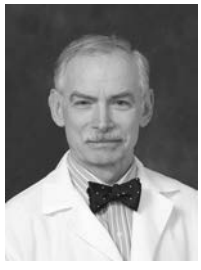
Editorial introduction

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 Editor for this issue.

SECTION EDITOR

W Joseph McCune



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REVIEW

OPEN

Cellular therapies for rheumatic disease

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Purpose of review
Cellular therapies, particularly chimeric antigen receptor (CAR)-modified lymphocytes, have progressed from experimental oncology into serious consideration for selected autoimmune rheumatic diseases. Autologous and emerging allogeneic CAR-T platforms now offer the possibility of deep, drug-free remission in systemic lupus erythematosus (SLE), idiopathic inflammatory myopathies (IIM), systemic sclerosis (SSc), and related conditions for which conventional therapies remain inadequate. This timely article reviews the rationale, current clinical experience, safety profile, and future directions of cell therapies in rheumatology with a focus on efficacy, safety, and "immune reset" in autoimmune rheumatic disease. The review is particularly pertinent as multiple parallel cell-based platforms (autologous and allogeneic CAR T cells, transient RNA CARs, CAR-NK, and T cell engagers) are entering the rheumatology space faster than practice guidelines or trial frameworks can fully adjust.

Recent findings
Recent studies show that CD19-directed CAR T cells can induce deep B-cell depletion with high rates of drug-free remission in refractory SLE and promising responses in SSc and IIM, accompanied by distinctive toxicity patterns such as mostly low-grade CRS, rare ICANS, and the newly described organ-specific LICATS. Parallel work demonstrates mechanistic "immune reset" (including type I IFN pathway suppression and naïve-skewed B-cell repopulation), expansion of indications to neurologic autoimmunity, emergence of off-the-shelf platforms (allogeneic CARs, $\gamma\delta$-CAR, CAR-NK, RNA CARs), and early human experience with CD19- and BCMA-directed T cell engagers in rheumatic disease.

Summary
Collectively, these findings position cellular therapies as powerful, potentially transformative options for highly selected patients with severe, refractory lupus and autoimmune rheumatic disease, but also underscore the need for disciplined trial design, long-term safety surveillance, and strategies to ensure equitable access.

Keywords
autoimmune rheumatic disease, bi-specific t-cell engagers, chimeric antigen receptor T, cellular therapies, systemic lupus erythematosus

FOUNDATIONS OF CELLULAR IMMUNOTHERAPY AND CHIMERIC ANTIGEN RECEPTOR DESIGN

The modern era of cellular immunotherapy began with studies showing that ex vivo-expanded lymphocytes could mediate regression of metastatic tumors when reinfused into patients [1▪,2,3]. These early efforts included systemic transfer of interleukin-2-expanded lymphoid cells and the use of tumor-infiltrating lymphocytes combined with high-dose cytokine therapy [1▪,2,3]. Subsequent work demonstrated that retroviral gene transfer could endow autologous T cells with tumor-reactive receptors, inaugurating the concept of genetically engineered cell therapy [4,5▪▪,6].

Chimeric antigen receptor (CAR)-T technology extends this framework by combining an extracellular single-chain variable fragment that recognizes a defined antigen with intracellular CD3ζ and one or more co-stimulatory domains, typically CD28 or 4-1BB. These design elements determine activation thresholds, proliferation, persistence, and cytokine secretion. CD28-based CARs often show brisk expansion but shorter persistence, whereas 4-1BB

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KEY POINTS

- Advancements in cellular therapies:
  Chimeric antigen receptor (CAR) T-cell therapies have transitioned from oncology to autoimmune rheumatic diseases. This advancement represents a significant shift as autologous and emerging allogeneic CAR T platforms show potential in inducing deep, drug-free remissions in diseases such as systemic lupus erythematosus (SLE), idiopathic inflammatory myopathies (IIM), and systemic sclerosis (SSc). Main targets include CD19, BCMA, CD20.
- Challenges in managing adverse effects:
  Patients undergoing CAR T treatment can experience severe adverse effects such as cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS). The occurrence of these conditions, along with local immune effector cell-associated toxicity syndrome (LICATs), has made the management of these therapies more complex given the need for comprehensive management strategies to mitigate these risks.
- Concept of immune reset:
  The concept of immune reset is crucial in understanding the long-term efficacy of CAR T-cell therapies. Immune reset refers to the idea of reprogramming the immune system to eliminate pathological autoimmunity while restoring normal immune function. This needs to be better defined but thus far is demonstrated by presence of CD19 B cell depletion and type-1 interferon pathway suppression, followed by repopulation with a naïve B cell phenotype in association to major clinical response.
- Future directions and optimizations:
  Future strategies include innovations such as dual-targeting CARs, allogenic products and bi-specific T-cell engagers to maximize access and therapeutic benefits while minimizing adverse effects.
  A significant challenge in the development of these therapies is the overabundance of concurrent clinical trials, which dilutes patient populations and stretches resources thin. To address this, innovative trial designs matching individuals with the most appropriate trials based on their unique genetic, phenotypic, and disease characteristics should be considered.

constructs expand more slowly but persist longer in vivo. Most autoimmune CAR-T programs have therefore adopted CD19–4-1BB architectures to balance robust B-cell depletion with manageable toxicity [7,8,9▪,27,28,29▪,30▪▪,36▪,37–40,41▪▪,42–44,46].

PERSISTENT UNMET NEED IN SYSTEMIC LUPUS ERYTHEMATOSUS AND RELATED DISEASES

Despite important advances, treatment of systemic lupus erythematosus (SLE) and lupus nephritis remains unsatisfactory for many patients. Conventional immunosuppressive regimens and newer targeted therapies such as interferon receptor blockade, B-cell activating factor (BAFF) inhibition, and calcineurin inhibitors have improved outcomes but often fail to induce durable, complete renal remissions, and cumulative glucocorticoid exposure continues to drive organ damage and comorbidity [9▪,10–17]. Attempts to taper or discontinue immunosuppression in proliferative lupus nephritis are frequently limited by relapse risk, reflecting the difficulty of truly resetting the autoimmune response [15–19].

B-cell-targeted biologics highlight both the promise and limits of antibody-mediated approaches. Phase II/III rituximab trials in SLE did not meet primary endpoints despite clear serologic and peripheral B-cell effects in some subgroups. More potent type II anti-CD20 antibodies such as obinutuzumab achieve deeper and more sustained B-cell depletion and have shown positive results in proliferative lupus nephritis, yet complete, durable drug-free responses remain uncommon. These observations suggest that broader and more efficient targeting of the B-lineage compartment, including tissue-resident cells and plasmablasts, may be necessary for true immune "reset" in some patients, which provides a strong rationale for CD19-directed cell therapy [7,8,9▪,20▪▪,21,22,23▪▪,27,28,29▪,30▪▪,36▪,37–40,41▪▪,42–44,47▪,48,49▪▪,50].

Notably, a paradoxical unmet need is occurring in the context of a rapidly expanding development pipeline. As illustrated in Fig. 1, more than 30 interventional trials currently explore cell based therapeutic strategies in lupus nephritis and related lupus indications, reflecting substantial momentum and investment in immune reprogramming approaches alongside more established pharmacologic modalities.

WHY CD19-DIRECTED CHIMERIC ANTIGEN RECEPTOR-T IS COMPELLING IN AUTOIMMUNITY

CD19 is expressed on a wide spectrum of B-lineage cells from early developmental stages through naïve and memory B cells, plasmablasts, and a subset of short-lived plasma cells, whereas CD20 is absent from pro-B cells and many antibody-secreting cells [7,20▪▪,21,22,23▪▪]. CD19 CAR-T cells can therefore deplete a broader swath of autoreactive B-cell and plasmablast pools, including populations that may be relatively inaccessible to monoclonal antibodies because of tissue localization or microenvironmental factors [7,8,9▪,20▪▪,21,22,23▪▪,27,28,29▪,30▪▪,37–40,41▪▪,42–44].

Preclinical lupus models support this concept: CD19–CAR-T therapy in murine systems can prolong

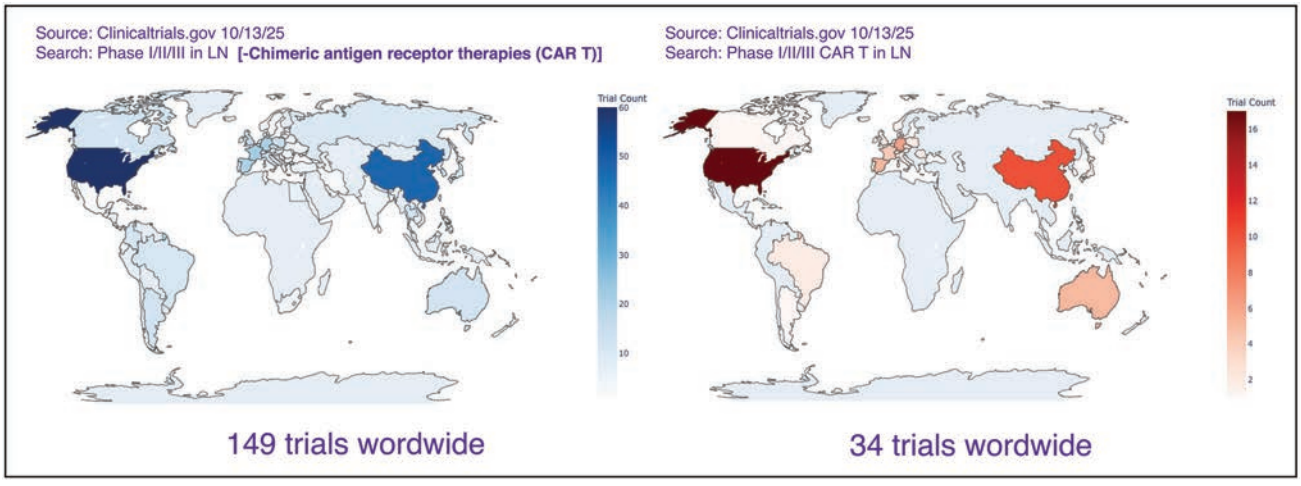

FIGURE 1. Ongoing interventional clinical trials in lupus nephritis by therapeutic mechanism. Summary of active interventional clinical trials in lupus nephritis as of 10/13/25, categorized by primary mechanism of action. Trials were identified through a structured search of public clinical trial registries via ClinicalTrials.gov using disease specific terms related to lupus nephritis and systemic lupus erythematosus, and were manually curated to exclude observational studies, supportive care interventions, and noninterventional designs. Therapeutic classes include B cell directed therapies, plasma cell targeting approaches, cytokine and interferon pathway inhibitors, complement inhibitors, intracellular signaling modulators, and cellular therapies. Trial counts reflect active registered studies at the time of analysis and are intended to describe the current mechanistic distribution of the development pipeline rather than comparative efficacy.

survival, prevent glomerulonephritis, and maintain long-term functional activity when B-cell depletion is sustained. In contrast, using the Fra2 TG murine model of systemic sclerosis, deep B cell depletion did not show efficacy but rather disease exacerbation [57].

In early human experience, leukapheresis and successful CAR-T manufacturing have been feasible even in patients maintained on immunosuppressive regimens, and ex vivo cytotoxicity of SLE-derived CAR-T products appear comparable to that of healthy donor-derived cells. These data support the practical viability of CAR-T approaches in heavily pre-treated autoimmune populations [27,28,29▪,30▪▪,36▪,37–40,41▪▪,42–44].

CLINICAL EXPERIENCE WITH CD19 chimeric antigen receptor-T IN SLE, IIM, AND SSc

The first landmark report of CD19 CAR-T in autoimmunity was a single young adult with severe refractory SLE and active lupus nephritis who achieved rapid B-cell depletion and complete clinical and serologic remission after CD19–4-1BB CAR-T infusion, remaining disease-free off immunosuppression. This was followed by a five-patient series of refractory SLE with nephritis, in which all patients reached DORIS-defined drug-free remission within three months, maintained normal complement and minimal or no proteinuria, and showed repopulation of the B-cell compartment predominantly by naïve cells.

Subsequently, the Erlangen group reported on 24 patients (17 women, 7 men) with a median (IQR) age of 39 years enrolled in a phase I/II basket study. 10 patients had SLE, 9 SSc and 5 IIM with a median number of 4 previous immunosuppressive treatments. 18/24 developed mild CRS (17 grade 1; 1 grade 2). No higher-grade CRS and no ICANS was observed. No clinically relevant neutropenia or thrombopenia >4 weeks were recorded. One grade 3 organ toxicity due to renal thrombotic microangiopathy in conjunction with CMV infection was reported. LICATs was reported in 88% of patients with grade 1/2 in the vast majority of patients. B-cells were depleted in all patients. Six-month efficacy data were available in 19/24 patients at data cut-off of May 12, 2025: All 7 SLE patients were in DORIS remission, all 8 SSc showed no disease progression and all 4 IIM patients met ACR/EULAR moderate or major response. In addition, clinical responses were also observed in the residual 5 patients, in whom follow-up time was still <6 months. All 24 patients discontinued immunosuppressive medications.

Aggregated analyses and 2024–2025 reviews of autoimmune rheumatic disease CAR-T cohorts now estimate that roughly 80–85% of SLE patients in early-phase trials achieve complete clinical responses, with the large majority in drug-free remission at six months

and many maintaining remission beyond one year [37–40,41▪▪,42–44]. Differentiating damage from disease activity, such as ongoing proteinuria in lupus nephritis related to damage, might make full clinical responses less apparent in these early studies. Smaller but consistent series in SSc and IIM report similar qualitative patterns of deep disease control after a single infusion, although longer follow-up and multi-center data are needed [27,28,29▪,30▪▪,36▪,37–40,47▪,48,49▪▪].

TOXICITY AND SAFETY CONSIDERATIONS

Cytokine release syndrome (CRS) and immune-effector-cell-associated neurotoxicity syndrome (ICANS) are the key toxicities associated with CAR-T therapy (Table 1) [31–33,49▪▪]. In hematologic malignancies, higher tumor burden correlates with more severe CRS and ICANS, often requiring intensive care and aggressive immunosuppression [24▪,25,26▪,31–33]. In contrast, early autoimmune cohorts have experienced predominantly grade 0–1 CRS, with occasional grade 2 events, and rare, usually low-grade ICANS manifesting as transient neurocognitive symptoms [29▪,30▪▪,31,36▪,37–40,41▪▪,42–44,49▪▪].

