectrum.

Summary
Distinguishing TR disease from broader D2M/C2M states is essential for avoiding inappropriate treatment escalation, and supporting personalized multidisciplinary care. Further research is needed to validate these definitions, determine contributing factors and their prevalence, and clarify the molecular mechanisms underlying treatment refractory disease.

Keywords
axial spondyloarthritis, difficult-to-manage, difficult-to-treat, psoriatic arthritis, treatment-refractory

INTRODUCTION

The conceptual understanding of difficult-to-treat (D2T) disease is rapidly evolving as a clinical and research need in immune-mediated diseases (IMIDs), including spondyloarthritis (SpA). Several terms are used in the literature, including "difficult-to-manage" (D2M), "complex-to-manage" (C2M), "treatment-resistant" and "treatment-refractory" (TR) [1▪▪,2▪▪,3▪▪] aiming to encompass the nuance of these disease states [4▪]. More than a terminological exercise, the current challenge is to determine the interchangeability of these terms and whether the underpinning constructs identify persistent objective inflammation, persistent symptoms driven by other, non-inflammatory, mechanisms, or overlapping phenotypes across the SpA spectrum, before fully understanding their potential clinical applicability.

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Curr Opin Rheumatol 2026, 38:343–348

DOI:10.1097/BOR.0000000000001173

KEY POINTS

- Difficult-to-manage and treatment-refractory disease represent emerging constructs aimed at better characterizing persistent symptoms and inadequate treatment response across the spondyloarthritis spectrum.
- Recent ASAS, EULAR, and GRAPPA initiatives have proposed definitions of difficult-to-manage and treatment-refractory disease in axial spondyloarthritis and psoriatic arthritis, with some similarities and differences.
- Distinguishing between persistent inflammation and non-inflammatory drivers of symptoms is essential to guide appropriate therapeutic and multidisciplinary management strategies.
- There is an unmet need to explore immunopathogenic mechanisms leading to refractory disease in axial spondyloarthritis (axSpA) and PsA, thereby contributing to a deeper and more unified understanding of the concept of SpA.

WHY WE NEED A DIFFICULT-TO-TREAT CONSTRUCT IN SPONDYLOARTHRITIS

The treatment of IMIDs has been transformed in the last 20 years with the rapid introduction of advanced therapies with multiple mechanisms of action aimed at specific biologic targets. In parallel, the instigation of treat-to-target strategies has contributed to more effective control of inflammation resulting in optimized outcomes for affected individuals with current treatment guidelines advocating for tight inflammatory control as the primary goal for maximizing health-related quality of life. However, at the bedside, challenges remain due to the inability to personalize treatment prescription due to a lack of biomarkers of treatment response, leading to a trial-and-error approach.

In the context of psoriatic arthritis (PsA) and axial spondyloarthritis (axSpA), the representative SpA phenotypes, the multiplicity of tissue involvement and added comorbidities make treatment decisions challenging with the main drivers being clinical phenotype and cost. The expanding therapeutic arsenal for PsA [5] and axSpA [6] presents real opportunities for patients who have suboptimal responses to first-line treatment. Approximately 30% of patients with PsA do not respond adequately to the first biologic disease-modifying antirheumatic drug (bDMARD), and drug survival tends to decrease with every subsequent bDMARD [7,8], highlighting the importance of knowing which drug to switch to and when. If a treatment is stopped and then restarted, there is no guarantee that the same efficacy of response will be achieved; hence, the consequences of an unsuccessful treatment switch are profound. For people living with these diseases, lack of treatment response also referred to as "treatment failure" means loss of disease control, which potentially has a significant impact on their health, physical, personal, and financial well being. Additionally, treatment failure can lead to suboptimal clinical outcomes, drug waste, and increased health service utilization and bears broader socioeconomic costs.

In SpA, the collision of diverse disease expression and symptoms occurs often through the aggregation of multiple tissue involvement and the high prevalence of inflammatory and non-inflammatory comorbidity, exacerbating the disease burden and prognosis. In addition, external drivers including social, environmental, educational or psychological factors may interact, leading to more complex health outcomes and affecting treatment response. Ultimately, as opposed to rheumatoid arthritis (RA), defining one overarching concept for D2T disease in SpA can be challenging. Indeed, D2T disease can be reasonably construed to mean different things to care providers and patients; as highlighted in recent surveys of expert and patients' opinion on the scope of the D2T PsA concept [9–11].

BEYOND SEMANTICS – WHY TERMINOLOGY MATTERS

When exploring D2T disease in SpA, two conceptual aspects are key. First, it is essential to address the multifaceted nature of these conditions, including multidomain/tissue involvement, and high morbidity burden including psychosocial factors. Second, it is paramount to distinguish between non-inflammatory and inflammatory clinical scenarios. Dissecting these concepts allows for full implementation of comprehensive targeted and holistic management approaches.

Indeed, clinical symptoms suggestive of treatment nonresponse can be impacted by co-existing secondary osteoarthritis, cardiometabolic disease, poor mental health, and chronic pain syndromes, among other factors, which often require a holistic and nonpharmacological intervention with input from a multidisciplinary team rather than a change in b/tsDMARD therapy. These scenarios need to be differentiated from those contributing to ongoing inflammation, which can be objectively assessed using serum or imaging markers. The latter, if persistent despite pharmacological intervention with multiple advanced therapies, may be referred to as treatment-refractory and represents a truly difficult-to-treat clinical scenario which may be ongoing for years. On the other hand, patients with other drivers of persistent symptoms, for instance drug intolerability, high infection risk or poor compliance would be classified as having difficult-to-manage disease at a certain moment and time, although a

satisfactory treatment response may eventually be achieved by a successful intervention for example a change of drug, administering device or an alternative dosing schedule as agreed with the patient. Thus, differentiating those D2T scenarios which may require intervention to address ongoing biological inflammation from those where nonbiological factors may be contributing to ongoing symptomatology is key, and represents a significant advance from one single overarching definition, as proposed for RA [12].

In RA, the distinction between persistent inflammatory and non-inflammatory mechanisms in refractory disease was introduced later with the concepts of persistent inflammatory and non-inflammatory mechanisms in refractory rheumatoid arthritis (PIRRA and NIRRA) proposed [13], specifying that these were not mutually exclusive. By contrast, this distinction was incorporated from the outset within the proposed frameworks for axSpA and PsA and incorporated within the concepts of D2M/C2M disease, encompassing multiple drivers of persistent symptoms, and TR disease, which represents a subset of D2M/C2M characterized by objective evidence of ongoing inflammation and the exclusion of alternative non-inflammatory drivers of symptoms.

