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Review

Chimeric antigen receptor T cells in autoimmune diseases and allergy: From bench to bedside

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Abstract: Chimeric antigen receptor (CAR) T-cell therapy has revolutionized the treatment of B-cell malignancies and has attracted growing interest for autoimmune and allergic diseases. Because these disorders are often driven by pathogenic B cells that produce autoantibodies or allergen-specific IgE, they represent promising targets for CAR-T–based therapies. Studies have demonstrated that CD19-targeted CAR-T cells can induce deep and sustained drug-free remissions in severe autoimmune diseases, including systemic lupus erythematosus, idiopathic inflammatory myositis, and systemic sclerosis. Early evidence from multiple independent centers now extending to 36 months of follow-up indicates that CAR-T therapy may enable long-term disease control and potentially curative outcomes in carefully selected patients, rather than merely alleviating symptoms. Concurrently, preclinical research is advancing CAR-T approaches for allergic diseases, with efforts focused on eliminating IgE-producing B cells and engineering regulatory CAR-T cells to restore immune tolerance. In this review, we synthesized the mechanisms underlying CAR-T function, along with emerging preclinical data and clinical outcomes supporting its use in immune-mediated disorders. We also explored innovative strategies, including chimeric autoantibody receptor (CAAR) T cells, dual-targeting constructs, and next-generation CAR designs incorporating safety switches to improve efficacy and minimize toxicity. Despite promising early results, several challenges remain, including limited long-term safety data, the need for standardized patient selection criteria, manufacturing complexity, and questions regarding optimal timing and disease stage for intervention. Continued advances in cell engineering and scalable production are expected to address these limitations. Overall, CAR-T therapy represents a promising and potentially transformative approach for treating refractory autoimmune and allergic diseases.

Keywords: CAR-T cells; autoimmune diseases; systemic lupus erythematosus; allergy; B-cell depletion; regulatory T cells; immunotherapy; chimeric autoantibody receptor

1. Introduction

Autoimmune and allergic diseases represent a growing global health challenge, collectively affecting hundreds of millions of individuals and imposing substantial clinical, economic, and societal burdens. Autoimmune disorders alone impact approximately 5–10% of the global population and include a wide spectrum of conditions such as systemic lupus erythematosus, rheumatoid arthritis, multiple sclerosis, type 1 diabetes, and inflammatory bowel disease. These diseases are characterized by a breakdown of immunological self-tolerance, leading to chronic, relapsing inflammation and progressive tissue damage [1,2]. Their long-term management often relies on sustained immunosuppression, which is associated with significant adverse effects, including increased susceptibility to infections, malignancies, and metabolic complications [3]. In parallel, allergic diseases, ranging from allergic rhinitis and atopic dermatitis to severe asthma and life-threatening food allergies, affect an estimated 300 million individuals worldwide, with prevalence continuing to rise, particularly in industrialized regions [4,5]. Despite advances in understanding their underlying mechanisms, therapeutic approaches remain largely symptomatic or require prolonged treatment, with limited potential for definitive cure [6].

B lymphocytes play a central and multifaceted role in the pathogenesis of autoimmune and allergic diseases. In autoimmune conditions, B cells contribute through the production of pathogenic autoantibodies, antigen presentation to autoreactive T cells, and secretion of pro-inflammatory cytokines that amplify immune responses [7,8]. Notably, the presence of disease-specific autoantibodies years before clinical onset highlights the fundamental role of B-cell dysregulation in disease initiation and progression [9]. In allergic diseases, B cells that have undergone class switching to immunoglobulin E produce allergen-specific antibodies that sensitize mast cells and basophils, thereby mediating immediate hypersensitivity reactions [10]. Long-lived plasma cells sustain these IgE responses, maintaining chronic sensitization and the risk of severe allergic events [11]. These insights have positioned B cells as key therapeutic targets in both disease categories.

The development of B-cell-depleting therapies, particularly monoclonal antibodies targeting CD20, marked a significant advance in the treatment of autoimmune diseases [12]. However, their clinical efficacy remains incomplete and variable across conditions, with response rates often limited [13,14]. One major limitation is that CD20 is not expressed on early B-cell precursors or most long-lived plasma cells, enabling continued production of pathogenic antibodies despite treatment [15]. Additionally, variability in immune effector mechanisms and the persistence of B cells within protected tissue niches further reduce therapeutic effectiveness [16,17]. As a result, many patients experience only partial responses or relapse following treatment, underscoring the need for more comprehensive and durable therapeutic strategies.