Hematologic toxicities such as prolonged cytopenias appear less frequent and less severe in autoimmune disease than in oncology, with most patients recovering counts within weeks and no consistent signal for long-lasting pancytopenia to date [29▪,30▪▪,31,36▪,37–40,41▪▪,42–44]. Long-term hypogammaglobulinemia and infection risk remain critical concerns; however, early SLE CAR-T studies report relative preservation of pre-existing protective antibody titers to standard vaccines and the ability to boost responses upon re-vaccination, consistent with sparing of CD19-negative long-lived plasma cells [29▪,30▪▪,36▪,37–40,41▪▪,42–44,49▪▪].

Managing disease activity during immunosuppressive washout remains a practical challenge in CAR T cell therapy for SLE. We recently reported that brief pulse corticosteroids can control severe lupus flare during washout without compromising CAR T cell expansion, B cell depletion, or the achievement of durable, drug-free remission, supporting their cautious use as a bridging strategy in selected patients [58].

A recently described local immune effector cell-associated toxicity syndrome (LICATS) has been observed as a frequent, usually mild and self-limited, organ-specific toxicity occurring in 77% of 39 patients with severe SLE, systemic sclerosis, or idiopathic inflammatory myopathy treated with CD19 CAR T cells, manifesting only in organs previously affected by the underlying autoimmune disease, with 54 total events that most often involved skin (35%), kidneys (22%), and musculoskeletal system (19%), typically arising around 10 days after infusion during B-cell aplasia and resolving over about 11 days, usually without intensive therapy and often with only brief glucocorticoid courses [49▪▪,51▪▪]. LICATS appear to be temporally and clinically distinct from early-onset systemic CRS, shows no serologic features of autoimmune flare or histologic evidence of active autoimmunity in limited biopsies, and is hypothesized to represent a local inflammatory "cleansing" process following deep tissue B-cell depletion [51▪▪]. Recognizing LICATS as a separate toxicity entity is important so as to avoid inappropriate use of immunosuppression yet should be systematically captured in future trials of CAR T and other deep B-cell-depleting therapies in autoimmune disease [51▪▪].

Table 1. Summary of car T related toxicities

Toxicity	Nature	Symptoms	Management	Timing
Cytokine release syndrome (CRS)	Systemic inflammatory response	Fever, hypotension, organ dysfunction	Supportive care, tocilizumab, corticosteroids	~1–7 days post-infusion
Immune effector cell-associated neurotoxicity syndrome (ICANS)	Neurological toxicity	Headache, confusion, seizures	Supportive care, corticosteroids, anti-seizure medications	~1–7 days post-infusion[a]
Local immune effector cell-associated toxicity syndrome (LICATS)	Immune-mediated reset toxicity related to clearance	Disease specific organ inflammation	self-limited Symptomatic treatment	Days to weeks
Immune effector cell (IEC)-associated enterocolitis	Cellular inflammation of the intestines with intra-epithelial lymphocytosis and villous blunting	Diarrhea, abdominal pain, colitis	Supportive care, anti-inflammatory medications, immunosuppressive agents (e.g. TNF inhibitors integrin blockers)	Variable, often weeks post-infusion

[a]Not observed in the CASTLE study.

In addition to CRS and LICATs, an immune effector cell-associated enterocolitis following chimeric antigen receptor T-cell therapy has been reported in several hematologic car T studies leading the FDA to issue update black box warnings for use of these agents in hematologic malignancy [52]. In a multiple myeloma CAR T study, one patient where CAR-specific immunofluorescence stains were available, CAR T-cell presence was confirmed within the lamina propria [53].

Regulators also have issued class-wide warnings about secondary T-cell malignancies following BCMA- and CD19-directed CAR-T in oncology, so emerging rheumatology series emphasize the need for long-term surveillance of autoimmune recipients [31–33,37–40,41▪▪,42–45]. Newer CAR designs incorporating non-integrating vectors, suicide switches, or transient RNA-based expression aim to reduce persistent insertional events while preserving the capacity to induce durable remission [7,8,38,43,46,47▪,48▪▪, 49▪▪,50,54▪,55,56▪]34▪–36].

BEYOND SLE: IIM, SSC AND NEUROLOGIC AUTOIMMUNITY

Beyond SLE, several reports describe CD19 CAR-T as rescue therapy for severe, refractory antisynthetase syndrome and other IIMs after failure of multiple B-cell-depleting antibodies and advanced immunosuppressive regimens. In these cases, CAR-T treatment led to major improvements in muscle strength, normalization of creatine kinase, and resolution of lung involvement, sometimes with later transient flares attributed to expansion of autoreactive $CD8^+$ effector cells likely driven by low-grade LICATs [51▪▪]. These observations highlight both the promise of CAR-T in IIM and the need for close T-cell monitoring and tailored inclusion criteria.

In SSc, early CD19 CAR-T experience suggests that a single infusion can stabilize or improve skin fibrosis, digital ischemia, and pulmonary function without ongoing background immunosuppression. Concurrently, cell-therapy strategies, including CAR-T and other B-cell-directed products, are being explored in SSc and fibrosing autoimmune conditions in early-phase trials [37–40,48,49▪▪].

BCMA- and CD19-targeted CAR-T strategies have also been applied to neuromyelitis optical spectrum disorder and myasthenia gravis, with phase 1 studies reporting marked reductions in pathogenic autoantibodies, relapse rates, and disability scores [34▪–36]. Although these indications fall outside classic rheumatology, they support the broader principle that B-lineage-directed cell therapy can reset pathogenic humoral immunity across diverse autoantibody-mediated diseases [27,28,29▪,30▪▪,34▪,35▪,44].

TRANSIENT AND ALTERNATIVE EFFECTOR PLATFORMS

To mitigate long-term risks and bypass procedures necessary for autologous CAR T, transient CAR-T approaches using RNA electroporation or mRNA vectors have been developed [34–36▪,38,43]. In a phase 1b/2a study in myasthenia gravis, ex vivo RNA-engineered BCMA CAR-T allowed patients to remain on baseline immunosuppression, eliminated the need for lymphodepleting conditioning, enabled outpatient infusion, and yielded clinically meaningful improvements with minimal CRS or ICANS. In another study an engineered CD8 T-cell-targeting LNP encapsulating CD19 CAR messenger RNA was tested in five patients with severe SLE in repeated doses. Each patient demonstrated CAR generation and B-cell depletion without high grade CRS [50].

Alternative effector cell types, including gamma-delta T-cells, CAR-natural killer (NK), and CAR-T regulatory cells (CAR-Treg), are also under active preclinical and early-clinical investigation [38–40,42,43,46,47▪,48▪▪,59]. CAR-NK and gamma-delta cells may combine potent cytotoxicity with a lower risk of severe CRS, ICANS, and graft-versus-host disease, while CAR-Treg aim to enforce antigen-specific immune tolerance rather than simply depleting B cells [42,43,46,47▪,48▪▪,59]. Although data in rheumatic indications remain limited, these platforms could ultimately broaden the therapeutic toolbox and may be particularly attractive for diseases where restoring tolerance is the primary objective.

EMERGING ALLOGENEIC AND "OFF-THE-SHELF" APPROACHES

Autologous CAR-T manufacturing is complex, time-consuming, and expensive, which constrains access to patients and scalability [7,24▪,25,26▪,31,36▪,37–40,41▪▪,42–44]. Allogeneic, gene-edited CAR products derived from healthy donors offer a potential solution by providing standardized potency and rapid availability. Early autoimmune experience with donor-derived CD19 CAR-T suggests feasibility and encouraging efficacy, although long-term safety and immunogenicity are still being defined. Cell types such as gamma delta T-cells and NK cells are being explored as alternative allogeneic cell types [37–40,41▪▪,42–44,47▪,48▪▪].

Recent reviews of the CAR-T trial landscape in autoimmune rheumatic diseases document multiple allogeneic CD19 and BCMA CAR-T trials, often run alongside autologous cohorts [37–40,41▪▪,42–44]. If durable remission can be achieved with short-lived CAR exposure, allogeneic products may prove particularly attractive, as their finite persistence reduces long-term risks while still

delivering intense, time-limited B-lineage depletion [37–40,41▪▪,42–44,47▪,48▪▪,59].

Bispecific T cell engagers (TCEs), mainly CD3 × B-cell-targeting antibodies, are emerging as a rapid, deep B-cell-depleting strategy for refractory rheumatic disease, with early human data now available. Blinatumomab use (CD19 × CD3) in small RA cohorts has produced profound B-cell depletion, immune "reset" toward naïve B cells, and rapid improvements in clinical activity and imaging, with mainly low-grade infusion-related cytokine symptoms and no high grade CRS reported. Broader programs using CD19- and BCMA-directed TCEs (for RA, systemic sclerosis, dermatomyositis/idiopathic inflammatory myopathy, and primary Sjögren) similarly suggest feasibility and a favorable short-term safety profile [54▪,55,56▪]. Early phase SLE and lupus nephritis trials are similarly proceeding.

TRIAL DESIGN AND RHEUMATOLOGY-SPECIFIC GUIDANCE

The rapid expansion of CAR-T trials in rheumatology has prompted the development of discipline-specific guidance on how to initiate and manage such studies. A recent consensus document from the Lupus Clinical Investigators Network outlines practical recommendations for trial design in autoimmune rheumatic diseases, including patient selection, timing and conditions of leukapheresis, management of background immunosuppression and glucocorticoids, CRS and ICANS grading and management, infection prophylaxis, and long-term follow-up. Together with oncology-derived toxicity frameworks, this guidance provides a blueprint for harmonized, multi-center ARD CAR-T trials [24▪,25,26▪,31–33,37–40,41▪▪,42–46,51▪▪,52,53].

Concurrently, systematic reviews and state-of-the-art articles have begun to synthesize early clinical experience across autoimmune rheumatic diseases, placing individual case series and small cohorts in a broader context [36▪,37–40,43]. These reviews emphasize consistently high remission rates in refractory SLE, promising signals in SSc and IIM, and a generally manageable safety profile when CAR-T is delivered in experienced centers [27,28,29▪,30▪▪,36▪,37–40,41▪▪,46,49▪▪,58].

POSITIONING CELL THERAPIES WITHIN RHEUMATOLOGY

Current evidence supports B-lineage-directed CAR-T therapy as a powerful option for selected patients with severe, refractory autoimmune rheumatic disease who have failed treatment with available biologic and small-molecule therapies [27,28,29▪,30▪▪,34–36▪,37–40,43–45,47▪,48,49▪▪,50]. Unlike chronic immunosuppressive regimens, CAR-T can induce profound B-cell depletion followed by reconstitution of a qualitatively different B-cell pool, with durable remission observed even after B-cell recovery, consistent with a "reset" of humoral memory [29▪,30▪▪,36▪,37–40,47▪,48,49▪▪,50].

At the same time, cost, infrastructure requirements, and long-term safety uncertainties limit near-term applicability, and equitable access will be a central ethical challenge [15–17,31,37–40,41▪▪,42–45]. The field is now moving from case reports and single-center series toward structured, guideline-informed clinical trials that will better define patient selection, comparative effectiveness versus optimized biologic regimens, and the role of newer platforms such as allogeneic CAR-T, CAR-NK, and TCEs [36▪,37–40,41▪▪,42,43,46,47▪,48▪▪,54▪,55,56▪].

For rheumatology, the emergence of cell therapy represents an opportunity to harness a transformative technology capable of deep, drug-free remission in otherwise intractable disease. It will be our responsibility to ensure careful patient selection, rigorous long-term monitoring, and a focus on safety, equity, and sustainability.

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Conflicts of interest

Lupus Research Alliance, Lupus Clinical Investigators Network, Adicet Bio, Alumis Inc., ICON Labs., Cabaletta Bio, BMS, Novartis, Astra Zeneca.

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- ▪ of special interest
- ▪▪ of outstanding interest

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Management of patients with antiphospholipid antibodies or antiphospholipid syndrome during pregnancy

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Purpose of review
Given the persistently high rates of adverse pregnancy outcomes (APOs) in women with antiphospholipid syndrome (APS) despite standard therapy, updated guidance is needed to support individualized care. This review summarizes current understanding of the obstetric management of APS, including pathogenic mechanisms, preconception evaluation, pregnancy management, and emerging therapeutic approaches.

Recent findings
Recent studies reinforce the central role of inflammation, rather than thrombosis alone, in APS-related pregnancy morbidity. This evolving paradigm has prompted interest in immune-modulating strategies alongside conventional treatment. Early prospective data suggest that TNF-α inhibition may significantly reduce APOs in pregnant women with APS. Animal studies demonstrate immunomodulatory effects of statins at the maternal–fetal interface, although human evidence regarding statins remains limited. Updated clinical recommendations also clarify management surrounding assisted reproductive technology, emphasizing the importance of preconception antiphospholipid antibody screening and risk-based thromboprophylaxis to mitigate complications during ovarian stimulation and early pregnancy.

Summary
Obstetric APS remains a major cause of maternal–fetal morbidity. Advances in understanding placental inflammation have expanded potential therapeutic targets, but standardized treatment remains limited. Optimal care requires risk-stratified, multidisciplinary management and further research to improve pregnancy outcomes.

Keywords
antiphospholipid syndrome, assisted reproductive technology, pregnancy, tumor necrosis factor-inhibition

INTRODUCTION

Antiphospholipid antibody syndrome (APS) is a pleomorphic disease with cardinal features that include thrombosis and/or pregnancy morbidity. APS can occur as an isolated condition or in association with systemic rheumatologic diseases, most commonly systemic lupus erythematosus (SLE). The 2023 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria define APS as the presence of macrovascular thrombosis, microvascular thrombosis and/or cardiac valvular vegetation in the setting of persistently positive antiphospholipid antibodies (aPL). Antiphospholipid antibodies include the lupus anticoagulant, antibeta two glycoprotein IgM/IgG ($\geq$ 40 units), and/or positive cardiolipin IgM or ($\geq$ 40 units) [1]. The definitions and categorizations of antiphospholipid antibody positivity are complex and are described in detail in the ACR/EULAR classification criteria.