CLINICAL AND BIOLOGICAL HETEROGENEITY BEHIND D2M AND TR PHENOTYPES

Part of this distinction between D2M and TR phenotypes may also reflect genuine biological heterogeneity across disease domains. Co-existing extra-musculo-skeletal manifestations, such as psoriasis, uveitis, or inflammatory bowel disease, may complicate treatment options and contribute to D2M or TR disease, such as the contraindication of interleukin (IL)-17 inhibitors in patients with active inflammatory bowel disease (IBD). The immunological and dynamic heterogeneity observed across different clinical domains in SpA provides insights into the development of D2M or TR phenotypes. For example, in PsA, IL-23 and IL-17 inhibitors show high efficacy in cutaneous disease but have more modest effects on synovitis or enthesitis. In axSpA, IL-17 inhibitors are effective for spinal disease, whereas IL-23 inhibitors have not shown efficacy in this domain [14]. However, the entheseal bone with predominantly osteitis driving axSpA and the inflamed soft tissues primarily involved in PsA have distinct immune cell and stromal compositions, which may explain the differential response to immunomodulatory therapy, especially IL-23 inhibition [15]. In general, the assessment of treatment nonresponse in PsA is both clinically challenging and dynamic, with patients moving in and out of a state of nonresponse in different disease domains at different time points.

CURRENT DEFINITIONS OF D2M AND TR AXSp-A AND PsA

Expert consensus definitions have been recently proposed almost contemporarily aiming to frame these constructs in axSpA by the Assessment for Spondyloarthritis International Society (ASAS) [1▪▪] and PsA by the European Alliance of Associations for Rheumatology (EULAR) [2▪▪] and the Group for Research and Assessments of Psoriasis and Psoriatic Arthritis (GRAPPA) [3▪▪]. Although methodologies varied between each project (Table 1), these expert groups aligned on the need to differentiate two stand-alone constructs encompassed under the overarching difficult-to-treat umbrella: difficult-to-manage covering the wider range of biological and nonbiological factors contributing to treatment nonresponse and treatment-refractory disease, characterized by objective evidence of biological inflammation. This is a key differentiator from the initial D2T proposals in RA [12] and other diseases.

However, differences exist in the conceptual approach behind each construct's framework. The ASAS axSpA and EULAR PsA definitions are aligned in the utilization of stricter entry thresholds aimed to capture the complexity of phenotypic and systemic manifestations of disease, whereas the GRAPPA PsA proposal utilizes a broader entry criterion reflected in new nomenclature ("complex-to-manage"). Encouragingly, many similarities are found between the different definitions, with wide appreciation of subsets of PsA that could be further defined based on objective markers of inflammation and ongoing disease activity. Clearly, the lack of background data makes this type of work more challenging as reflected on the different weighting of patients and physician perspectives used in the definitions, and on the number of b/tsDMARD failures required to characterize a D2M/C2M or "treatment refractory" state. Patient representatives and clinical experts contributing to the EULAR task force for example, were in agreement that considering failure to respond to one single drug or mechanism of action did not constitute a difficult to manage scenario, just "real life" since a high proportion of patients, particularly female, do not achieve low disease activity states or full remission of symptoms and signs over the course of their disease. In addition, the reasons behind treatment "failure" need to be fully explored at the individual level, as these will be different in everyone, with lack of compliance (of multiple origin) being a main contributor. Importantly, these definitions reflect a dynamic state that may fluctuate over time, with further work needed to establish whether a temporal framework may be feasibly incorporated.

Table 1. Comparison between the ASAS difficult-to-manage axial spondyloarthritis (D2M-axSpA), EULAR difficult-to-manage psoriatic arthritis (D2M-PsA), and GRAPPA complicate to-manage psoriatic arthritis (C2M-PsA) and treatment-refractory (TR) definitions

	D2M and TR-axSpA (ASAS)	D2M and TR-PsA (EULAR)	C2M and TR-PsA (GRAPPA)	
Literature review strategy	Scoping review s Set by the steering committee then later presented to the wider TF	3-research question SLR Set by the steering committee based on scope/aims agreed at the 1st TF meeting	Scoping review Set by the steering committee then later presented to the wider TF	
Supporting surveys	None	One international survey (healthcare professionals) Conducted prior to SLR	Two international surveys (healthcare professionals and patients) Conducted prior to SLR	
Formulation and refining of the definition	Formulation by the TF Input from patient representatives	Formulation by steering committee only Input from patient representatives	Formulation by the TF Input from patient representatives and pharmaceutical industry	
Validation of the definition	Consensus-based definition (2 Delphi rounds)	Consensus-based definition (EULAR SOPs)	Consensus-based definition (2 Delphi rounds)	
D2M or C2M definition	Therapeutic failures	Inadequate response to ≥2 b/tsDMARDs with ≥2 MoA	Inadequate response to ≥2 b/tsDMARDs with ≥2 MoA	Inadequate response to ≥1 b/tsDMARDs
	Signs of active disease	At least 1 of: - High or very high disease activity - Signs or symptoms suggestive of active disease - Rapid radiographic spinal progression - Reduction in quality of life	At least 1 of: - Failure to achieve or maintain LDA - Objective evidence of inflammation - Active EMMs - Other drivers: comorbidities, psychosocial, etc.	Persistent PsA-related symptoms
	Subjective perception	Symptoms considered as problematic by patient and/or rheumatologist	Management perceived as problematic by patient and/or rheumatologist	Symptoms considered as problematic by patient and/or rheumatologist
TR definition	D2M-axSpA and: - Objective evidence of inflammation (CRP+ or MRI +) - Other drivers excluded - High disease activity (ASDAS ≥2.1)	D2M-PsA and: - Objective evidence of inflammation - Other drivers excluded - Failure to achieve or maintain LDA OR active EMMs	C2M-PsA and: -Objective evidence of inflammation - Other drivers excluded - Inadequate response to ≥3 PsA therapies including ≥2 b/tsDMARDs with ≥2 MoA - Symptoms considered as problematic by patient AND rheumatologist	
Temporal element	No	No	No	
Drug intolerance/contraindication/side effects considered	Yes	Yes	Yes	

EMMs, extra-musculo-skeletal manifestations, LDA, low disease activity, MoA, mode of action, SLR, systematic literature review, SOPs, standard operating procedures, TF, task force.