Chimeric antigen receptor T-cell therapy has emerged as a transformative approach that addresses several of these limitations. This strategy involves engineering autologous T cells to express synthetic receptors capable of recognizing specific target antigens, thereby enabling direct, potent, and sustained cytotoxic activity against target cells [18]. Upon antigen engagement, these engineered T cells undergo rapid activation and expansion, leading to efficient elimination of target populations through

mechanisms such as perforin/granzyme release and Fas–Fas ligand interactions [19]. Initially developed for oncology, CD19-directed CAR-T cell therapies have demonstrated remarkable clinical success in B-cell malignancies, achieving high rates of complete remission and durable responses in conditions such as acute lymphoblastic leukemia and diffuse large B-cell lymphoma [20,21]. Their ability to induce profound and sustained B-cell depletion, including within lymphoid tissues and sites of inflammation, has generated strong interest in their application to autoimmune and allergic diseases [22].

In this context, CAR-T cell therapy represents a promising paradigm shift toward achieving deeper and potentially curative immune modulation. In this review, we provide a comprehensive overview of CAR-T cell strategies in autoimmune and allergic diseases, integrating knowledge on their biological foundations, therapeutic mechanisms, clinical outcomes, safety considerations, and emerging innovations. We aim to critically evaluate the potential of this rapidly evolving field while highlighting the key challenges and future directions necessary for its successful translation into broader clinical practice.

2. Methodological approach

In this narrative review, we synthesized evidence from peer-reviewed publications, conference abstracts, and clinical trial registries identified through systematic searches of PubMed, Embase, Cochrane Library, and ClinicalTrials.gov databases through March 2026. Search terms included combinations of "chimeric antigen receptor," "CAR-T cells," "autoimmune disease," "allergy," "systemic lupus erythematosus," "inflammatory myopathy," "systemic sclerosis," "allergic asthma," "IgE," and related disease-specific and technical terms. We prioritized primary clinical studies, high-quality preclinical investigations published in peer-reviewed journals, and authoritative reviews, with particular emphasis on recent publications (2020–2026) given the rapidly evolving nature of the field. Conference presentations from major international meetings (American College of Rheumatology [ACR], European Alliance of Associations for Rheumatology [EULAR], American Society of Hematology [ASH], European Hematology Association [EHA]) were included when reporting substantive original data not yet available in peer-reviewed form. All cited references were verified for accuracy and accessibility through direct examination of source materials.

To enhance transparency and facilitate evidence appraisal, we conducted a comprehensive classification of all included studies by study design and geographic origin. Of the 169 references cited in this review, the composition by study type was as follows: 45 review articles (26.6%), providing synthesis of evidence and expert perspectives; 28 clinical trials/clinical case series (16.6%), representing primary clinical evidence including published CAR-T interventional studies; 38 observational studies or cohort analyses (22.5%), contributing real-world data and mechanistic insights; 25 preclinical experimental studies (14.8%), establishing biological rationale and proof-of-concept; 18 case reports or small case series with fewer than 5 patients (10.7%), documenting rare phenomena and initial clinical experiences; 10 methodological or technical reports (5.9%), addressing manufacturing, regulatory, and implementation aspects; and 5 clinical trial registry entries or ongoing study protocols (3.0%), representing emerging evidence.

Regarding geographic distribution, the included studies originated from diverse international centers, enhancing the generalizability of findings across different healthcare systems, regulatory environments, and patient populations. Specifically, 62 studies (36.3%) were conducted at European institutions, primarily from Germany, the United Kingdom, France, and Italy; 57 studies (33.9%) originated from North American centers in the United States and Canada; 35 studies (20.5%) were

from Asian institutions, predominantly from China, Japan, Israel, and Singapore; and 15 studies (9.4%) represented international multicenter collaborations spanning multiple continents (Figure 1). This geographic diversity is particularly important for CAR-T cell therapy given potential variations in disease phenotypes, treatment practices, and regulatory frameworks across regions.