Obstetric APS is defined as persistently positive aPL in the presence of one of the following: three consecutive early fetal losses before 15 weeks 6 days gestation; a single otherwise unexplained late fetal death between 16 weeks' gestation and 33 weeks 6 days gestation; or preeclampsia with severe features and/or evidence of placental insufficiency prior to 34 weeks' gestation [1]. The estimated annual incidence and prevalence of APS, including obstetric APS, are one to two cases per 100 000 and 40–50 cases per 100 000, respectively [2,3].

Obstetric APS is associated with adverse pregnancy outcomes (APOs) such as fetal growth

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KEY POINTS

- Despite standard therapy, APS is still associated with high rates of adverse pregnancy outcomes.
- Emerging therapies targeting inflammation, such as TNF-α inhibitors, show early promise and highlight a shift toward immunomodulation in APS management during pregnancy.
- Optimal care requires early preconception counseling, risk-stratified, multidisciplinary management, and future research to improve pregnancy outcomes.

restriction, prematurity, preeclampsia, and fetal loss. Fetal mortality remains high despite conventional treatment with low molecular weight heparin and aspirin, with rates approaching 10–12% [4]. Patients who are lupus anticoagulant-positive and particularly those who also have the anti beta-2 glycoprotein and anticardiolipin antibody (triple-positive) have a 30–40% risk of APOs despite standard therapy [5–7]. Accordingly, close maternal and fetal monitoring is essential.

PATHOGENESIS RELATED TO REPRODUCTION

Both APS and isolated aPL positivity are associated with APOs. Among aPL, the lupus anticoagulant confers the highest risk, with one study reporting a relative risk of 12.15 despite guideline-directed treatment [5,7,8]. The mechanisms underlying pregnancy morbidity are not fully understood but are thought to involve abnormal placental vascularization driven by inappropriate inflammation at the maternal–fetal interface.

A systematic review of 580 placentas from aPL-positive pregnancies identified six recurring histopathologic features compared with controls: placental infarction, decidual inflammation, impaired spiral artery remodeling, increased syncytial knots, decreased vasculo-syncytial membranes, and complement deposition. Notably, intravascular thrombosis within placental tissue was rare [9].

Mechanistically, trophoblast and decidual endothelial cells express β2-glycoprotein I [10,11], which serves as a target for pathogenic aPL. Binding triggers complement activation, increased TNF-α production, and trophoblast apoptosis [12–14▪▪]. The trophoblast injury leads to insufficient spiral artery remodeling and contributes to still birth, intrauterine growth restriction, and preeclampsia [15].

Excessive neutrophil extracellular taps (NETS) also appear to play a role. NETS are released by neutrophils to defend against pathogens. Proteins embedded in NETS can contribute to thrombosis [16,17]. NETS have been detected in the intervillous space of aPL-positive placentas and may impair trophoblast function [4,18]. Excessive NET formation has been associated with maternal–fetal interface hemorrhage and thrombotic vasculopathy [18,19].

PRECONCEPTION COUNSELING AND ASSISTED REPRODUCTIVE TECHNOLOGY

Reproductive health discussions should occur early and often in SLE patients' disease course and can improve pregnancy outcomes. Up to 40% of patients with SLE have positive aPL and 20–30% meet APS classification criteria [20]. For those planning pregnancy, the American College of Rheumatology recommends aPL screening in SLE patients once prior to conception or early in pregnancy [8]. Evaluation for aPL is also advised in individuals with a history of unprovoked thrombosis, recurrent early pregnancy loss, late fetal loss, or stillbirth.

Patients with SLE who plan to undergo assisted reproductive technology (ART) or egg retrieval/cryopreservation should be screened for aPL beforehand. The background risk of venous thromboembolism is two to three-fold higher in pregnancies conceived via ART, particularly during ovarian stimulation and early pregnancy [21]. This hypercoagulability is driven largely by supraphysiologic estrogen levels during ovarian hyperstimulation [22]. Ovarian hyperstimulation syndrome, a known ART complication, carries a 4.1% thrombosis risk in severe cases [23]. Minimizing hyperstimulation risk is important for all patients but is especially crucial for those with APS or aPL positivity.

Routine thromboprophylaxis is not recommended for ART in the absence of ovarian hyperstimulation syndrome [23]. However, patients with positive aPL without clinical APS and those with obstetric APS should receive prophylactic low-molecular-weight heparin (LMWH) during ART. Patients with thrombotic APS require therapeutic LMWH [8]. Prophylactic enoxaparin dosing is usually 40 mg daily. Therapeutic dosing is usually 1 mg/kg daily [8]. A summary of ART medication management in aPL positive and APS patients can be found in Table 1.

PREGNANCY MANAGEMENT

Asymptomatic antiphospholipid antibody positivity

APS Management differs among individuals with isolated aPL positivity, obstetric APS, and thrombotic APS and is summarized in Table 2. A 2007 randomized,

Table 1. Antiphospholipid antibody syndrome ART management recommendations

	Prophylactic LMWH[2]	Therapeutic Heparin[3]
aPL positive[1]	✓	
Obstetric APS	✓	
Thrombotic APS		✓

✓ Recommended during ART
[1] Refers to patients who do not meet criteria for thrombotic or obstetric APS but are found to have high titer positive aPL.
[2] Low Molecular Weight Heparin (enoxaparin 40 mg daily).
[3] enoxaparin 1 mg/kg daily.

double-blind, placebo-controlled trial found no difference in thrombosis rates between asymptomatically aPL-positive patients receiving aspirin versus placebo [24]. However, because aPL positivity independently increases the risk of preeclampsia, low-dose aspirin (81–100 mg daily) is recommended beginning after 12 weeks of gestation for preeclampsia prevention [25]. Evidence supporting hydroxychloroquine (HCQ) as primary thrombosis prophylaxis is limited to a few observational studies in SLE and is insufficient for routine recommendation [26,27].

Obstetric antiphospholipid syndrome

Patients who meet criteria for obstetric APS should receive low-dose aspirin (81–100 mg daily) plus prophylactic LMWH (40 mg daily) through 6–12 weeks postpartum. This combination improves live-birth rates compared with aspirin alone [28]. Small studies of refractory obstetric APS without SLE suggest that HCQ may further increase live-birth rates [29,30]; therefore, HCQ is recommended for this population [8].

Despite standard therapy, APO rates remain unacceptably high [4,31▪], prompting evaluation of adjunctive treatments. Prednisone has been studied in refractory APS but does not improve live-birth rates and increases the risk of preterm birth and preeclampsia; therefore, it is not recommended [8,32]. Statins improve placental perfusion and inhibit NETS in animal models, but human data are limited, and statins are not currently recommended [8,31▪].

A 2025 prospective study of 51 patients with APS reported a 20% APO rate when certolizumab was added to conventional therapy, substantially lower than the approximately 40% rate observed in earlier studies [14▪▪]. While additional research is needed, these findings highlight the potential role of TNF-α inhibitors in obstetric APS patients who have failed guideline-directed therapy.

Thrombotic antiphospholipid syndrome

Thrombotic APS should be managed with low-dose aspirin (81–100 mg daily) and therapeutic-dose heparin (1 mg/kg daily) through 6–12 weeks postpartum. Heparin appears beneficial not only due to its anticoagulant effects but also due to anti-inflammatory and anticomplement activity [4]. HCQ is also recommended in subgroup based on evidence described above.

OTHER CONSIDERATIONS

Although guidelines provide general therapeutic frameworks, management should be individualized using shared decision-making. Risk varies significantly among patients; individuals with high-titer, triple-positive aPL have a substantially higher risk of APOs than those with an isolated moderate-titer cardiolipin IgM [33]. For example, in a 37-year-old pregnancy naive triple-positive aPL

Table 2. Antiphospholipid antibody pregnancy management recommendations

	Low dose aspirin[2,3]	Prophylactic LMWH[3,4]	Therapeutic Heparin[3,5]	HCQ[6]	Certolizumab[9]	Statins
aPL positive[1]	✓					
Obstetric APS	✓	✓		✓	?	?
Thrombotic APS	✓		✓	✓	?	?

✓ Recommended during pregnancy
? Not formally recommended based on 2020 ACR guidelines but emerging as a potential therapy
[1] Refers to patients who do not meet criteria for thrombotic or obstetric APS but are found to have high titer positive aPL.
[2] 81–100 mg.
[3] To be continued 6–12 weeks post-partum.
[4] Low Molecular Weight Heparin (enoxaparin 40 mg daily).
[5] enoxaparin 1 mg/kg daily.
[6] Hydroxychloroquine.
[9] Consider for those refractory to standard therapy with aspirin and LMWH.

patient, the decision to initiate heparin therapy during their first pregnancy may be considered after discussion of the risks and potential benefits. Patients who conceive via ART also require special consideration.

Positive aPL laboratories during pregnancy should be interpreted with caution and the laboratories should only be checked when indicated. Lupus anticoagulant testing may yield false-positive results due to physiologic increases in coagulation factors [1,34]. In a prospective study of 152 pregnant patients with positive aPL, 25% of those with a positive lupus anticoagulant later tested negative during pregnancy [35]. However, a single positive aPL laboratory during pregnancy should be used to direct pregnancy management when clinically relevant.

Noncriteria aPL, including phosphatidylserine antibodies, β2-glycoprotein I IgA, and cardiolipin IgA, have been associated with APS and may pose independent thrombosis risks. However, their clinical relevance in pregnancy remains uncertain [4,36,37].

CONCLUSION

Antiphospholipid antibody syndrome is a heterogeneous thrombo-inflammatory disorder that continues to confer substantial pregnancy risk despite established therapies. Although APS was historically viewed primarily as a prothrombotic condition, emerging evidence highlights inflammation at the maternal–fetal interface as a central driver of obstetric morbidity. This evolving understanding has broadened the search for novel therapeutic targets, including NET inhibition, complement modulation, and TNF-α blockade, with early studies focused on TNF-inhibition showing promising results. Given the variability in antibody profiles, clinical manifestations, and treatment response, optimal care requires an individualized, multidisciplinary approach. Continued research will be essential to refine risk stratification and develop more effective strategies to improve pregnancy outcomes in patients with APS.

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Conflicts of interest

There are no conflicts of interest.

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Revisiting the CD40-CD40L axis: from mechanistic insight to therapeutic renewal in autoimmune disease

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Purpose of review
CD40 ligand (CD40L, CD154) is a costimulatory molecule required for adaptive immune responses. It arms $CD4^+$ T cells to provide critical "help" to B cells, dendritic cells, and other antigen-presenting cells through interactions with CD40. Enhanced CD40L signaling promotes autoreactive B cell activation, germinal center hyperactivity, and autoantibody production, processes central to autoimmune pathogenesis. Recognition of the pathway's importance in autoimmunity prompted clinical trials of anti-CD40L monoclonal antibodies in lupus, but early enthusiasm faded after unexpected thrombotic events. These first generation anti-CD40L antibodies were later found to trigger platelet activation through an Fc-mediated mechanism and led to re-engineering of antagonist therapeutic proteins.

Recent findings
Preclinical studies confirm that CD40L inhibition ameliorates disease across diverse autoimmune models by restraining aberrant B-cell and T-cell responses. Novel Fc-silent anti-CD40L antibodies, nonantibody CD40L antagonists, and anti-CD40 antibodies have since been developed to overcome prior safety concerns. These new-generation CD40L and CD40 antagonists have shown promising results in phase 2 trials spanning multiple autoimmune settings, renewing interest in therapeutic blockade of this pathway.

Summary
Next-generation CD40L and CD40-directed therapies are redefining costimulatory blockade in autoimmunity. Integrating preclinical discoveries with clinical translation offers new opportunities to optimize treatment and transform management of B cell-driven autoimmune disease.

Keywords
autoimmunity, B cell activation, CD40, CD40L, costimulation

INTRODUCTION

Often described as the field's "holy grail", the central challenge of rheumatology is how to suppress autoreactivity, or induce immune tolerance, in patients with autoimmune disease while preserving the mechanisms essential for effective host defense. However, many therapies in the rheumatologists' toolbox rely on broad immunosuppression to achieve disease control. Although effective, these traditional approaches compromise protective immunity, increasing susceptibility to infections, impairing vaccine responses, and in some cases increasing the risk for malignancies. A road to advance the therapeutic paradigm can be found in selectively interrupting the aberrant signaling mechanisms controlling the key pathogenic drivers, most relevantly the autoreactive lymphocytes.

Generation of successful adaptive immunity requires multiple molecular signals to ensure the activation and expansion of antigen-specific lymphocytes. Costimulatory signals act in concert with antigen receptor engagement to enhance both the strength and specificity of the response. Among these costimulatory pathways, the CD40-CD40L signaling axis stands out for its central role in coordinating key aspects of adaptive immunity. CD40L, which is transiently expressed on activated T cells, plays an instrumental role in promoting the activation of B cells, dendritic cells, and stromal cells [1]. In the setting of autoimmunity, dysregulated CD40-CD40L signaling

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KEY POINTS

- The CD40-CD40L axis delivers essential costimulatory signals linking adaptive and innate immunity across T cells, B cells, APCs, platelets, and stromal cells.
- Dysregulated CD40-CD40L signaling drives autoreactive B-cell activation, germinal center pathology, and tissue inflammation in systemic autoimmune diseases.
- Early anti-CD40L antibodies demonstrated biologic activity but were limited by Fc-mediated platelet activation and thrombotic events.
- Fc-silent and engineered domain antibodies have revived CD40L blockade as a well tolerated, selective, and potent therapeutic approach with promising efficacy across autoimmune diseases.
- CD40L inhibition offers a distinct approach within the landscape of B cell-targeted therapies by interrupting T-cell "help" rather than depleting B cells, enabling more selective suppression of autoreactive responses.

drives the persistence of autoreactive B cells, promotes autoantibody production, and amplifies inflammatory cascades by stimulating antigen-presenting cell (APC) function [2,3]. Thus, the CD40-CD40L axis is a central hub for cross talk between adaptive and innate immune responses. In this review, we examine how this signaling axis influences normal host defense and drives pathogenic responses in the context of autoimmunity. We focus on the CD40L-CD40 pathway as a compelling target for emerging therapies in autoimmunity and highlight both the opportunities and hurdles in targeting this pathway for therapeutic benefit.