Prospective studies are now needed to fully evaluate the performance of these definitions in the research field to standardize populations. This is key to avoid misuse of the definitions in routine clinical setting, and before their clinical utility is confirmed, including possible applicability in healthcare systems that treat different ethnicities and have differing access to resources such as MRI or genetic testing.

THE CONSTRUCT OF D2M AND TR DISEASE AS ARGUMENT FOR A UNIFYING SpA DISEASE SPECTRUM

Overall, the heterogeneity of these challenging clinical scenarios becomes even more apparent when difficult-to-manage and treatment-refractory phenotypes are examined across the broader SpA spectrum. A key finding of the recent literature was the report, in D2M axSpA cohorts, of peripheral joint involvement and psoriasis [16,17▪,18], which could classify these patients as having PsA. Furthermore, in the context of PsA, axial involvement, which may classify some patients as having axSpA, was noted in some PsA studies reporting difficult-to-manage clinic scenarios [19▪]. Indeed, earlier studies reporting on D2T SpA populations described this mixed phenotype with highly inflammatory, progressive and erosive peripheral and axial manifestations requiring novel therapeutic interventions such as IL-6 inhibition or biologic combination therapy [20,21]. This

phenotypic convergence in complex scenarios of D2M axSpA and PsA warrants careful consideration, as it challenges the conventional nosological distinction between the two clinical entities while reinforcing the concept of a phenotypic continuum within the SpA disease spectrum [22] (Fig. 1). A more systematic investigation of these overlaps could reveal whether the current classification systems inadvertently obscure shared pathogenic pathways or clinical domains that are more relevant to therapeutic decisions. Ultimately, embracing the complexity of SpA phenotypes, particularly in clinical scenarios considered to have TR disease, will lead to more individualized and effective management strategies.

The studies published to date remain few and are widely heterogeneous in terms of the patients included and the methods used to apply definitions. Nevertheless, the high frequency of certain characteristics associated with D2M, including TR status, shows a certain consistency, notably female sex and high baseline disease activity. Clearly, our current understanding represents an evolving framework. Going forward, studies are needed to validate the robustness of the recently proposed definitions of D2M/C2M and TR axSpA [1▪▪] and PsA [2▪▪,3▪▪], establish their true prevalence, and to explore the factors more likely to be associated with these disease states.

CONCLUSION

In conclusion, there is increasing awareness of the need to dissect the factors contributing to D2M and TR disease in SpA, with new definitions expected to help direct research in this area. The clinical scenarios of TR disease in axSpA and PsA cohorts represent a challenge at the clinical level, requiring a paradigm shift in their therapeutic approach. In this light, the emerging literature underscores the need to explore immunopathogenic mechanisms leading to treatment refractory disease, thereby contributing to a deeper understanding of the concept of SpA.

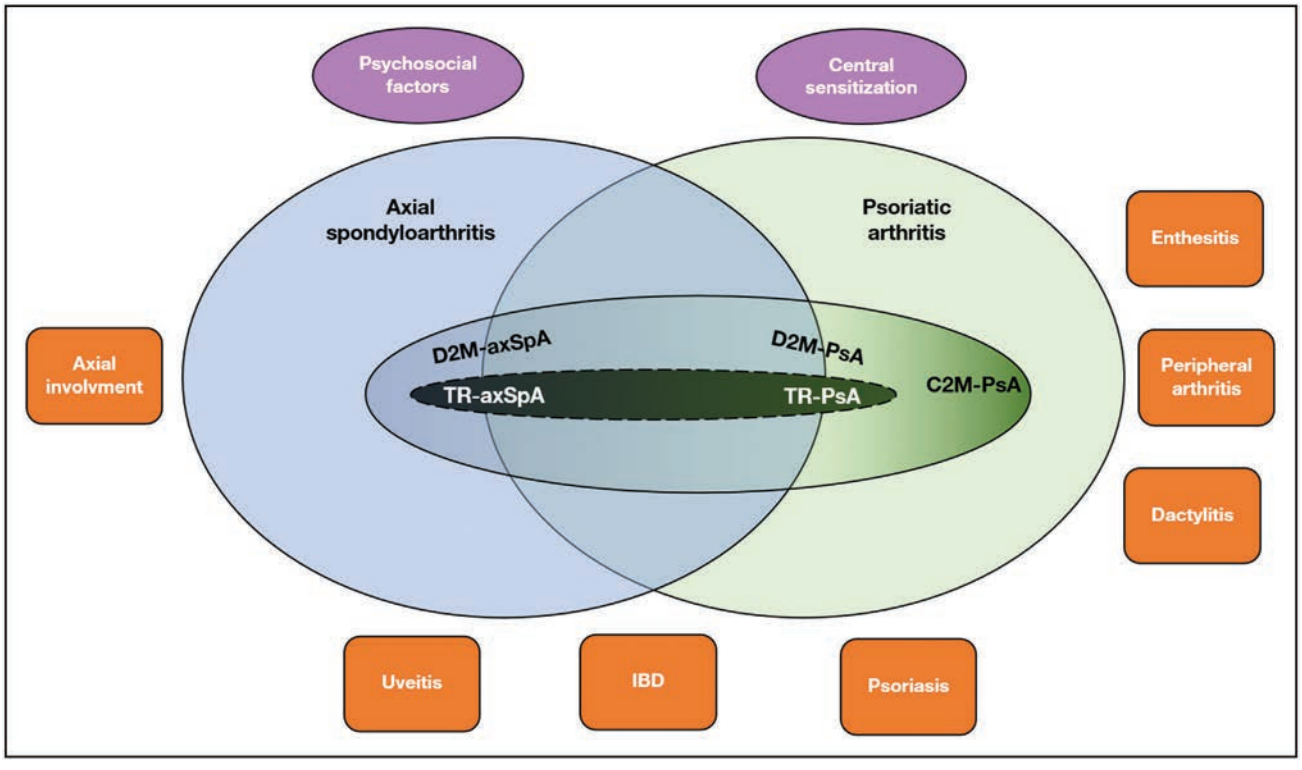

FIGURE 1. Management constructs (D2M/C2M and TR) across the SpA spectrum, and their relationship with transversal clinical domains and contextual drivers. The two overlapping circles represent predominantly axial spondyloarthritis (axSpA) and psoriatic arthritis (PsA) disease phenotypes. The central shaded area depicts difficult-to-manage (D2M) disease as an umbrella concept, within which difficult-to-manage axial SpA (D2M-axSpA) and difficult-to-manage/complex-to-manage PsA (D2M/C2M-PsA) are positioned – C2M-PsA being wider than D2M-PsA, and treatment-refractory subsets (TR-axSpA and TR-PsA) are shown as narrower constructs within D2M/C2M, representative of a smaller group. External boxes illustrate transversal elements that may occur anywhere across the SpA spectrum: orange boxes represent key clinical inflammatory manifestations, while purple ellipses represent contextual/non-inflammatory drivers that may contribute to symptom burden and perceived nonresponse. IBD, Inflammatory bowel disease.