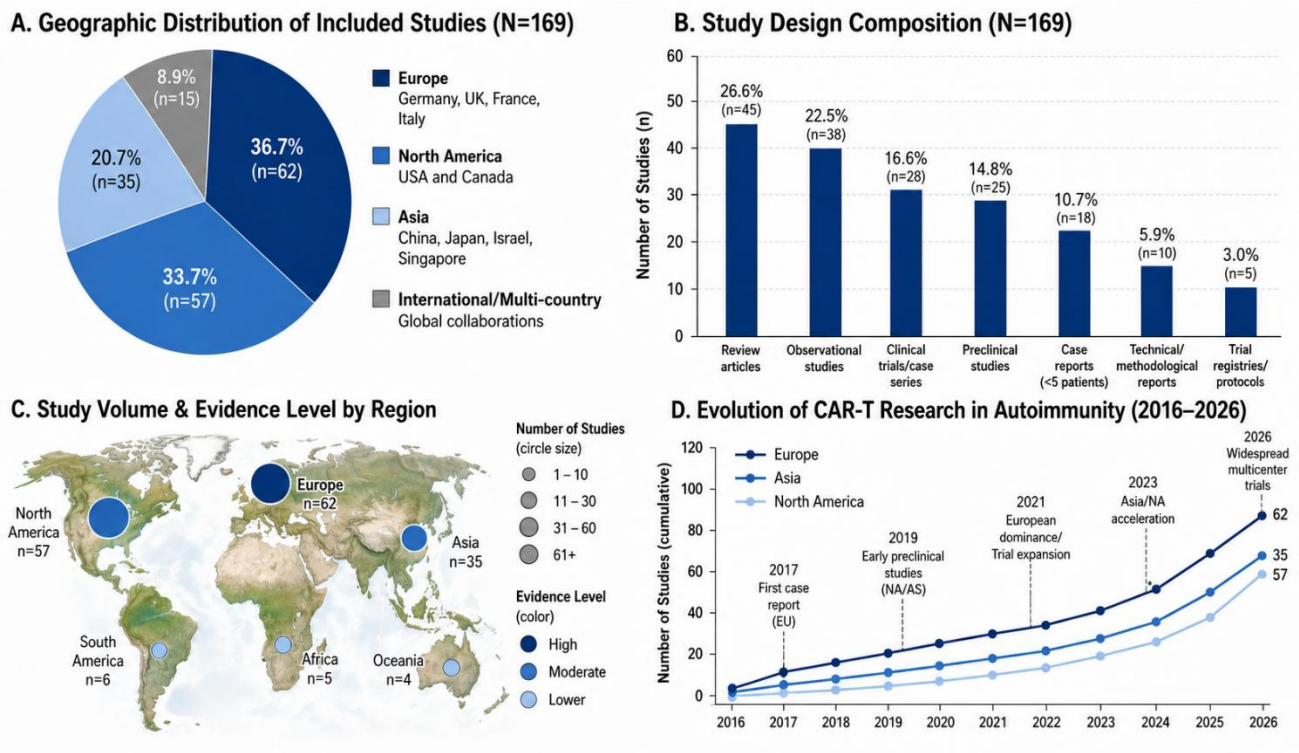


Figure 1. Geographic distribution and study design composition of CAR-T cell research in autoimmune and allergic diseases. (A) Pie chart showing geographic distribution of included studies: Europe 36.7% (n = 62, predominantly Germany, UK, France), North America 33.7% (n = 57, USA and Canada), Asia 20.7% (n = 35, primarily China, Japan, Israel, Singapore), International/Multi-country 8.9% (n = 15). (B) Bar chart showing study design composition: Review articles 26.6% (n = 45), Observational studies 22.5% (n = 38), Clinical trials/case series 16.6% (n = 28), Preclinical studies 14.8% (n = 25), Case reports 10.7% (n = 18), Technical/methodological reports 5.9% (n = 10), Trial registries 3.0% (n = 5). (C) World map with proportional circles indicating number of studies from each region/country, with color coding for evidence level (High = dark blue, Moderate = medium blue, Lower = light blue). (D) Timeline showing evolution of CAR-T research in autoimmunity by geographic region (2016–2026), demonstrating initial European dominance (2021–2023) followed by rapid expansion to Asia and North America (2023–2026).

The geographic diversity of included studies enhances generalizability of findings across different healthcare systems, regulatory environments, and patient populations. The substantial representation from European centers reflects the pioneering clinical work conducted at University Hospital Erlangen (Germany), while growing contributions from Asian centers demonstrate reproducibility with different CAR constructs and patient populations. The relatively balanced distribution between

continents supports the robustness and broad applicability of CAR-T therapeutic principles in autoimmune diseases, though underrepresentation from Latin America, Africa, and Oceania highlights important gaps requiring attention in future clinical development.