CD40L (CD154): A NEXUS OF INNATE AND ADAPTIVE IMMUNE SIGNALING

The CD40-CD40L signaling axis mediates T cell "help" to B cells, APCs such as dendritic cells, and stromal cells. While CD40L expression is low to absent on resting T cells, CD40L is rapidly expressed and transiently upregulated on activated $CD4^+$ T cells in response to T cell receptor (TCR) engagement (*Signal 1*), additional co-stimulatory cues (*Signal 2*), and cytokine signals (*Signal 3*) [4–6]. CD40L is also expressed on activated platelets [7] and, to a lesser extent, on other leukocytes and nontraditional immune subsets. In contrast to CD40L, CD40 expression is relatively widespread on both hematopoietic and nonhematopoietic cells. CD40 is expressed on B cells and APCs as well as on a range of stromal cells [8]. While CD40L operates primarily as a membrane-bound protein, it also exists in a soluble form with comparable bioactivity [9,10].

Initially characterized by Clark and Ledbetter as a B cell surface molecule [11], CD40 has emerged as a key player in the generation of humoral immunity, including clonal B cell expansion, B cell survival, germinal center maintenance, class-switch recombination, and affinity maturation [6,12] (Fig. 1). When CD40 engages CD40L, it undergoes conformational changes that facilitate recruitment of TNF receptor-associated factors (TRAFs) to its cytoplasmic tail, in turn triggering downstream signaling cascades that result in activation of nuclear factor κB (NF-κB), phosphoinositide 3-kinase (PI3K), and the mitogen-activated protein kinases (MAPK) [13,14]. The necessity of the CD40-CD40L pathway for B cell activation and germinal center responses is supported by the fact that CD40L signaling is required for T follicular helper cell differentiation [15]. In dendritic cells (DCs), CD40L-mediated CD40 activation induces cellular maturation, increases the production of T-cell activating cytokines, and upregulates expression of both MHC class I and II molecules and costimulatory molecules such as CD80 and CD86, enabling effective priming of naive T cells [16]. Patients with CD40L deficiency that develop X-linked hyper-IgM syndrome demonstrate profound defects in class-switch recombination and memory B cell responses [17,18] and experience recurrent infections and have impaired antibody responses. Similarly, CD40 or CD40L-deficient mice exhibit defective T cell-dependent antibody production and lack mature germinal centers [19,20].

CD40 signaling also enhances type I interferon (IFNα) production by plasmacytoid dendritic cells [21], promotes cytokine release and tissue-remodeling responses by monocytes, macrophages, and fibroblasts, and induces endothelial production of inflammatory mediators and adhesion molecules that facilitate leukocyte recruitment [22,23]. As noted earlier, CD40L expression on platelets contributes to platelet activation and thrombus formation [24] and plays a key role in sustaining immune responses. Through their ability to form aggregates with CD40-expressing leukocytes, CD40L-positive platelets have been shown to direct leukocyte trafficking to sites of inflammation [25]. Furthermore, plasmacytoid dendritic cells engaged by platelet-leukocyte aggregates further amplify type I interferon production through CD40-CD40L signaling [26].

CD40L IN THE DEVELOPMENT OF AUTOIMMUNE DISEASE

Upon activation through the B-cell receptor (BCR), B cells rely on additional co-stimulatory signals to avoid apoptosis, a safeguard that normally prevents the survival of autoreactive clones [27]. Accordingly, CD40 and CD40L interactions are tightly regulated

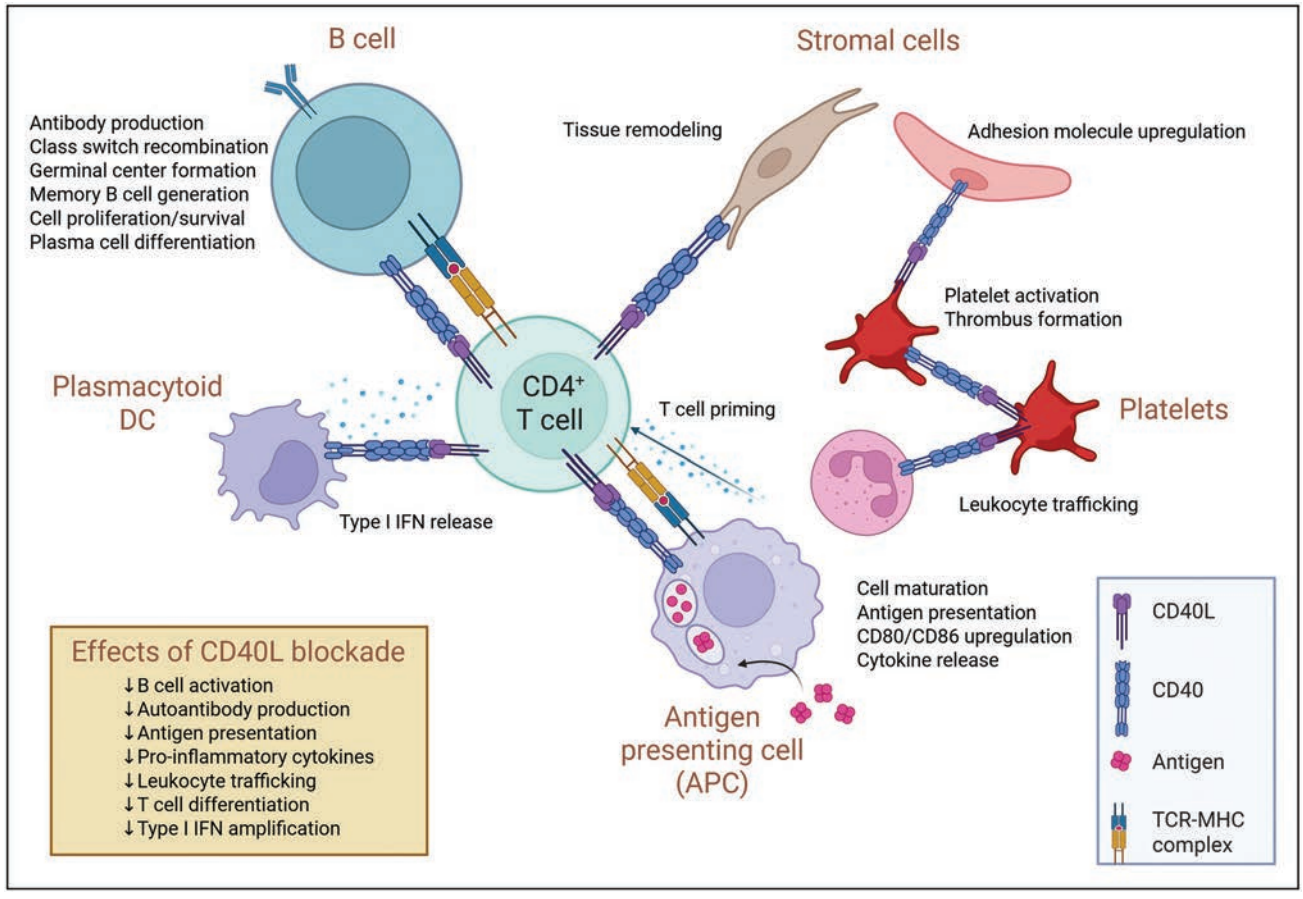

FIGURE 1. The CD40-CD40L signaling axis coordinates adaptive immune activation by linking $CD4^+$ T cells with B cells, antigen-presenting cells (APCs), platelets, plasmacytoid dendritic cells, and stromal targets. Engagement of CD40 by CD40L drives lymphocyte activation, cytokine release, and immune-stromal crosstalk central to autoimmune pathology. Therapeutic CD40L blockade interrupts this costimulatory network, dampening aberrant immune activation while preserving immune homeostasis. IFN, interferon; MHC, major histocompatibility complex; TCR, T cell receptor. Created in BioRender. Bracken, S. (2026) https://BioRender.com/hkwbp6t.

to prevent inappropriate lymphocyte activation. However, dysregulation of this axis is a hallmark of multiple autoimmune diseases and drives pathogenic lymphocyte activation, autoantibody production, and tissue inflammation [28].

Most interestingly, CD40L expression is not strictly confined to activated T cells. Studies in patients with systemic lupus erythematosus (SLE) have shown that B cells aberrantly upregulate CD40L, reaching expression levels comparable to those observed on activated T cells [2]. Hyperexpression of CD40L on B cells correlates with disease activity and supports autocrine B cell activation by circumventing the requirement for T cell help, further destabilizing immune tolerance. Transgenic mice overexpressing CD40L on B cells develop a lupus-like phenotype characterized by spontaneous germinal center formation, hypergammaglobulinemia, and immune complex-mediated organ damage, demonstrating that dysregulated CD40L expression is sufficient to trigger systemic autoimmunity [29]. Overexpression of CD40L in murine epidermal cells results in chronic inflammation and features of systemic autoimmunity [30]. In the tight skin (TSK) mouse model of systemic sclerosis, blockade of CD40L markedly attenuates hypodermal thickening, B cell activation, and autoantibody production, directly linking CD40L signaling to the pathogenesis of immune-mediated fibrosis [31]. Moreover, anti-CD40L therapy prevents or reverses autoimmune pathology in murine models of Sjögren disease, autoimmune thyroiditis, and type 1 diabetes and has been shown to eliminate spontaneous germinal centers that sustain organ-specific immune response [32]. Collectively, these studies establish CD40L as a pivotal mediator of both systemic and organ-specific autoimmunity in mice.

Human studies reinforce the concept that CD40L plays a pathogenic role in autoimmune disease. Heightened CD40L expression has been detected

in renal biopsies from patients with lupus nephritis and has been shown to correlate with disease severity [33]. In Sjögren disease, CD40L is upregulated in salivary gland mononuclear infiltrates, while increased CD40 is expressed on acinar and ductal epithelial cells [34,35]. Elevated surface CD40L is also consistently observed on circulating T cells in a variety of autoimmune diseases, including SLE, rheumatoid arthritis, and multiple sclerosis [2]. Moreover, soluble CD40L levels often correlate with markers of disease activity, underscoring its potential as both a biomarker of disease activity and contributor to disease pathogenesis [36].

THE RISE, FALL, AND RENEWAL OF CD40L BLOCKADE IN AUTOIMMUNITY

The nonredundant role of the CD40-CD40L axis in immune activation and its broad influence across immune compartments justify this pathway's emergence as a high-profile therapeutic target. The earliest attempts to block the CD40-CD40L pathway in patients with autoimmunity date back to the early 2000s, when toralizumab (IDEC-131), a humanized monoclonal antibody against CD40L, was tested in patients with SLE. The trial failed to demonstrate that CD40L blockade could reduce disease activity scores or disease biomarkers beyond that observed in the placebo-treated group [37]. The results from a trial of ruplizumab (BG9588), a humanized anti-CD40L directed monoclonal antibody, were reported soon thereafter in a small group of patients with proliferative lupus nephritis receiving concomitant immunemodulating therapy [38]. Treatment with ruplizumab was associated with a moderate reduction in autoantibody levels (antidsDNA) without any changes in the serum levels of total immunoglobulins or vaccine-specific immunoglobulins, suggesting that anti-CD40L selectively targeted antigen-activated, autoreactive B cells. However, this study lacked a comparator group and was prematurely terminated after multiple participants experienced thromboembolic complications [39]. These thrombotic adverse events were subsequently attributed to anti-CD40L Fc-mediated platelet activation, derailing the field for nearly two decades [40]. The lessons learned from these early studies led to the design of Fc-silent or nonantibody CD40L inhibitors.

Frexalimab, a next-generation anti-CD40L antibody, has shown striking early efficacy in relapsing multiple sclerosis. In a phase 2, double-blind, randomized, placebo-controlled trial, patients receiving frexalimab in the absence of background disease-modifying therapy demonstrated significant reductions in inflammatory brain MRI lesions, a surrogate marker of clinical disease activity, and decreases in biomarkers of inflammation (CXCL13) and neuronal damage [41]. Demonstrable efficacy was observed with both a high-dose intravenous regimen and a low-dose subcutaneous regimen. Additionally, these benefits occurred without any observable thromboembolic events, though a higher percentage of patients receiving frexalimab experienced COVID-19 infection and headache. While long-term effects on disease progression, relapse rates, and safety outcomes remain to be determined in phase 3 studies, frexalimab revived the potential of CD40L inhibition to be a potent, nonlymphocyte-depleting therapeutic strategy.

Recent results from a randomized, placebo-controlled phase 2 trial of the CD40L antagonist dazodalibep (DAZ), a novel nonantibody fusion protein, provide evidence that therapeutic blockade of CD40L can potentially benefit patients with Sjögren disease [42▪]. In this study, DAZ treatment produced statistically significant improvements in both systemic disease activity and patient-reported symptoms. The study was conducted in two patient groups: moderate to high systemic disease activity and high symptoms burden and low disease activity. In the group with moderate to high systemic disease activity, the ESSDAI, a validated tool designed to measure systemic disease activity across 12 domains, declined by a mean of 6.3 points in the DAZ group versus 4.1 points in the placebo group. The ESSPRI, a validated endpoint calculated from the combined ratings from visual analog scales measuring dryness, fatigue, and pain, showed a mean change of -1.8 points in the DAZ group compared with -0.5 in the placebo group. The between-group differences (-2.2 for ESSDAI in group 1, -1.3 for ESSPRI in group 2) were statistically significant and considered to be clinically meaningful [43]. DAZ therapy was also associated with reduced circulating biomarkers of B cell activity, such as CXCL13 and rheumatoid factor. Treatment with DAZ was generally well tolerated in all patients, although a higher incidence of COVID-19 infections was observed in the DAZ group. The progress in the development of other next-generation inhibitors of the CD40L-CD40 pathway in clinical development, including dapirolizumab pegol, iscalimab, and abiprubart, is detailed in Table 1 [44,45,46▪▪,47] and underscores the renewed interest in CD40-CD40L-directed therapy.

THERAPEUTIC POSITIONING OF CD40L AND CD40 BLOCKADE IN AUTOIMMUNE DISEASE

The therapeutic roles of CD40L and CD40 blockade must be considered in the context of their specific mechanisms of action and the autoimmune setting.