Acknowledgements

H.M.O. is supported by the NIHR Leeds Biomedical Research Centre (LBRC), The Leeds Teaching Hospitals National Health Service (NHS) Trust and is in receipt of an NIHR Senior Clinical and Practitioner Research Award (NIHR304573). The views expressed are those of the authors and not necessarily those of the (UK) NHS, the NIHR, or the (UK) Department of Health.

Author contributions: O.F., S.R.H. and H.M.O. conceptualized the manuscript. O.F. and S.R.H. wrote the first draft of the manuscript with support from H.M.O. All authors contributed to manuscript writing and read and approved the final version of the manuscript.

Financial support and sponsorship

S.R.H. received speaker fees for a nonpromotional educational talk from Janssen, UCB and Novartis. She has received support to attend conferences from UCB and Janssen.

H.M.O. has received institutional research support from Janssen, Novartis, Pfizer and UCB and consultancy honoraria and/or speaker fees from AbbVie, Advanz Pharma, Amgen, Biogen, Eli-Lilly, Janssen, Moonlake, Novartis, Pfizer, Takeda, UCB and Zuellig-Pharma.

Funding: No funding was awarded for this work.

Conflicts of interest

O.F. has received consultancy honoraria and speaker fees from U.C.B.

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- ■ of special interest
- ■■ of outstanding interest

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New approaches to the management of cutaneous lupus

Kathie Velez[a], *Grace A. Osborne*[a,b] *and Allison C. Billi*[a]

Purpose of review
Cutaneous lupus erythematosus (CLE) is a heterogeneous inflammatory skin disease that can be disfiguring and profoundly affect patient quality of life. CLE is frequently challenging to manage and may remain refractory even when systemic disease is well controlled. Currently, no therapies are FDA-approved specifically for isolated CLE. This review summarizes established treatment approaches and highlights emerging targeted therapies informed by recent advances in disease pathogenesis.

Recent findings
Recent studies expand the role of biologics and highlight the promise of additional interferon (IFN)-targeted therapies for the treatment of refractory CLE. Therapies targeting B cells, plasmacytoid dendritic cells, the type I IFN receptor, and downstream pathways – including JAK, TYK2, TLR7/8, and IRAK4 inhibitors – continue to broaden therapeutic options. Importantly, the incorporation of skin-specific outcome measures into systemic lupus erythematosus (SLE) clinical trials has supported the evaluation of cutaneous responses within broader SLE programs, which in turn has expanded the use of newer SLE therapies for CLE. This evolution in trial design may also facilitate future FDA approval pathways for treatments aimed at isolated CLE, an area currently lacking approved therapies.

Summary
A deepening understanding of CLE pathogenesis has yielded multiple promising new treatments for CLE, with targeting of type I IFN and downstream signaling proving especially fruitful.

Keywords
cutaneous lupus, interferon, Janus kinase signaling

INTRODUCTION

Lupus erythematosus (LE) is an autoimmune disease that encompasses a spectrum of clinical phenotypes ranging from skin-limited cutaneous lupus erythematosus (CLE) to systemic lupus erythematosus (SLE), which may involve virtually any organ system. Cutaneous involvement is common in SLE, occurring in up to 69% of patients [1]. CLE is classified according to the pattern of inflammation and acuity – acute (ACLE), subacute (SCLE), or chronic (CCLE) – each with characteristic clinical and laboratory features. A clinically meaningful subset of patients with skin-limited disease will ultimately develop systemic involvement, with risk varying by clinical subtype. Risk of progression varies considerably across studies, ranging from 0% to 42%, depending on study design, patient risk factors, and criteria for SLE diagnosis [2].

CLE has a profound impact on quality of life, even among patients with mild disease activity, as it can result in alopecia, scarring, dyspigmentation, and disfigurement [3▪▪]. Even if skin-limited or skin-predominant, CLE carries an increased risk of comorbid conditions related to systemic inflammation such as atherosclerotic cardiovascular disease [4▪▪].

There is a critical need for targeted therapeutics to improve outcomes for patients with CLE and reduce progression to SLE. This review summarizes current treatment approaches and recent advances in therapies informed by evolving insights into CLE pathogenesis, including interferon-directed agents and JAK/TYK2 signaling inhibitors (Fig. 1).

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Curr Opin Rheumatol 2026, 38:349–357

DOI:10.1097/BOR.0000000000001175

KEY POINTS

- Cutaneous lupus erythematosus (CLE) imposes a quality-of-life burden that rivals or exceeds that of major chronic medical conditions, underscoring the need for more effective therapies.
- Despite conventional topical and systemic treatments, many patients with CLE continue to experience refractory or relapsing disease.
- Advances in lupus immunopathogenesis have driven the development of targeted therapies – particularly those modulating type I interferon signaling – that show meaningful benefit in CLE.
- Incorporation of validated skin-specific outcome measures into systemic lupus erythematosus trials has expanded therapeutic options for CLE and clarified treatment effects on skin disease.
- Continued progress in CLE management will depend on intentional trial designs that prioritize cutaneous endpoints and include patients with skin-predominant or -isolated disease.

CONVENTIONAL MANAGEMENT

Treatment for CLE requires a multifaceted approach that involves avoidance of triggers as well as topical and systemic therapies based on disease severity, CLE subtype, and patient comorbidities. To date, there are no treatments approved by the FDA specifically for treatment of CLE.

Preventive measures

Photosensitivity is a hallmark of LE, reported in up to 64.8% of patients and associated with active skin disease. Patient counseling should emphasize strict photoprotection including daily use of broad-spectrum sunscreen, preferably mineral-based tinted formulas (which avoid concerns about systemic absorption and block visible light), as well as sun-protective clothing.