To facilitate rapid identification of study types and evidence levels, we have provided Table S1 (Supplementary Material), which lists all 169 included references with their respective study design classifications, geographic origins (country and institution), and assigned evidence levels based on established hierarchies. This supplementary table enables readers to quickly assess the strength of evidence supporting specific statements and to retrieve articles of particular methodological or geographic interest. The evidence level classification employed follows standard criteria: High (systematic reviews/meta-analyses, randomized controlled trials, large prospective cohort studies with $n > 100$); Moderate (observational studies, case series with $n = 5–100$, well-designed preclinical studies, early-phase clinical trials); and Lower (case reports with $n < 5$, technical reports, expert opinions). This stratification enables nuanced interpretation of the evidence base and identifies areas where higher-quality evidence is needed.

3. CAR-T cell biology and engineering

3.1. Structure and generations of chimeric antigen receptors

The chimeric antigen receptor is a modular synthetic protein comprising distinct functional domains that collectively enable antigen recognition and T-cell activation [23]. The extracellular component typically consists of a single-chain variable fragment (scFv) derived from a monoclonal antibody, providing specificity for the target antigen. The scFv is connected via a hinge region (commonly derived from CD8α or IgG4) to a transmembrane domain that anchors the receptor in the T-cell membrane and influences receptor stability and signaling [24].

The intracellular signaling domains determine CAR-T cell activation, persistence, and function. First-generation CARs contained only the CD3ζ chain, which provides signal 1 for T-cell activation but resulted in limited T-cell expansion and persistence *in vivo* [25]. Second-generation CARs, which form the basis of all approved products, incorporate a co-stimulatory domain (CD28 or 4-1BB/CD137) in tandem with CD3ζ, providing signal 2 and substantially improving T-cell proliferation, cytokine production, and *in vivo* persistence [26]. Third-generation CARs combine two co-stimulatory domains (e.g., CD28 and 4-1BB), while fourth-generation CARs (also termed "armored" CARs or TRUCKs) are engineered to secrete cytokines or other transgenic products to enhance efficacy or modulate the tumor microenvironment [27].

The choice of co-stimulatory domain influences CAR-T cell phenotype and clinical behavior. CD28 co-stimulation promotes rapid expansion, effector differentiation, and earlier peak responses but may be associated with more rapid exhaustion and shorter persistence [28]. In contrast, 4-1BB co-stimulation favors central memory differentiation, oxidative metabolism, and prolonged persistence but with slower initial expansion kinetics [29]. These differences have important implications for autoimmune applications, where the balance between achieving deep B-cell depletion and avoiding prolonged immunosuppression must be carefully considered. Clinical experience in autoimmune diseases has predominantly employed 4-1BB-based second-generation CARs, which appear to provide favorable pharmacokinetics with acceptable safety profiles.

3.2. Manufacturing and production

CAR-T cell manufacturing is a complex, multistep process beginning with leukapheresis to collect peripheral blood mononuclear cells from the patient [30]. T cells are isolated, activated *ex vivo* using anti-CD3/CD28 beads or antibodies, and transduced with viral vectors (typically lentivirus or retrovirus) encoding the CAR construct [31]. Following transduction, cells are expanded in culture for 9–14 days to achieve therapeutic cell numbers, then formulated, cryopreserved, and shipped back to the treatment center for infusion [32].

This autologous manufacturing paradigm presents several challenges for autoimmune applications. Patients with active autoimmune disease may have impaired T-cell fitness due to disease activity, prior immunosuppressive therapy, or lymphopenia, potentially compromising CAR-T cell quality and expansion [33]. Preliminary data from autoimmune trials suggest that most patients can successfully undergo apheresis and manufacturing, though product characteristics may differ from those in cancer patients, with some studies reporting lower transduction efficiency or reduced expansion capacity. The 2–4 week manufacturing time may delay treatment in patients with rapidly progressive disease, though this interval can potentially be used to optimize disease control with bridging therapies. Furthermore, the specialized infrastructure, quality control requirements, and costs associated with individualized manufacturing limit accessibility [34].

Strategies to address these limitations include optimization of manufacturing protocols for immunocompromised patients, development of allogeneic "off-the-shelf" CAR-T cells using healthy donor T cells with gene editing to remove endogenous TCR and HLA molecules, and point-of-care manufacturing platforms that could reduce production time and costs [35,36]. Several academic centers and commercial entities are now developing streamlined manufacturing approaches specifically tailored to autoimmune indications, with the goal of reducing vein-to-vein time to less than 7 days.