Table 1. Snapshot of recently completed and enrolling CD40L and CD40-targeted clinical trials across autoimmune diseases

Target	Drug (Alternative name)	Modality	Disease indication	Latest phase	Sponsor	Key outcomes
CD40L	Frexalimab	Fc-engineered mAb	Multiple sclerosis	3	Sanofi	90% reduction in new gadolinium-enhancing T1 lesions; no thromboembolic signal [41]
			Type 1 Diabetes	2		Phase 2b study (FABULINUS, NCT06111586) ongoing; primary endpoint includes preservation of stimulated C-peptide at 52 weeks. No peer-reviewed efficacy data reported to date
CD40L	Dapirolizumab pegol	Fc-free CD40 ligand signaling inhibitor	Systemic lupus erythematosus	3	UCB Biopharma SRL	Numerical BICLA, SLEDAI-2K, and serologic marker improvement but primary dose-response endpoint not met; well tolerated [44]
CD40L	Dazodalibep (VIB4920)	Nonantibody CD40 ligand antagonist	Sjögren disease	3	Amgen	Met coprimary ESSDAI and ESSPRI improvements; reduced CXCL13 and RF; well tolerated [42▪]
CD40	Iscalimab (CFZ533)	Humanized anti-CD40 mAb	Myasthenia gravis	2	Novartis	Composite MG score improvement [45]
			Sjögren disease	2		Disease-modifying signal with modest reduction in ESSPRI score [46▪▪]
CD40	Abiprubart (KPL-404)	Humanized anti-CD40 IgG4 mAb	Rheumatoid arthritis	2	Kiniksa Pharmaceuticals	Reduction in DAS28-CRP at 12 weeks; no safety signal [47]

BICLA, British Isles Lupus Assessment Group-Based Composite Lupus Assessment; CRP, C-reactive protein; DAS28, Disease Activity Score-28; ESSDAI, EULAR Sjögren's Syndrome Disease Activity Index; ESSPRI, EULAR Sjögren's Syndrome Patient Reported Index; MG composite, myasthenia gravis composite; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000.

While CD40L blockade offers a compelling strategy to selectively disrupt T-dependent B cell activation, questions remain regarding its efficacy across the spectrum of autoimmune diseases. In particular, it is unclear whether CD40L blockade will suffice in conditions where pathogenic B cells are activated through T-cell independent, TLR-driven mechanisms. Age-associated B cells (ABCs), an extrafollicular subset implicated in SLE, Sjögren disease, systemic sclerosis, and other systemic autoimmune conditions, commonly arise through these TLR-mediated, CD40L-independent mechanisms. Because ABCs expand with age and are strongly linked to autoantibody production and tissue inflammation, their persistence may circumvent the therapeutic impact of CD40L inhibition. This raises the possibility that optimal B cell-directed therapy in some autoimmune diseases will require strategies that target both CD40L-dependent germinal center responses and CD40L-independent extrafollicular B cell activation, including interactions between autoreactive B cells and T peripheral helper (Tph) cells [48,49].

In the broader landscape of B cell-targeted therapies for autoimmune disease, it remains unclear where CD40-CD40L pathway blockade will ultimately fit. Anti-CD20 antibodies effectively deplete circulating B cells but spare most tissue-resident B cells, potentially leading to incomplete suppression of autoantibody production [50▪]. BAFF pathway inhibition attenuates B-cell survival yet provides modest efficacy as monotherapy. By contrast, CD19-directed strategies, including CAR T cells, achieve deep and durable B cell depletion but carry greater risks and logistical barriers. CD40L targeting may offer a potentially distinct advantage. Instead of wholesale depletion of B cells, it interrupts the T cell "help" required by antigen-activated B cell clones and thus preferentially silences autoreactive B cell responses. How the clinical efficacy of CD40-CD40L axis inhibition will compare to that of B cell depletion will require additional studies. It should also be considered these two approaches may be complementary in some settings.

Targeting CD40 as opposed to CD40L could yield similar or somewhat different clinical outcomes.

Drawing parallels with the DAZ trial in Sjögren disease, the phase 2b TWINSS trial of iscalimab, a CD40-directed monoclonal antibody, in a similar study population showed statistically significant clinical efficacy for reducing systemic disease activity, as measured by the ESSDAI [46▪▪]. However, patient-reported symptom improvements, as measured by the ESSPRI, were modest and not significantly different from placebo [42▪]. CD40 blockade acts on a broader array of immune cells. However, a possible distinguishing feature of CD40L-directed therapy is that its target, CD40L, mediates not only forward signaling to CD40-bearing cells but also reverse signaling into the CD40L-expressing cell by engagement with CD40 *in trans*. Recent work has shown that the cytoplasmic tail of CD40L interacts with receptor for activated C kinase 1 (RACK1), linking CD40L to downstream pathways (e.g. PKC, AKT, ERK, STAT1) that enhance T-cell activation and cytokine production [51]. Consequently, CD40L blockade may interrupt activation of B cells and APCs, as well as the CD40L-dependent signals that amplify T-cell effector responses. Although CD40L blockade can transiently reduce vaccine responsiveness and T cell-dependent immunity, such effects are a predictable consequence of its mechanism of action [52]. With continued refinement, this approach may bring the field of rheumatology closer to achieving durable disease control without dangerously sacrificing immune competence.

EMERGING FRONTIERS IN CD40L-TARGETED THERAPY

The ongoing clinical development of CD40 and CD40L-targeted therapies highlights several emerging directions for future study. One important step will be the integration of biomarkers that reflect both target engagement (e.g. soluble CD40L) and downstream immunologic effects (e.g. B cell activation markers, autoantibodies, and key cytokine levels) to guide individual responses to therapy. Incorporating such biomarkers into trial design could refine the clinical use of CD40 and CD40L inhibitors and enable a precision medicine approach.

Because pathogenic B cells may also be activated through CD40L-independent pathways, dual targeting approaches could enhance therapeutic efficacy particularly when nongerminal center responses are dominant aspects of disease pathology. For example, combining CD40L blockade with BAFF antagonism, TLR antagonism, or additional costimulatory signal inhibitors that suppress T cell-driven B cell responses might more comprehensively suppress autoreactive B cell responses. Notably, combination blockade strategies including CTLA4-Ig and emerging CD40L-directed agents are currently being explored in solid organ transplantation to prolong graft survival and reduce alloantibody formation [53]. Sequential strategies may also hold promise: B-cell depletion followed by CD40L blockade could debulk pathogenic B cells and subsequently prevent repopulating B cells from re-entering autoreactive germinal center-dependent pathways. Early experience with sequential B cell-directed therapies further supports the concept that targeting distinct immune pathways can improve patient responses and disease activity markers [54,55].

The expansion of CD40 and CD40L-targeted therapy across diseases is an area of considerable interest. Beyond lupus, multiple sclerosis, and Sjögren's disease, blockade of this pathway may have utility in systemic sclerosis, myasthenia gravis, autoimmune cytopenias, and even following transplantation, where selective immunomodulation without broad immunosuppression is desirable [45,56–58]. Together, these directions highlight both the breadth of potential applications and the importance of continued mechanistic and clinical investigation to define the role of CD40-CD40L axis inhibition across immune-mediated diseases.

CONCLUSION

Targeting the signaling mechanisms that sustain autoreactive B cell responses is the next frontier for the treatment of autoimmune disease. Among these possibilities, CD40L blockade offers a uniquely attractive strategy through selective disruption of the T cell "help" that sustains pathogenic B cell activation, germinal center maintenance, and autoantibody production. Advances in antibody engineering have addressed earlier safety concerns, reviving the CD40-CD40L pathway as a viable therapeutic target. While early clinical trials show promising biologic activity and improved safety, long-term efficacy and potential for infection require additional investigation. Nevertheless, CD40L-directed therapies should inspire cautious optimism for their potential to bring rheumatology closer to its long-sought goal of achieving precise and durable immune modulation.

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- ■ of special interest
- ■■ of outstanding interest

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Advances in the use of Janus kinase inhibitors

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Purpose of review
Over the last two decades, oral small molecules that target intracellular protein kinases that mediate intracellular signaling have been found to be effective in multiple immune mediated inflammatory diseases (IMIDs). Tofacitinib was the first Janus kinase inhibitor (JAKi) approved for rheumatoid arthritis (RA) in 2012 and subsequently baricitinib, upadacitinib, and filgotinib have been approved by various regulatory agencies around the world. Substantial efficacy in RA as well as other rheumatic diseases (axial spondyloarthritis, psoriatic arthritis, giant cell arteritis) and other IMIDs (inflammatory bowel disease, atopic dermatitis) has been demonstrated. Various JAKi are in trials for lupus, inflammatory myopathies and Sjogrens with recent positive results noted in phase 2/3 clinical trials.

Recent findings
Although efficacy has been clearly demonstrated safety concerns have been raised based on the oral surveillance postmarketing clinical trial which demonstrated in RA patients ≥50 years old with cardiovascular risk factors treated with tofacitinib have an increase risk of venous thromboembolism and possibly major adverse cardiovascular events/malignancy compared to tumor necrosis factor inhibitor treated patients. Extensive investigations in clinical trials and real world observations over the last few years have addressed the safety issues with mixed results but have allowed for risk stratification and appropriate use of JAKi. Efforts to develop JAKi that are more selective for specific JAK isoforms are ongoing such as deucravacitinib – a TYK2 inhibitor with a different mechanism of action compared to other JAKi that might have an enhanced safety profile.

Summary
Increased use of JAKi in the management of IMIDs is ongoing and will accelerate if the positive results noted in trials for lupus, inflammatory myopathies, and psoriatic arthritis result in regulatory approval. The article highlighted in this review provide an update on the progress being made in newer rheumatic disease indications as well as efforts to better understand the adverse event profile for patients on treatment.

Introduction
Delineation of the JAK–STAT pathway critical for type 1/II cytokine signaling in late 1990s resulted in the development of multiple JAKi for IMIDs. Tofacitinib was the original JAK inhibitor approved in 2012 followed by baricitinib in 2017 and upadacitinib in 2019 with filgotinib and pefecitinib approved ex-US all for rheumatoid arthritis. Since the original approval JAK inhibitors have been approved for multiple IMIDs. In this manuscript, data from clinical trials evaluating JAK inhibitors for new IMID indications will be reviewed as well as an update on safety data from real world experience.

Keywords
breprocitinib, deucravacitinib, Janus kinases, major adverse cardiovascular events, pseudokinase, venous thromboembolic events

EFFICACY

Efficacy similar to biologic DMARDs has been observed and overall safety has been similar to biologic DMARDs except for an increase risk of some opportunistic infections, primarily herpes zoster (i.e., "shingles"). To date there have been no head to head studies of Janus kinase inhibitor (JAKi) in immune mediated inflammatory diseases (IMIDs), and professional societies consider the efficacy of various JAKi to be similar in rheumatic diseases [1▪▪]. In inflammatory bowel disease, upadacitinib 30 mg was effective in both ulcerative colitis and Crohn's, but tofacitinib which is approved for ulcerative

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KEY POINTS

- Janus kinase inhibitors (JAKi) are widely used for various immune mediated inflammatory diseases with similar efficacy to biologic DMARDS-disease modifying anti rheumatic drugs (bDMARDs).
- Efforts to develop more selective JAKi are ongoing in efforts to improve safety and limit off target toxicity.
- Real-world evidence has provided conflicting evidence regarding venous thromboembolism/malignancy/major adverse cardiovascular events risk.

colitis failed to demonstrate efficacy in Crohn's clinical trials [2,3].

The approved JAKis are orthostatic competitive antagonists to ATP, blocking ATP binding to JAKs preventing protein phosphorylation. Although preclinical studies have suggested there may be a modest difference in selective JAK isoform inhibition, most consider the approved JAKis to be "pan JAK" inhibitors with activity to multiple JAKs. The exception would be filgotinib, which is more Jak1 selective [4▪▪]. In pre-clinical studies JAK selectivity varies by cell type and is concentration-dependent, limiting the interpretation of the results [5]. Nevertheless, developing a more specific JAKi could potentially be advantageous due to the tremendous overlap in cytokines inhibited by pan JAKi as well as potential off target effects and in theory should improve safety. JAK molecules consist of an ATP binding region (kinase) and a regulatory pseudokinase domain which interacts with the kinase domain to prevent signaling in the absence of stimulation. The pseudokinase region when activated enables ATP binding to the kinase region. Interest in targeting the pseudokinase domain has resulted in the development of allosteric inhibitors to this domain with deucravacitinib – a TYK2 inhibitor – the first to be approved with a for psoriasis indication [6▪]. This higher specificity has been speculated to be associated with a better safety profile, which to date has been suggested by clinical trial results in psoriasis, lupus and psoriatic arthritis [6▪,7,8].

Deucravacitinib has completed two phase 3 clinical trials in psoriatic arthritis enrolling 1399 patients with primary endpoint at week 16 of american college of rheumatology (ACR) response/PASI75 response with a 52 weeks follow-up and is under regulatory review [8,9▪]. The dose studied was 6 mg once daily and statistical difference from placebo was observed in ACR responses (ACR20 54%, ACR50 24.7%, ACR70 11.6%), and psoriasis activity and severity index (PASI75) 51.9% was observed. Deucravacitinib also achieved statistical superiority on multiple secondary endpoints – DAPSA, DAS28CRP, enthesitis, dactylitis. As deucravacitinib blocks TYK2 activity through which type 1 interferons signal potential benefit in interferonopathies are being investigated. In a phase 2 study in systemic lupus erythematosus, deucravacitinib was evaluated at 3 mg b.i.d., 6 mg b.i.d. and 12 mg daily or placebo [7]. At week 32, the percentage of patients achieving the primary endpoint SRI-4 response was statistically superior for the two lower doses of deucravacitinib (3 mg–58%, 6 mg–50%, 12 mg–45%, PLA 34%), Infections and rashes generally acneiform were more frequent with deucravacitinib than placebo. Of the 363 patients enrolled in the phase 2 study, 261 were enrolled in a long-term extension and the week 222 data has been presented. Persistence of clinical response was reported for all three doses. Numerically more serious adverse events and treatment discontinuations were observed in patients treated with the 12 mg once daily dose [10▪]. Phase 3 trials recently completed enrollment. In the phase 2 trial, significant improvement in cutaneous lupus activity was noted. Other TYK2 inhibitors, including zasocitinib, are under development for psoriasis/psoriatic arthritis, and inflammatory bowel disease (IBD) [11,12].