Current smokers with CLE have more severe disease and worse quality of life than nonsmokers [5]. A recent study found that concurrent cigarette smoking was associated with 3.15-fold odds of moderate-to-severe CLE-related skin damage in patients with DLE, as measured by Cutaneous Lupus Erythematosus

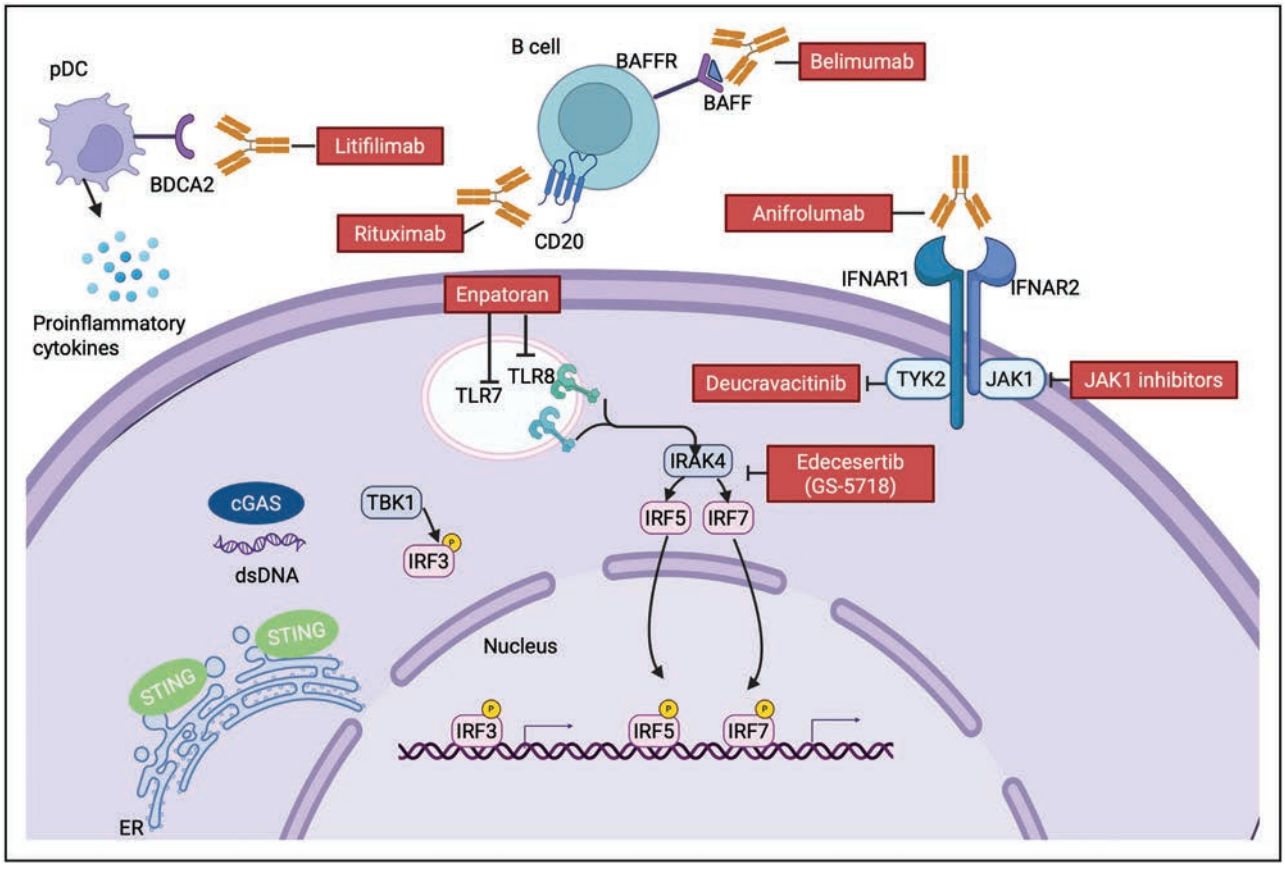

FIGURE 1. Therapeutic targets in cutaneous lupus erythematosus (CLE). Schematic depicting key innate and adaptive immune pathways implicated in CLE and select targeted agents acting on these factors.

Disease Area and Severity Index (CLASI) damage score [6▪]. This cross-sectional study of 154 adult patients with DLE demonstrated that smoking was independently associated with increased disease severity when controlling for other confounders including area deprivation index and race [6▪]. Cigarette smoking also decreases the efficacy of antimalarials [7], underscoring the importance of smoking cessation counseling [8].

Topical treatments

Mid- to high-potency topical corticosteroids (TCS) remain first-line for limited skin involvement, with generally good efficacy; side effects with prolonged use include skin atrophy and telangiectasias. Intralesional triamcinolone injections may be effective for localized DLE.

Topical calcineurin inhibitors (TCIs) – namely, tacrolimus and pimecrolimus – are effective steroid-sparing agents for DLE and SCLE [9▪] and serve as helpful adjuncts in areas such as the face and skin folds that are at risk of TCS-induced atrophy.

Nicotinamide is a nonsteroidal topical agent with anti-inflammatory, immunomodulatory, and potential photoimmunoprotective properties. A recent network meta-analysis reported that nicotinamide 4% demonstrated the highest efficacy among topical treatments for CLE based on CLASI score, followed by clobetasol 0.05% (a class I TCS) and tacrolimus [10]. In the United States, nicotinamide is widely incorporated into over-the-counter skincare formulations and is commonly used to support epidermal barrier function and reduce cutaneous inflammation; however, its routine use as a targeted therapy for CLE remains limited. Given its favorable safety profile and broad availability, nicotinamide could be readily integrated into existing treatment paradigms, although prospective studies and real-world experience will be needed to determine whether the efficacy suggested by recent analyses translates into consistent clinical benefit for patients with CLE.

Recent case reports suggest that topical Janus kinase (JAK) inhibitors show promise in treatment of CLE [11,12], although randomized control trials demonstrating efficacy are lacking.

Systemic treatments

Antimalarials and systemic glucocorticoids are recommended as first-line systemic therapy for active skin disease. In cases of persistent disease activity or to minimize systemic steroid use, additional immunosuppressive and immunomodulatory agents may be added.