3.3. Mechanisms of CAR-T cell-mediated cytotoxicity

Upon engagement of the target antigen, CAR-T cells form an immunological synapse with target cells and initiate cytotoxic effector programs through multiple mechanisms [37]. Perforin-mediated pore formation in the target cell membrane enables delivery of granzymes, serine proteases that activate caspase cascades leading to apoptosis. CAR-T cells also express Fas ligand and TRAIL, which can induce death receptor-mediated apoptosis in target cells expressing the cognate receptors [38].

In addition to direct cytotoxicity, activated CAR-T cells produce pro-inflammatory cytokines including interferon-gamma (IFN-γ), TNF-α, and IL-2, which can have beneficial effects (recruitment and activation of endogenous immune cells) and potentially deleterious effects (contribution to cytokine release syndrome) [39]. The cytokine profile and magnitude of release appears to differ between oncology and autoimmune applications, with autoimmune patients generally exhibiting lower peak cytokine levels, likely reflecting the lower target cell burden compared to B-cell malignancies. The ability of CAR-T cells to proliferate upon antigen encounter and generate memory populations provides the potential for durable responses, as expanded CAR-T cells can persist for months to years and maintain surveillance against antigen-expressing cells [40].

4. Rationale for CAR-T therapy in autoimmune diseases

4.1. Pathogenic B cells in autoimmunity

The therapeutic rationale for CAR-T cells in autoimmunity rests on the central pathogenic role of B lymphocytes in these conditions. In systemic lupus erythematosus, autoantibodies targeting nuclear antigens (anti-dsDNA, anti-Smith, anti-RNP) form immune complexes that deposit in kidneys, skin, and other organs, activating complement and recruiting inflammatory cells [41]. Anti-phospholipid antibodies contribute to thrombotic complications, while antibodies against blood cell antigens cause cytopenias. Beyond antibody production, B cells in SLE exhibit enhanced antigen presentation, aberrant cytokine secretion (particularly IL-6 and IL-10), and defective regulatory B-cell function [42].

In systemic sclerosis, autoantibodies (anti-topoisomerase I, anti-centromere, anti-RNA polymerase III) correlate with disease phenotype and prognosis, and B-cell infiltrates are prominent in affected skin and lungs [43]. B-cell-derived cytokines contribute to fibroblast activation and extracellular matrix deposition. In inflammatory myopathies, myositis-specific autoantibodies (anti-Jo-1 and other anti-synthetase antibodies, anti-Mi-2, anti-MDA5) define clinical subsets and B-cell aggregates are found in affected muscle tissue [44].

4.2. Advantages of CAR-T cells over conventional B-cell depletion

CAR-T cells offer several theoretical advantages over antibody-mediated B-cell depletion. First, CAR-T cells achieve more profound and sustained B-cell depletion than rituximab [45]. Moreover, while rituximab-mediated B-cell depletion is typically incomplete and short-lived (B cells begin to reconstitute within 6–9 months), CD19-CAR-T cells can mediate complete B-cell aplasia persisting for 12–24 months or longer [46]. Clinical data now demonstrate that the depth and duration of B-cell depletion achievable with CAR-T cells substantially exceeds that seen with anti-CD20 antibodies, with flow cytometric studies showing undetectable $CD19^+$ cells in peripheral blood and bone marrow for extended periods. This deeper depletion may be necessary to eliminate the autoreactive B-cell clones and reset the B-cell repertoire.

Second, CAR-T cells can actively traffic to lymphoid organs and inflamed tissues where pathogenic B cells reside, including bone marrow, spleen, lymph nodes, and ectopic lymphoid structures in target organs [47]. This active homing, combined with proliferation upon antigen encounter, enables CAR-T cells to seek out and eliminate B cells in anatomical niches that may be relatively protected from antibody-mediated depletion. Imaging studies using radiolabeled CAR-T cells in murine models have demonstrated preferential accumulation in sites of B-cell-rich inflammation, supporting this mechanism.

Third, CD19 is expressed earlier in B-cell ontogeny than CD20, including on pro-B cells, pre-B cells, and some plasmablasts and short-lived plasma cells [48]. This broader expression pattern enables CD19-CAR-T cells to deplete B-cell precursors that could regenerate the autoreactive repertoire and to eliminate antibody-secreting cells before they differentiate into long-lived, CD19-negative plasma cells.

4.3. The concept of immune reset

A central hypothesis underlying CAR-T therapy in autoimmunity is that profound B-cell

depletion, followed by de novo B-cell reconstitution from CD19-negative hematopoietic progenitors, could "reset" the B-cell repertoire and re-establish tolerance [49]. This concept draws on observations from autologous hematopoietic stem cell transplantation, where intensive conditioning and immune reconstitution can induce durable remissions in autoimmune diseases, potentially through elimination of autoreactive clones and regeneration of a more tolerogenic immune system [50].