Upadacitinib is also under investigation in systemic lupus erythematosus (SLE) and has progressed to phase 3 trials. In the phase 2 trial at week 24, 55% of SLE patients on upadacitinib 30 mg achieved the primary endpoint of SRI-4 response and glucocorticoid dose $\leq$10 mg compared to 37% on placebo [13▪▪]. Similar results were reported for 30 mg upadacitinib in combination with elsubrutinib a bruton tyrosine kinase (BTK) inhibitor with no additional efficacy seen for the combination. Week 104 results in 127 patients entering the long-term extension demonstrated persistence of benefits as determined by SRI-4 response, BICLA and LLDAS [14▪]. No new safety issues were identified. Upadacitinib 15 mg has been approved for treatment of giant cell arteritis based on a clinical trial in 428 patients evaluating 15 mg and 7.5 mg daily with a 26-week corticosteroid taper or placebo with a 52-week taper [15▪▪]. 15 mg upadacitinib but not the 7.5 mg dose demonstrated persistence of efficacy in the setting of a more rapid glucocorticoid tapering over 26 weeks compared to tapering over 52 weeks. Week 104 results on 181 patients who achieved >24 weeks remission in the first 52 weeks demonstrated 90% reduction in disease flare if continued on upadacitinib compared to those who switched to placebo [16▪].

Several small studies and case reports have suggested that JAKi provide benefit in inflammatory muscle disease with greater benefit for skin than

muscle [17▪▪,18]. Breprocitinib a TYK2/JAK1 inhibitor recently reported positive results in a clinical trial for dermatomyositis with improvement in muscle strength and cutaneous disease [19]. A total of 241 patients were enrolled on 15 mg, 30 mg daily or placebo. Enrollment criteria included CDASI-A $\geq$6 and MMT-8 $\leq$142 and the majority of the patients were on corticosteroids/oral immunosuppressant which were continued with a mandatory steroid taper after week 12. In the press release, the 30 mg dose achieved a statistically significant improvement in the primary endpoint the Total Improvement Score (TIS) compared to placebo at week 52 with a rapid response by weeks 4–8. Breprocitinib was also evaluated at 15 mg and 45 mg in a small open label study in non-infectious non-anterior uveitis ($n = 26$) [20]. Treatment failure at week 24 after corticosteroid taper was the primary endpoint. Better persistence of treatment effect was seen for the two doses of breprocitinib suggesting this as a possible treatment option for non-anterior uveitis. A phase 3 clinical trial is in progress.

Multiple recent publications have demonstrated that switching JAKi in rheumatoid arthritis due to lack of efficacy or adverse events is an appropriate treatment strategy. In a Japanese observational registry, 138 rheumatoid arthritis (RA) patients who were considered JAKi nonresponders, there was no difference in the retention rate at 6 months in patients switched to JAKi (87%) or switched to biologic DMARDs (75.6%) [21▪]. Of interest, greater CDAI LDA and remission were reported in JAKi to JAKi cycling compared to JAKi switch to biologic DMARDS. The JAKpot study which evaluated retention rate of JAKI in 17 international registries demonstrated similar retention rate of JAKi cyclers to those who switched to biologics over 2 years. Improvement in disease activity was similar as well [22▪▪].

SAFETY

The safety of JAKi in IMID was well delineated in the clinical trials resulting in regulatory approval and confirmed in real world experience. Similar to biologic DMARDs, in clinical trials JAKi are associated with a modest increase in serious infectious episodes more frequent in elderly patients with no reported increased risk of malignancies. Rare cytopenias predominantly lymphopenia have been reported and elevations in total cholesterol without change in HDL/LDL ratio secondary to interleukin 6 (IL6) inhibition. The major difference in adverse events is an increase in opportunistic infections primarily the reactivation of latent viruses which appears to be a class effect. Most notably, Herpes Zoster incidence is significantly higher in those using JAKi, with highest rates in Asian populations. This increased risk has also been observed in real world registry data [23]. Vaccination with Shingrix is recommended prior to initiation of treatment and has been demonstrated to prevent Herpes Zoster in real world data of those using biologic and non-biologic DMARDs [24].

The most significant concern with JAKi have been concern over venous thromboembolism (VTE) and possible increased risk of major adverse cardiovascular events (MACE) and malignancies in older patients with underlying cardiovascular risk. Registry and claims-based data has demonstrated an increase risk of VTE in RA compared to age and sex matched healthy controls and a recent study from the Mayo clinic reported a hazard ratio of 2.26 for VTE and I.61 for pulmonary embolism (PE) in 2818 RA patients followed over 18 years [25,26,27▪]. VTE/PE risk was greater in patients with increased disease activity as noted in other datasets [28]. Concern over VTE risk with JAKi was first raised due to an imbalance of VTEs in the placebo-controlled phase 3 trials of baricitinib in RA patients with six events on 4 mg baricitinib and none on placebo, influencing the FDA decision to only approve the 2 mg dose and restricting use for patients who have failed a tumor necrosis factor (TNF) inhibitor.

Subsequently the phase 3/4 Oral Surveillance trial evaluating tofacitinib 5 mg b.i.d. and 10 mg b.i.d. in comparison to TNFi (adalimumab or etanercept) in RA patients 50 and older with cardiac risk factors demonstrated an increase in VTEs primarily pulmonary embolism with the 10 mg b.i.d. dose [hazard ratio (HR) 5.96; 95% confidence interval (CI),1.75, 20.33] and a trend for the 5 mg b.i.d. (2.99; 95% CI 0.81, 11.06) dose that was not statistically significant [29]. In addition, overall mortality was greater for the 10 mg bid dose compared to the TNF inhibitors.

Meta-analyses of clinical trials of the approved Jaki in IMIDs have failed to demonstrate an increase risk of VTEs, and multiple real world studies have been conducted and the majority have not demonstrated an increase risk of VTE in RA patients [30,31▪,32]. The Swedish Quality Registry evaluated 85 722 RA patients enrolled from 2010 to 2021 comparing JAK inhibitors primarily baricitinib and tofacitinib to TNF inhibitors and other MOA did demonstrate an increase risk of VTE again primarily PE (HR 3.21; 95% CI 2.11–4.88) [33▪▪]. Upadacitinib conducted a post-hoc analysis in RA patients with cardiac risk factors and did not demonstrate an increase risk of VTE but the number of patients evaluated was small [34]. Baricitinib did conduct a prospective trial in RA patients enriched for VTE but

the study was terminated and the results have not yet been released or published.

Although the etiology of the possible VTE signal is not clear, impact on JAK2 has been raised as a possibility and the newer JAKi under development are being designed to limit JAK2 inhibition. Indirect evidence for involvement of JAK2 is the increased risk of VTE in patients with JAK2 mutant clonal hematopoiesis [35▪].

No increase in VTEs have been reported in IMIDs other than RA in clinical trials or real world experience. Incidence of VTE in the ulcerative colitis trials was no different from placebo for tofactinib, upadacitinib, and filgotinib [36▪,37,38▪]. Similar lack of a signal for VTE has been reported in psoriatic arthritis, alopecia disorders, or axial spondyloarthritis [39–41▪]. It must be acknowledged however that these populations were much different than those in Oral Surveillance with regard to age, comorbidities, and baseline risk for VTE.

In the clinical trials no increase in MACE events or malignancy was reported for the approved JAKi. However in the Oral Surveillance trial in RA patients on tofactinib 5 and 10 mg twice daily, MACE events were numerically increased compared to etanercept/adalimumab and noninferiority for tofacitinib was not observed [29]. Subsequent post-hoc analyses have demonstrated that MACE and malignancy risk was greatest in patients with a history of atherosclerotic cardiovascular disease (ASCVD), and patients without ASCVD history had no increased risk compared to patients on TNF inhibitors [42▪▪,43▪▪]. Increased MACE risk began early, but malignancy risk increased after a latency period of 18 months which is what would be expected for a malignancy signal. Overall real-world data from claims-based data and observational databases have not confirmed the observation from Oral Surveillance study although as expected an increase in MACE events was seen in patients with cardiovascular risk factors [44▪,45,46].

A recent publication from the German Rabbit registry did report an increase in malignancy risk in RA patients on JAKi (primarily baricitinib/tofacitinib) compared to TNFi or other mechanism of actions followed for 47–50 months and enrolled in the registry between 2017 and 2020 [47▪▪]. Among 2285 JAKi and 4259 bDMARD initiators 88 and 135 malignancies occurred respectively. Incidence ratios were 11.6 (95% CI: 9.3, 14.3) in JAKi-and 8.9 (95% CI: 7.4, 10.5) in bDMARD-treated groups. No specific malignancies were noted with as expected the most common malignancy being lung cancer followed by breast cancer, bladder cancer, prostate cancer and gynecological malignancies. The adjusted hazard ratio comparing JAKis with bDMARDs was 1.40 (95% CI: 1.09, 1.80). The increase in malignancy risk was seen only in patients on treatment for 16 months or longer. The greatest risk was observed in patients over 60 with higher disease activity and who had received multiple csDMARDs.

Although the evidence is conflicting and we still lack a mechanistic understanding of the possible VTE/cardiovascular/malignancy signal, the FDA has limited use to patients failing TNF inhibitors and the EMA allows use in higher risk patients over 65 with cardiovascular risk factors only if no other alternatives exist.

CONCLUSION

JAK inhibitors are now widely used in the management of IMIDs with efficacy similar, to or in some cases, superior to other biologics as noted in the clinical trials. Being an oral small molecule provides an advantage for treatment compared to parenteral biologics and with tofacitinib already generic ex US, and soon to be generic in the US, utilization will increase if the cost savings occur as expected. Efforts to develop more selective JAKi are ongoing and time will tell if this will result in better safety as suggested by the early results with the TYK2 inhibitors. Multiple clinical trials in Lupus and other interferonopathies will read out in the next year or two which hopefully will provide additional treatment options for these patients. Studies are still ongoing further evaluating the VTE/MACE/malignancy signal in high risk patients, and for now adherence to regulatory agencies recommendations for risk stratification to avoid use in patients with high risk for cardiovascular disease and VTE is warranted.

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Conflicts of interest

There are no conflicts of interest.

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Eosinophilic granulomatosis with polyangiitis: recent therapeutic advances

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Purpose of review
The aim of this review is to describe the substantial advances that have been made in the past 2 years on new treatment options in eosinophilic granulomatosis with polyangiitis (EGPA).

Recent findings
The therapeutic scenario in EGPA has been recently broadened by the publication of the results from the multicenter, double-blind randomized MANDARA trial, which proved the noninferiority of benralizumab to another anti-interleukin-5 (IL-5) drug, mepolizumab, for the induction of remission in patients with EGPA. A few real-world studies have confirmed these results. Furthermore, the first randomized controlled trial exploring the efficacy of rituximab (anti-CD20) in induction of remission of EGPA was recently published. Targeting other molecular pathways did not always show adequate control of systemic manifestations of EGPA, with only limited evidence of effectiveness from small case series. Interestingly, cases of EGPA onset in severe asthma patients treated with monoclonal antibodies were described.

Summary
Biological drug therapy targeting IL-5 consolidated its role in the management of EGPA, becoming the cornerstone of the treatment of this rare disease. Future guidelines should consider these recent findings to improve the management of EPGA. Notably, while selective IL-5 targeting is highly effective for remission maintenance, its role in inducing remission in EGPA remains to be fully established. Rituximab was non-superior to standard therapy in induction of remission in patients with EGPA, demonstrating a similar rate of response. The role of other targeted therapies, albeit promising in some cases, remains a matter of debate.

Keywords
benralizumab, biologics, eosinophilic granulomatosis with polyangiitis, mepolizumab, tezepelumab

INTRODUCTION

Eosinophilic granulomatosis with polyangiitis (EGPA) is a rare small-vessel, anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis. The hallmarks of EGPA are asthma, chronic rhinosinusitis, eosinophilia and granulomatous or vasculitic involvement of several organs. Oral glucocorticoids and immunosuppressive drugs have long been the cornerstone of treatment for EGPA, despite the high burden of side effects. Interleukin 5 (IL-5) is a cytokine that plays a central role in eosinophil biology and therefore in the pathogenesis of EGPA; targeting IL-5-driven eosinophilic inflammation has been increasingly recognized as a key strategy in EGPA management. Mepolizumab, a monoclonal antibody that inhibits eosinophil activity by binding and sequestering IL-5, was the first targeted therapy that proved efficacious and safe in EGPA [1]. After the Food and Drug Administration (FDA) approval of mepolizumab at the dosage of 300 mg/4 weeks subcutaneously, a European multicenter observational study indicated the efficacy of mepolizumab also at 100 mg/4 weeks [2]. Since then, only one randomized controlled trial on anti-IL-5 treatment, namely benralizumab, has been concluded [3▪▪]; however,

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KEY POINTS

- Biologic therapies have a primary role in the management of EGPA.
- Targeting IL-5 is an already affirmed strategy in refractory and relapsing EGPA.
- The recent results of the MANDARA study made benralizumab part of the standard of care for EGPA.
- The REOVAS trial was the first to assess efficacy and safety of rituximab in inducing remission of severe EGPA.
- Targeting other molecular pathways, as well as combination therapies, long-acting anti-IL5 drugs and ANCA-driven strategies will be pursued in the next few years.

evidence has also grown about targeted therapies against other Th2-mediated inflammation markers (such as thymic stromal lymphopoietin, TSLP) and novel potential pathways (e.g. JAK signaling). The anti-CD20 monoclonal antibody rituximab, although already commonly used in clinical practice, is still an off-label therapy for induction of remission in EGPA: the first randomized controlled trial on rituximab in this disease was recently published [4▪▪].

EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS: FROM PATHOGENESIS TO TARGETED THERAPIES

EGPA is a rare small-vessel vasculitis characterized by asthma and eosinophilia with potential multiorgan involvement. Distinctive histological findings include tissue eosinophilia, necrotizing vasculitis and eosinophil-rich granulomatous inflammation. The reported incidence of EGPA ranged between 0.6 and 7.5 cases per million person-years over a period from 1994 to 2022, and its prevalence ranged from 9.0 to 58.6 cases per million people [5], with non-significant differences between men and women, and a mean age at diagnosis of ~50 years. Reported all-cause mortality in the overall EGPA population was 17.6% at 10 years according to a recent meta-analysis [5]. EGPA usually evolves through three distinct phases: a prodromic 'allergic' phase, hallmarked by asthma and chronic rhinosinusitis; an eosinophilic phase, during which eosinophilia and end-organ involvement appear; and a vasculitic phase, characterized by clinical manifestations due to small-vessel vasculitis [6]. ANCA, usually against myeloperoxidase (MPO), are detectable in about 30–40% of cases [7,8] and are associated with a more frequent occurrence of vasculitic manifestations (i.e. glomerulonephritis, peripheral neuropathy and purpura), whereas the so-called eosinophilic features (e.g. cardiac and gastrointestinal involvement, lung infiltrates) are more frequent in ANCA-negative patients. Asthma and ear-nose-throat (ENT) involvement are the most frequent clinical manifestations, irrespective of ANCA status. The pathogenesis of EGPA is driven both by genetic and environmental factors. The main *locus* having risk alleles associated with MPO-ANCA-positive EGPA is *HLA-DQ*, whereas ANCA-negative EGPA is mainly associated with genetic variants related to eosinophil biology or barrier dysfunction, such as *GPA33* and *IL5*[9].