Antimalarials

Hydroxychloroquine (HCQ) remains the antimalarial of choice given its favorable efficacy and safety profile [13]. A recent longitudinal observational cohort study of 286 patients found that early initiation of HCQ was associated with an 87% reduction in the risk of progression to SLE [hazard ratio: 0.13, 95% confidence interval (CI): 0.06–0.27, $P < 0.001$] [14]. Progression occurred in only 4.8% of patients treated with HCQ compared to 27% of those treated with topical therapies. Notably, among the 186 patients treated with HCQ, no cases of retinopathy or other serious adverse events were reported [14]. This aligns with the broader safety data showing retinopathy occurs in less than 2% of patients taking HCQ for 10 years or fewer when dosed appropriately ($\leq$5.0 mg/kg actual body weight) [15]. However, risk of retinopathy from HCQ is increased in patients with exposure to tamoxifen, renal insufficiency, and, to a lesser degree, liver disease; use of HCQ in these patients requires careful consideration of potential risks and benefits, with involvement of eye care specialists in shared decision-making. In patients with partial response to HCQ, quinacrine may be added. Quinacrine monotherapy has not been associated with retinal toxicity [16].

Conventional disease modifying antirheumatic drugs

For CLE patients who do not respond to first-line treatment, methotrexate, mycophenolate mofetil, and other immunosuppressive agents such as cyclosporine, azathioprine, and tacrolimus may be considered as second-line options, but studies comparing efficacy in CLE are limited. Prior studies suggest response rates for second-line treatments including methotrexate and mycophenolate are similar [17]. Case reports support the use of dapsone for bullous LE [18,19]. Thalidomide and lenalidomide demonstrate high efficacy (response ~90%) [20,21] but are teratogenic and carry significant risks of toxicity, including peripheral neuropathy and thromboembolic events [20,21], restricting use to select refractory cases.

THERAPIES TARGETING PATHOGENIC IMMUNE CELLS

B cell reduction

Rituximab, a chimeric monoclonal antibody (mAb) against the protein CD20, did not meet primary endpoints in phase III SLE studies (EXPLORER, LUNAR) [22]. However, seven cohort studies reported partial or complete response rates ranging

from 33% to 71% for mucocutaneous disease [23], suggesting benefit in patients with CLE.

Belimumab is a fully humanized monoclonal antibody (mAb) against B-cell activation factor (BAFF, also known as BLyS), and was the first biologic drug approved for SLE. Post hoc analyses of large phase III Trials (BLISS-52, BLISS-76, BLISS-NEA, EMBRACE, BLISS-SC) demonstrated significant improvement in CLE in belimumab compared to placebo, especially in patients with high disease activity and serologically active disease [24▪▪,25,26]. A systematic review and meta-analysis synthesizing data from 14 clinical trials and observational studies reported 44% higher odds of CLE clinical response at 52 weeks compared to nonusers (placebo plus standard therapy), with the first significant response noted at 20 weeks [27]. Dedicated clinical trials for isolated CLE are still needed.

Plasmacytoid dendritic cell inhibition

Although plasmacytoid dendritic cells (pDCs) have classically been implicated as a key source of type I IFN in CLE, recent immunophenotyping data indicate that in many discoid and subacute CLE lesions, pDCs do not themselves produce detectable type I IFN, suggesting that their pathologic roles may involve IFN-independent mechanisms [28]. Litifilimab is a mAb that binds blood DC antigen 2 (BDCA2), an inhibitory receptor on pDCs, and induces internalization to inhibit production of type I IFNs. In the phase II LILAC trial, litifilimab significantly improved skin disease activity [CLASI activity (CLASI-A)] scores in CLE compared to placebo [29]. A recent meta-analysis demonstrated that litifilimab was more effective than placebo in achieving a 50% reduction in CLASI-A (CLASI-50) [30▪▪]. Recent pharmacodynamic data from the LILAC trial cohort reveals rapid and sustained reductions in type I IFN gene signature (IFNGS) scores and IFNγ concentrations [31]. In high IFNGS patients, litifilimab 150 and 450 mg produced significant reductions in CLASI-A scores vs. placebo in a dose-dependent manner [31]. Two phase III trials – TOPAZ-1 (NCT04895241) and TOPAZ-2 (NCT04961567) – are ongoing [32].

Cereblon modulation

Iberdomide is a cereblon modulator that enhances degradation of the transcription factors Ikaros (IKZF1) and Aiolos (IKZF3) in leukocytes, reducing B and T cell activation. A randomized phase II trial showed rapid, sustained improvement in CLASI-A scores for SCLE and CCLE when added to background therapy [33▪▪].

THERAPIES TARGETING TYPE I INTERFERONS

With mounting evidence indicating a critical role for type I interferon (IFN) signaling in the pathogenesis of CLE, several monoclonal antibodies (mAb) and small molecule inhibitors are emerging that target type I IFNs and downstream signaling. Therapies targeting cellular sources, the type I IFN receptor (IFNAR), and downstream pathways, including JAK inhibitors, will be discussed below.

Reducing type I interferon production

TLR7/8 signaling in CLE drives immune cell activation in response to nucleic acid sensing, amplifying local inflammation and tissue injury. Enpatoran is a novel, highly selective, orally administered, dual TLR7/8 inhibitor currently in phase II trials. A recent randomized, placebo-controlled phase Ib study of patients with SLE and CLE demonstrated safety as well as improvement in biomarkers of disease activity [34▪▪].

IRAK4 activity is essential for the downstream activation of TLR-induced type I IFN production and perpetuating the inflammatory cycle in CLE lesions. Edecesertib (GS-5718), a selective IRAK4 inhibitor, has shown promise in preclinical lupus models [35]. A phase IIa proof-of-concept trial in CLE completed recruitment in January of 2026 (NCT05629208), with results not yet posted.

IFNAR blockade

All type I IFNs signal through the heterodimeric type I IFN receptor (IFNAR), activating downstream JAK–STAT pathways. Anifrolumab, a monoclonal antibody targeting IFNAR1, blocks signaling from all type I IFN family members. In the pivotal phase III TULIP–I trial, anifrolumab demonstrated significant improvement in CLE compared to placebo across multiple skin-specific endpoints [36]. In pooled post hoc analysis of patients with moderate-to-severe skin disease (defined as baseline CLASI-A score of $\geq$10) from both TULIP trials, 46% of anifrolumab-treated patients achieved a >50% reduction in CLASI-A score at week 52, compared with 25% of placebo-treated patients (P=0.0015) [37]. This treatment effect was evident as early as week 12 and maintained throughout the study period [36]. Recent case series support the TULIP trial results and show a rapid and sustained improvement in refractory CLE, with 89–100% of patients responding despite having failed a mean of 6.3 prior therapies [38]. In one series of 18 patients with SLE and multirefractory skin disease, mean CLASI-A scores decreased from 13.9 to 2.1 after a

mean of 8.5 months, with 89% achieving CLASI-50 response and mean prednisone dose decreasing from 4.9 mg to 2.4 mg daily. Another series of 10 patients reported rapid responses within the first 2 months of treatment that were sustained throughout follow-up [39▪]. A phase II clinical trial of subcutaneous anifrolumab showed dose-dependent suppression of a type I IFN gene signature and improvement in skin disease activity, with safety and tolerability similar to the intravenous formulation [40].

Downstream interferon signaling

Janus kinase inhibition

The JAK/STAT signaling pathway transmits proinflammatory, immunomodulatory, and proliferative signals from many cytokines and growth factors. By inhibiting this pathway, JAK inhibitors block many cytokines, including type I IFN, implicated in lupus pathogenesis.

Baricitinib is a selective inhibitor of JAK1/2 that showed promise in phase II trials [41▪] but did not meet skin endpoints in phase III trials [42]. Baricitinib may, however, confer benefit in specific lupus subtypes: in a very small pilot randomized, double-blind trial of baricitinib for lupus panniculitis-a rare and frequently recalcitrant form of CCLE involving the subcutaneous fat – two of three patients met the primary endpoint of 20% reduction in CLASI-A score at week 20, whereas the two placebo recipients improved only following crossover to baricitinib at week 13 [41▪].

Tofacitinib, an inhibitor of JAK1/3, has shown efficacy in case reports of refractory CLE [43]. A recent safety trial of tofacitinib in SLE showed improvement in cardiometabolic and immunologic parameters associated with premature atherosclerosis, which will need to be followed in long-term studies [44]. Filgotinib, a highly selective JAK1 inhibitor, failed to meet endpoints in a phase II CLE trial [45,46], underscoring that not all JAK-pathway targets are equally effective in CLE.

TYK2 inhibition

Tyrosine Kinase 2 (TYK2) is a key signaling mediator downstream of type I IFNs, interleukin (IL)-12, and IL-23-cytokine pathways that contribute to the inflammatory milieu characteristic of CLE. Deucravacitinib is an oral, selective, allosteric inhibitor of TYK2 that binds the enzyme's regulatory (pseudokinase) domain and locks it in an inactive conformation, distinguishing it from conventional JAK inhibitors that target the highly conserved active (kinase) domains. This unique selectivity limits off-target inhibition of JAK1/2-mediated pathways involved in thrombopoiesis, erythropoiesis, and other hematopoietic functions, providing a more favorable safety profile compared with pan-JAK inhibitors. In a phase II SLE trial, deucravacitinib improved skin outcomes and produced acceptable safety signals [47]. A recent systematic review and meta-analysis reported that deucravacitinib was superior in both efficacy and safety in CLE compared to emerging biologics; deucravacitinib achieved a markedly higher likelihood of CLASI-50 response [odds ratio (OR) 8.28 vs. placebo], significantly outperforming litifilimab (OR 2.54) and anifrolumab (OR 2.25) [30▪▪]; however, additional head-to-head trials at major lupus centers are needed to corroborate these findings. Importantly, there were no significant differences in adverse events between deucravacitinib and placebo [30▪▪]. Deucravacitinib may be a safe and efficacious option for patients with refractory CLE or patients with significant comorbid conditions.

APPLICATION OF EMERGING SLE THERAPIES IN CUTANEOUS LUPUS ERYTHEMATOSUS

Chimeric antigen receptor T cell therapy

Additional therapies under investigation for SLE are also demonstrating benefit in CLE. Perhaps most notable among these is anti-CD19 chimeric antigen receptor (CAR) T cell therapy. The most substantial early evidence supporting CAR T cell therapy comes from a compassionate use-program at the University Hospital Erlangen, where five patients with refractory SLE received autologous anti-CD19 CAR T cells [48]. All five patients achieved drug-free remission and resolution of clinical symptoms including cutaneous manifestations, following CD19 CAR T cell therapy [48]. This work was corroborated by a larger case series of 15 patients with severe autoimmune diseases, including 8 patients with SLE. All SLE patients achieved drug-free remission by 6 months [49]. There are several ongoing trials in SLE. CAR T therapy in autoimmune disease is reported to be well tolerated, with only mild cytokine release syndrome (predominantly grade 1) and no cases of graft-vs.-host disease in the allogeneic setting or treatment-related deaths reported [48,49]. CAR T studies in autoimmune disease research remain largely phase I, with only 7.14% progressing to phase II [50]. Larger randomized trials are needed to define their role in SLE management. While CAR T therapy is far too invasive for isolated CLE, future lower-risk adaptations may eventually make its application in skin-predominant disease feasible. Other novel CAR-based strategies are also being explored for lupus

Table 1. Emerging therapeutics for cutaneous lupus erythematosus (CLE)