Several cell types contribute to the immunopathogenesis of EGPA. Eosinophils play a leading role, as they are the main effectors of tissue damage. Eosinophilic inflammation driven by IL-5, a survival factor for eosinophils, is crucial in EGPA pathogenesis, as demonstrated by the efficacy of IL-5 inhibitors. CD4+ T cells with a helper 2 (Th2) phenotype orchestrate the adaptive immune response and enhance eosinophilic inflammation, while other T-cell phenotypes (Th1 and Th17) might have a role in vasculitis and granuloma formation. Finally, B cells also have pathogenic relevance, both in ANCA-positive and ANCA-negative patients; B-cell-depleting agents, namely rituximab, proved effective in inducing remission of EGPA in several real-world studies and in a recent randomized controlled trial, especially in patients with severe forms [4▪▪]. Intriguingly, a recent case series reported a reduction in ANCA levels associated with mepolizumab add-on treatment [10], suggesting a complex molecular and cellular cross-talk in EGPA.

Other molecular pathways involved in EGPA are related to interleukin-4 (IL-4) and interleukin-13 (IL-13), two effector cytokines produced by Th2 cells that play a role in early-phase Th2 inflammation, enhance IgE production and modulate eosinophilic inflammation. Dupilumab, a monoclonal antibody that engages the IL-4 receptor alpha (IL-4Rα) subunit (a shared component of both the IL-4 and IL-13 receptor complexes), has been tested with variable results in EGPA [11].

TSLP is an epithelium-derived cytokine released after environmental stimuli, which promotes eosinophil activity. Patients with EGPA have elevated levels of TSLP, and a *TSLP* gene polymorphism is associated with the risk of developing EGPA. Hence, TLSP is another molecule assessed as a potential target in EGPA, although still in very few reports [12,13].

Finally, the Janus kinase/signal transducer and activator of transcription (JAK/STAT) signaling pathway has been recently assessed as a potential target for EGPA [14▪], due to its pleiotropic role in immune system regulation, similarly to other systemic autoimmune diseases (e.g. rheumatoid arthritis).

Figure 1 summarizes EGPA pathogenesis including therapeutic molecular targets.

BIOLOGICS FOR EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS TREATMENT

The current treatment approach to EGPA is summarized in the last update of the EULAR recommendations for the management of ANCA-associated vasculitis [15]: mepolizumab and rituximab are the only biologic therapies mentioned, due to their already consolidated role in EGPA management at the date of guideline publication. Since then, the role of biologics in EGPA has been broadened by the publication of two randomized controlled trials (MANDARA, testing benralizumab, and REOVAS, testing rituximab) and several real-world evidence about other targeted therapies.

We performed a comprehensive literature search across major online bibliographic databases, including Ovid MEDLINE, Embase, and the Cochrane Library (CENTRAL). The following MeSH terms were employed: 'Eosinophilic Granulomatosis with Polyangiitis', 'EGPA', 'biological agents', 'biologics'. The

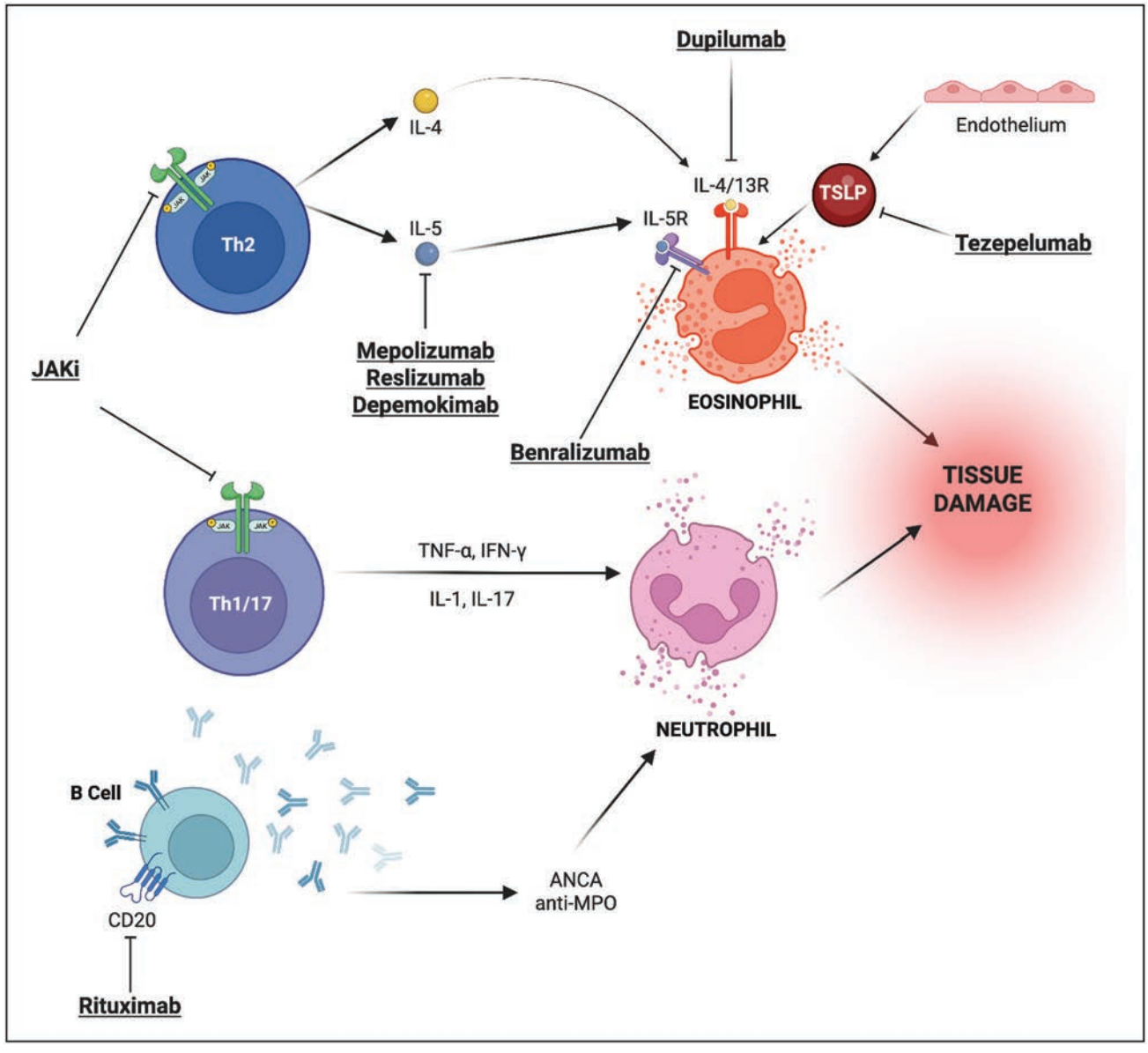

FIGURE 1. Main pathogenetic pathways of eosinophilic granulomatosis with polyangiitis with current and future therapeutic molecular targets.

search was implemented by screening the references of relevant systematic reviews and key original articles identified in the full-text screening process. Studies published in English language within the last 2 years (2024–2025) were included, as well as some other cornerstone studies published prior to 2024. Case reports and case series with a sample size of fewer than five patients were excluded.

Anti-IL5 therapies

Mepolizumab was the first anti-IL5 monoclonal antibody approved by FDA in EGPA. Regarding therapeutic positioning, mepolizumab is the preferred drug for maintenance of remission of relapsing EGPA with non-organ-threatening or non-life-threatening manifestations [15]. Long-term data on mepolizumab at the dosage of 300 mg/4 weeks were consistent with the known safety and efficacy profile of the drug in the MARS study [16]. However, while the dosage in the MIRRA trial was 300 mg/4 weeks [1], the asthma dosage (100 mg/4 weeks) [2] was frequently employed in patients with EGPA in a large observational retrospective study. This real-life study included both patients who received 100 and 300 mg/4 weeks: patient outcomes were quite similar, although the proportion of complete responses at month 24 was numerically higher among patients who received 300 mg/4 weeks. A step-down approach from 300 mg/4 weeks to 100 mg/4 weeks in patients with EGPA in stable remission, recently showed no asthma or vasculitis exacerbations over a median follow-up of 27.5 months [17▪], confirming the efficacy and safety of the lower dosage. In this real-life single-center study, 50% of patients maintained complete remission without glucocorticoid (GC) therapy, while 50% of patients had sinonasal symptoms relapses, treated with either increased mepolizumab dose or optimization of local therapy [17▪]. From the patient's perspective, mepolizumab was associated with a quick and remarkable improvement of health-related quality of life, according to the AAV-PRO questionnaire [18▪].

Benralizumab is a humanized monoclonal antibody that specifically binds the human interleukin-5 receptor α subunit (interleukin-5Rα) expressed on eosinophils, currently approved by the FDA for the treatment of severe eosinophilic asthma and EGPA. As an additional therapeutic mechanism, benralizumab leads to eosinophil apoptosis through antibody-dependent, cell-mediated cytotoxicity (ADCC). A first retrospective study of Cottu *et al*. [19] proved that benralizumab was effective for refractory asthma and ENT manifestations in EGPA and allowed GC sparing, but with a lower efficacy after failure of mepolizumab. A subsequent large retrospective, multicenter, cohort study by Bettiol *et al*. [20] further supports the use of benralizumab in clinical practice.

The MANDARA study was the first randomized controlled trial investigating benralizumab in EGPA. The trial showed noninferiority nor superiority of benralizumab (30 mg subcutaneously every 4 weeks) to mepolizumab (300 mg subcutaneously every 4 weeks) in inducing remission in adults with relapsing or refractory EGPA who were receiving standard care. Both drugs had a similar rate of achievement of the primary endpoint at weeks 36 and 48, defined as a Birmingham Vasculitis Activity Score (BVAS) = 0, indicating no disease activity, and an oral GC dose of 4 mg/day or less, and a similar frequency of relapses (30% in both arms). However, at weeks 48–52, the mean GC dose was lower in the benralizumab group and the percentage of patients who completely tapered off GC was higher in this group. The open-label extension of the MANDARA trial confirmed durable rates of remission, with discontinuation of oral GC, blood eosinophil depletion and low relapse rates; switching from mepolizumab to benralizumab resulted in deeper blood eosinophil depletion and oral GC sparing [21▪]. Accordingly, in a post-hoc analysis of MANDARA, benralizumab showed a greater rate of complete remission (BVAS = 0 and oral GC dose $\leq$0 mg/day at weeks 36 and 48) and of complete sustained remission (complete remission criteria met by week 48 and sustained until the end of 52 weeks). The overall results of the MANDARA study were also recently confirmed by a large European real-life retrospective comparative study performed by the European EGPA Study Group that investigated similar primary and secondary endpoints [22▪]. In this study, both benralizumab and mepolizumab were used at asthma-approved dosage. In detail, benralizumab achieved a higher complete response rate at 12 months, together with a deeper peripheral eosinophil reduction. An overall high percentage of complete remission together with a significant reduction in GC dose (estimated effect of −8.25 mg/day) was also confirmed in a meta-analysis of eight studies, including both randomized controlled trials and observational studies [23].

Reslizumab is the third IL-5 inhibitor currently approved for asthma treatment. This monoclonal antibody binds to the alpha chain of the IL-5 receptor on the eosinophil surface, inhibiting the activation and proliferation of eosinophils. We have found only an open-label, pilot study about intravenous reslizumab (3 mg/kg every 4 weeks) in EGPA in 10 patients that showed a significant reduction in daily oral GC. Of the 10 subjects, three experienced an EGPA exacerbation during treatment, while one had a severe adverse event, requiring treatment withdrawal [24]. This treatment option remains off-label and requires

further validation (ongoing open-label trial – RITE study, NCT02947945).

Finally, a randomized, double-blind controlled trial on depemokimab vs. mepolizumab is currently ongoing (NCT05263934). Depemokimab is an ultra-long-acting biologic therapy with enhanced binding affinity for IL-5 that may enable 6-month dosing intervals. The new molecule SHR-1703 (Jiangsu Hengrui Pharmaceuticals Co., Lianyungang, Jiangsu, China) is a novel humanized IgG1 monoclonal antibody with high IL-5 affinity and prolonged half-life, and is currently under investigation in a double-blind, placebo-controlled trial (NCT05583227).

Taken together, the data obtained so far regarding IL5 pathway-targeting agents support the use of benralizumab as an effective option for EGPA, and confirm mepolizumab long-term efficacy and safety profile. The main additional advantages of benralizumab suggested by few studies seem to be a higher rate of complete remission and a greater GC-sparing effect. Some studies also showed a deeper blood eosinophil rate depletion, while traditional immunosuppressants tapering was poorly investigated. We can hypothesize that these findings can be partially explained by the double effect of benralizumab in inhibiting eosinophilic-driven inflammation: the direct binding of IL-5Rα and the ADCC. Clinicians should take into account these differences when prescribing anti-IL5 therapies in patients with EGPA. Reslizumab, depemokimab and other molecules targeting IL-5 and eosinophils are currently under investigation.

Table 1 describes the main differences between mepolizumab and benralizumab according to registration studies.