Therapy	Mechanism	Trial(s)	Skin measure (primary/secondary/exploratory endpoint)	Outcome and comments	Ref
Rituximab	Anti-CD20 mAb	EXPLORER (phase II/III) and LUNAR (phase III); mucocutaneous endpoints analyzed post hoc Cohort study	None (no dedicated skin endpoint); BILAG mucocutaneous domain (secondary)	Failed to meet primary SLE endpoints; posthoc mucocutaneous analyses suggest partial improvement 75% of patients treated with rituximab had improvement at 6 months, 61% at 12 months	[22,23]
Belimumab	Anti-BAFF mAb	BLISS-52, BLISS-76, BLISS-NEA, EMBRACE, and BLISS-SC (phase III program)	BILAG; SLEDAI-2K (secondary)	Improved mucocutaneous disease; best responses in serologically active disease	[24▪▪,27]
Litifilimab	Anti-BDCA2 mAb	LILAC Part A (phase II; SLE) and Part B (phase II; CLE)	CLASI-A (primary)	Significant CLASI-A reduction, decreased IFN-related biomarkers, reduced immune infiltrates in skin lesions	[29,31]
Anifrolumab	Anti IFNAR1 mAb	MUSE (phase IIb); TULIP-1 and TULIP-2 (phase III)	CLASI-A (secondary)	Consistent improvement in CLASI-A; strongest effect in patients with baseline CLASI-A $\geq$10	[36–38]
Baricitinib	JAK1/2 inhibitor	SLE-BRAVE-I and SLE-BRAVE-II (phase III SLE trials; skin endpoints not met)	BILAG (secondary)	Skin benefit only in SLE-BRAVE-I; overall trial did not meet primary endpoints	[42,54]
Tofacitinib	JAK1/3 inhibitor	Phase II open-label trial in SLE (in patients with active mucocutaneous manifestations)	CLASI-A (secondary); Skindex-29 (secondary/exploratory)	Improved CLASI-A and Skindex-29 scores in the open-label SLE trial, indicating potential benefit for CLE; randomized trials are needed	[55]
Filgotinib	Selective JAK1 inhibitor	Phase II randomized, double-blind, placebo-controlled study in CLE	CLASI-A (primary); CLASI-50 (secondary)	Failed to meet primary CLASI-A endpoint; CLASI-50 responses not significantly different from placebo	[46]
Deucravacitinib	TYK2 inhibitor	Phase II randomized, double-blind, placebo-controlled trial in SLE	CLASI-A; CLASI-50 (secondary)	Higher CLASI-50 response rates vs. placebo, particularly in patients with baseline CLASI-A $\geq$10; consistent skin improvement across secondary endpoints	[30▪▪,47]
Enpatoran	TLR7/8 inhibitor	WILLOW (phase II randomized, double-blind, placebo-controlled basket trial in SLE and CLE; ongoing)	CLASI-A; CLASI-50 (secondary)	Phase II WILLOW trial press release and abstracts report higher CLASI-A and CLASI-50 responses vs. placebo in patients with active rash†; full trial results pending	
Iberdomide	Cereblon modulator	Phase II randomized, double-blind, placebo-controlled trial in SLE with cutaneous endpoints	CLASI-A (secondary)	Rapid and sustained CLASI-A improvement when added to background therapy	[33▪▪]
CAR T-cell therapy	Anti-CD19 CAR T cell therapy	Case series	None	All 5 patients achieved drug-free remission and resolution of symptoms including cutaneous manifestations	[48]

Table 1 (*Continued*)

Therapy	Mechanism	Trial(s)	Skin measure (primary/secondary/exploratory endpoint)	Outcome and comments	Ref
Telitacicept	TACI-Fc fusion protein	Phase III randomized controlled trial in SLE	None	No skin endpoints reported in phase III trial; case report suggests improvement in refractory CLE	[53]

Table shows select therapeutic agents discussed in the text.
†Enpatoran phase II results referenced from EMD Serono company press release (May 21, 2025): https://www.emdserono.com/us-en/company/news/press-releases/enpatoran-phase-2-data-21–05–2025.html.
Abbreviations: BILAG, British Isles Lupus Assessment Group; CAR, chimeric antigen receptor; CI, confidence interval; CLASI, cutaneous lupus activity and severity index; CLASI-A, CLASI activity; CLASI-50, ≥50% reduction in CLASI-A; IFNAR1, type I IFN receptor 1; JAK, Janus kinase; mAb, monoclonal antibody; SLE, systemic lupus erythematosus; SLEDAI, SLE disease activity index; TLR, Toll-like receptor; TYK2, tyrosine kinase 2.

and other autoimmune diseases, including anti-B cell maturation antigen (BCMA) CAR T cells.

Other emerging systemic lupus erythematosus therapies

Other emerging therapies under investigation for SLE may also hold promise for CLE. Dapirolizumab pegol, a PEGylated anti-CD40L Fab' fragment, demonstrated improvements in CLASI scores as a secondary endpoint in a phase IIb SLE study, although detailed response rates quantifying the magnitude and statistical significance of skin improvement were not reported [51]. Ongoing phase III trials may further clarify its potential cutaneous benefits. Telitacicept, a TACI-Fc fusion protein that neutralizes both BAFF and APRIL to suppress development and survival of mature B cells and plasma cells, is also in phase III global development for SLE and is currently approved in China [52] (NCT05306574). Although the pivotal Chinese phase III trial did not report skin-specific outcomes, a single case report describes clinical improvement in recalcitrant CLE [53].

CONCLUSION

Cutaneous lupus erythematosus imposes a substantial disease burden that extends beyond visible skin findings, affecting both quality of life and long-term health. Zhang *et al*. showed that the psychological impact of CLE rivals or exceeds that of chronic hypertension, congestive heart failure, or type 2 diabetes [3▪▪]. These findings highlight that CLE meaningfully impairs daily functioning and emotional well being, exposing the need to account for these aspects of morbidity in clinical trial design [6▪]. Beyond psychosocial morbidity, CLE – even when skin-limited – confers increased risk of diseases related to chronic inflammation [4▪▪].

Significant unmet therapeutic needs persist for patients with CLE. Increasing recognition of the central role of type I IFNs has accelerated the development of targeted therapies that show meaningful benefit in clinical trials and early case series (Table 1). Future progress will depend on intentional enrollment of patients with skin-predominant or isolated cutaneous lupus in clinical trials, incorporation of robust skin disease outcome measures, and continued integration of mechanistic insights into therapeutic development.

In the meantime, in addition to strict photoprotection, HCQ remains foundational therapy for all patients with CLE unless contraindicated, and the authors' enthusiasm for this treatment is further bolstered by the recent evidence suggesting benefit in prevention of progression to SLE [14]. Along with this, smoking cessation counseling is offered to patients who smoke cigarettes. We further recommend topical management for all patients; in practice, selection of topical agents in the United States is often dictated by insurance coverage, with typical progression being corticosteroids followed by calcineurin inhibitors and finally JAK inhibitors. For persistent disease despite this management, addition of quinacrine may be valuable; unfortunately, this is no longer readily available in the United States. In patients with extensive CLE refractory to this regimen, authors often attempt addition of anifrolumab or deucravacitinib. In patients for whom these are not options, other common considerations include methotrexate, mycophenolate mofetil, or belimumab. Third-line agents such as retinoids, dapsone, and thalidomide or lenalidomide may be considered in specific CLE subtypes or as adjuncts in particularly challenging cases.

Acknowledgements

None.

Financial support and sponsorship

None.

Conflicts of interest

There are no conflicts of interest.

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