Inducing remission in new-onset eosinophilic granulomatosis with polyangiitis: limitations of anti-IL5 therapies

Despite the remarkable results described above, anti-IL5 therapies were poorly assessed in inducing remission in new-onset EGPA, particularly in severe cases, and are not currently used for this indication. A retrospective study involving 19 European EGPA Study Group centers showed that out of 529 EGPA patients, 30 (5.7%) developed the disease during anti-Th2 therapy for severe asthma. Eight of these 30 cases (27%) were on benralizumab, four (13%) were on mepolizumab 100 mg and one (3%) on reslizumab at the time of EGPA onset [25▪]. Most patients (87%) were not on GC at the time of vasculitis onset and had higher blood eosinophilic count. Notably, after the induction of EGPA remission, 24/30 (80%) patients were treated again with an anti-Th2 monoclonal antibody for remission maintenance; nine patients received the same drug that was administered at EGPA onset (benralizumab-1, mepolizumab-6) [25▪]. Despite most cases occurred on other anti-Th2 therapies (omalizumab, dupilumab), these findings may suggest that anti-IL5 drugs could fail in preventing EGPA onset. These results could be explained by the features of study population (off GC and high eosinophil count at EGPA onset) and by EGPA pathogenesis, as anti-IL5 therapies only partially address the pathogenic mechanisms of the disease.

Anti-CD20 therapies

Rituximab is a chimeric monoclonal antibody against CD20, an antigen found on the surface of B cells. While rituximab is already approved by the FDA for inducing and maintaining remission in other ANCA-associated vasculitis (i.e. microscopic polyangiitis and granulomatosis with polyangiitis), it is off-label for EGPA. The first consistent data supporting its use for EGPA was the retrospective study by Mohammad *et al*. [26], showing efficacy of rituximab in 41 patients with refractory, relapsing or new-onset EGPA with also a GC-sparing effect. In this study, ANCA positivity at baseline was associated with a higher remission rate at 12 months. Two subsequent retrospective studies supported the efficacy of rituximab in EGPA: one reporting its benefit in maintaining remission, and another showing overall efficacy but limited control of asthma and ENT relapses. In both studies, the ANCA-positive subset appeared to respond slightly better [27,28]. On this basis, Bettiol *et al*. [20] conducted a retrospective study on sequential rituximab and mepolizumab in EGPA, confirming previous literature evidence on the efficacy of rituximab for the control of systemic EGPA manifestations, while mepolizumab allowed reducing asthma and contributed to the sustained remission of systemic features and GC-sparing.

The recent REOVAS trial was the first to investigate rituximab for EGPA in a randomized controlled setting [3▪▪]. The study compared GC plus rituximab (1 g 2 weeks apart) with the conventional strategy (GC alone or in combination with cyclophosphamide in severe forms) for induction of remission in 105 patients with active disease, defined as a BVAS of 3 or greater. There was no statistically significant difference between the two groups in rate of primary end-point (remission defined as a BVAS = 0 and a prednisone dose of 7.5 mg/day or less at day 180) and secondary end-points: duration of remission during the study, relapse and major relapse rates, average daily GC dose and adverse events. In detail, 63.5% of patients in the rituximab group achieved the primary end-point compared with 60.4% in the control group [relative risk, 1.05 (95% CI, 0.78–1.42); $P = 0.75$]. The mean duration

Table 1. Main findings of the MIRRA and MANDARA trials

Study	Design and sample size	Dosage	Primary end-point	Complete remission	GC-sparing effect	AEs
MIRRA trial, Welscher *et al.*, 2017	Multicenter, double-blind, parallel-group trial; 168 patients with relapsing or refractory EGPA	1 : 1 SOC plus placebo vs. SOC plus mepolizumab 300 mg/4 weeks for 52 weeks	Accrued weeks of remission over a 52-week period, and the proportion of participants in remission at both week 36 and week 48	28% of accrued weeks of remission in mepolizumab group vs. 3% in the placebo group [odds ratio, 5.91; 95% confidence interval (CI), 2.68–13.03; $P < 0.001$); higher percentage of participants in remission at both week 36 and week 48 (32 vs. 3%; odds ratio, 16.74; 95% CI, 3.61–77.56; $P < 0.001$)	Average daily dose of prednisolone or prednisone of 4 mg or less per day during weeks 48 through 52 in 44% of the participants in the mepolizumab group and in 7% of those in the placebo group	No significant difference between the mepolizumab group and the placebo group in adverse event (97 and 94%, respectively); serious adverse events 18 vs. 26%
MANDARA trial, Welscher, 2024	Multicenter, double-blind randomized, active-controlled noninferiority trial; 140 patients with relapsing or refractory EGPA	1 : 1 SOC plus mepolizumab 300 mg/4 weeks vs. SOC plus benralizumab 30 mg/4 weeks for 52 weeks	Remission at weeks 36 and 48	59% in the benralizumab group and 56% in the mepolizumab group [difference, 3 percentage points; 95% confidence interval (CI), –13 to 18; $P = 0.73$ for superiority)	Complete withdrawal of oral GC during weeks 48 through 52 in 41% of benralizumab group and 26% of mepolizumab group	90% of the patients in the benralizumab group (6% serious) and 96% of those in the mepolizumab group (13% serious)

EGPA, eosinophilic granulomatosis with polyangiitis; GC, glucocorticoid; SOC, standard of care

of remission was 48.5 ± 6.5 weeks in the rituximab group and 49.1 ± 7.4 weeks in the conventional strategy group ($P = 0.41$) [3▪▪]. The trial results, therefore, suggest that adding rituximab to conventional GC for non-severe EGPA does not provide a significant advantage, while in severe forms, the drug seems to have comparable efficacy to that of cyclophosphamide. It must be acknowledged, however, that the trial design could not allow the assessment of equivalence between rituximab and cyclophosphamide.

Beyond IL-5: emerging targeted therapies

Dupilumab is an anti-IL-4/IL-13 antibody primarily investigated in patients with EGPA and refractory ENT symptoms [11]. The results coming from a European multicenter retrospective study suggested that dupilumab may be effective in treating patients with EGPA-related ENT manifestations, but with a considerable number of EGPA flares (one-third of patients), often preceded by eosinophilia (88% of relapses). Caution is required in using dupilumab, especially in patients with uncontrolled systemic manifestations. Another recent small prospective observational study confirmed the efficacy of dupilumab in controlling refractory chronic rhinosinusitis in EGPA [29]; again, a high rate of adverse events, including hypereosinophilia, was observed, with need of dupilumab discontinuation in a few cases.

To date, tezepelumab, a monoclonal antibody that specifically binds TSLP, proved efficacious in EGPA only in small case series [13]. Nanzer *et al.* [13] described the effectiveness of tezepelumab in eight patients with refractory, GC-dependent EGPA despite anti-IL5/5R therapy, reporting a significant improvement in BVAS, a reduction in the median annualized relapse rate and a non-significant GC dosage reduction. Two ongoing randomized clinical trials will clarify the role of tezepelumab in EGPA (RACEMATE study – NCT06230354, CROSSING study – NCT05583227).

With regards to JAK inhibitors, only a small prospective single-center study was conducted so far [14▪]. Eleven active patients, of which five newly diagnosed and six with refractory EGPA, received oral tofacitinib 5 mg twice daily with a follow-up period

of 3–48 months. Three months after tofacitinib treatment, most patients (10/11) responded with a rapid relief of clinical symptoms. The response rate (complete and partial remission) was 100% at 6 and 9 months. The complete response rate at 6 and 9 months was 60 and 80%, respectively. Tofacitinib showed efficacy also in controlling laboratory parameters (normalization of erythrocyte sedimentation rate and C-reactive protein at 6 months, significant decrease in eosinophil count), together with a consistent GC-sparing effect and no relapse during the median follow-up period of 15 months [14▪]. An ongoing trial on a new JAK inhibitor (NS-229, NCT06046222) will provide further data about the usefulness of targeting this molecular pathway in EGPA.

Figure 2 reports the main completed and ongoing trials on biologics in EGPA.

CONCLUSION

Biologic therapies targeting the IL-5 pathway have changed the management of EGPA in the last few years. Both mepolizumab and benralizumab are effective in maintaining remission in EGPA with a remarkable GC-sparing effect and complete remission rate. However, the onset of EGPA in asthma patients on anti-IL5 therapies suggest that mepolizumab and

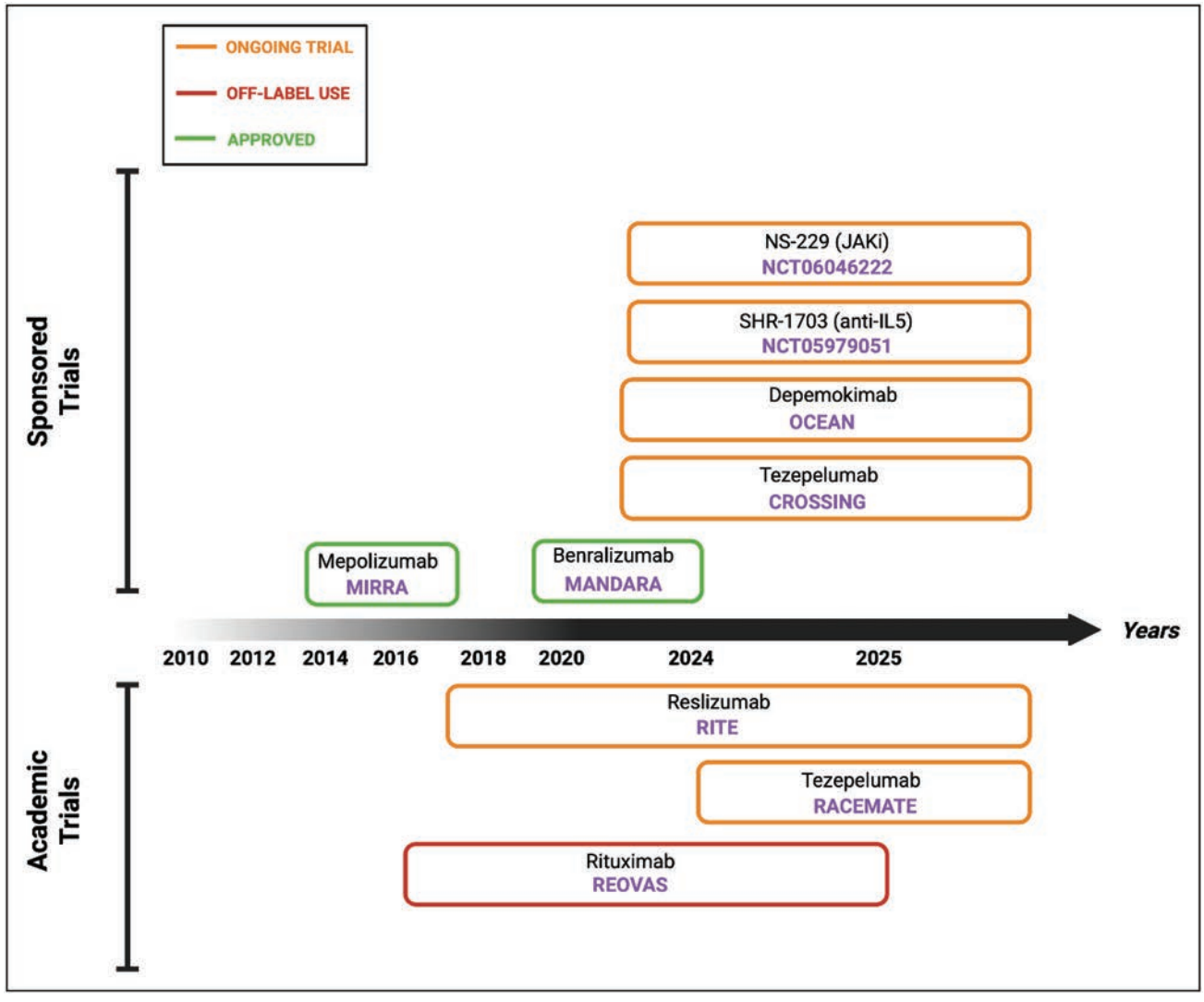

FIGURE 2. The main sponsored and academic trials on biologic therapies for eosinophilic granulomatosis with polyangiitis. Two drugs are currently approved by regulatory agencies (green boxes): mepolizumab (FDA and EMA) and benralizumab (FDA). The REOVAS trial (red box) was recently completed, but rituximab is still used as an off-label therapy. Finally, the ongoing trials are shown in the orange boxes: three trials on anti-IL5 therapies (reslizumab, depemokimab, SHR-1703); two trials on anti-TSLP (tezepelumab); one trial on a novel JAKi (NS-229). EGPA, eosinophilic granulomatosis with polyangiitis; EMA, European Medicines Agency; FDA, Food and Drug Administration.

benralizumab might fail in fully preventing EGPA occurrence of new-onset cases, highlighting the need for a careful therapeutic positioning of these biologics. Future research is needed to investigate the usefulness of other anti-IL-5 drugs (e.g. reslizumab), while targeting IL-4/IL-13 seems to be an option for selected patients only (namely those with ENT refractory manifestations, with mild systemic involvement). Regarding induction of remission, the REOVAS trial showed no superiority of rituximab as compared to standard regimens (GC or GC plus cyclophosphamide). Although the trial's aim was to investigate superiority of rituximab and the result was negative, this is the first randomized trial assessing an anti-CD20 therapy in inducing remission of EGPA.

Looking ahead, there are still some interesting points to assess to improve EGPA management. First, the ultra-long-acting anti-IL5 drug depemokimab could offer an effective and patient-smart alternative to traditional monthly anti-IL5 therapies, targeting a well-known pathogenetic pathway. Second, tezepelumab (anti-TSLP) and tofacitinib (JAKi) could broaden the landscape of molecular targets in EGPA, overcoming the central role of IL-5. Third, combination therapies have been poorly investigated, but could be an effective option for difficult-to-treat manifestations. Finally, although a clinical phenotype of patients with EGPA based to the ANCA status has been proposed in the last years, data is still lacking to suggest specific ANCA-driven therapeutic strategies.

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Conflicts of interest

There are no conflicts of interest.

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This trial was the first to investigate rituximab efficacy and safety in inducing remission of EGPA. Designed to demonstrate superiority of rituximab to standard therapies (GC or GC plus cyclophosphamide in nonsevere and severe EGPA, respectively), it showed no significant differences in rate of remission and other secondary end-points. The trial was not powered to investigate noninferiority of rituximab, but the overall results were similar for each arm.

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JAK inhibitors already proved effective in other systemic autoimmune diseases and are currently under investigation also in EGPA. This study provided preliminary but interesting data regarding JAK-inhibitors for EGPA.

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Efficacy and safety of mepolizumab also at the dosage of 100 mg/4 weeks were reported in this real-life study.

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