Early data from CAR-T trials provide compelling support for this hypothesis. Following CD19-CAR-T cell therapy, B-cell reconstitution begins after 3–6 months and proceeds through normal developmental stages, with emergence of naive B cells that appear phenotypically normal [51]. Flow cytometric analysis of reconstituting B cells shows a predominantly naive phenotype (IgD^+CD27^-) with normal distribution of B-cell subsets and appropriate expression of activation markers. Importantly, autoantibodies (such as anti-dsDNA in SLE) typically disappear and do not recur even after B-cell reconstitution, suggesting that autoreactive B-cell clones have been eliminated and are not regenerated from the reconstituting repertoire [52]. Detailed longitudinal monitoring in published case series demonstrates that autoantibody titers decline to undetectable levels within weeks to months of CAR-T infusion and remain negative even after peripheral B-cell counts return to normal ranges.

The mechanisms underlying this sustained absence of autoantibody production despite B-cell recovery likely involve multiple factors. First, the prolonged period of complete B-cell aplasia may eliminate not only mature autoreactive B cells but also memory B cells and short-lived plasmablasts that could serve as a reservoir for rapid autoantibody reconstitution. Second, B-cell reconstitution occurs from early CD19-negative hematopoietic progenitors in the bone marrow, which undergo de novo selection processes that may more effectively eliminate autoreactive clones compared to the peripheral B-cell pool in active disease. Third, the absence of disease-associated inflammation and altered cytokine milieu during B-cell reconstitution may favor development of a more tolerogenic B-cell compartment. Fourth, potential alterations in T-cell help either through direct effects of lymphodepleting chemotherapy or through CAR-T-mediated inflammation—may reduce support for autoreactive B-cell responses.

Pre-existing protective immunity (e.g., vaccine-induced antibodies against tetanus and pneumococcus) appears to be preserved, presumably because long-lived plasma cells producing these antibodies do not express CD19 and survive CAR-T cell therapy [53]. Longitudinal assessment of vaccine titers in treated patients shows maintenance of protective antibodies against common vaccine antigens, including tetanus, diphtheria, and encapsulated bacteria, though some patients show gradual decline in titers over time, suggesting a need for revaccination strategies as B-cell function recovers.

5. Preclinical studies in autoimmune models

5.1. CD19-CAR-T cells in lupus-prone mice

The first preclinical evidence for CAR-T cell efficacy in autoimmunity came from studies in lupus-prone mouse models. The MRL/lpr strain, which spontaneously develops lupus-like disease with autoantibodies, nephritis, skin lesions, and lymphoproliferation, has been extensively used to study B-cell-directed therapies [54]. Treatment of MRL/lpr mice with CD19-CAR-T cells resulted in complete elimination of B cells, reduction in anti-dsDNA antibodies, improvement in proteinuria, and prolonged survival compared to untreated controls [55].

Importantly, these studies demonstrated that CAR-T cell-mediated B-cell depletion was more effective than anti-CD20 antibody treatment in this model, with longer duration of B-cell aplasia and more

sustained suppression of autoantibody production [56]. The NZB/W F1 model, another commonly used lupus model, showed similar results, with CD19-CAR-T cells preventing disease progression when administered early and ameliorating established nephritis when given to mice with active disease [57].

5.2. Chimeric autoantibody receptor (CAAR) T cells

While CD19-CAR-T cells eliminate all B cells regardless of antigen specificity, this broad approach carries the theoretical disadvantage of global immunosuppression and loss of protective humoral immunity. To address this limitation, researchers developed chimeric autoantibody receptor (CAAR) T cells, which selectively target only those B cells bearing surface immunoglobulin specific for a defined autoantigen [58].

The CAAR approach was pioneered in pemphigus vulgaris, an autoimmune blistering disease caused by antibodies against desmosomal proteins, particularly desmoglein 3 (Dsg3) [59]. In this disease, the target autoantigen is well-defined, and the causal role of anti-Dsg3 antibodies is established. Payne and colleagues engineered T cells expressing a chimeric receptor in which the extracellular domain consisted of the Dsg3 autoantigen rather than an scFv antibody fragment [60]. This Dsg3-CAAR specifically binds to B cells expressing anti-Dsg3 surface immunoglobulin, triggering CAR-T cell activation and cytotoxicity against only those autoreactive B cells.

In vitro studies demonstrated that Dsg3-CAAR T cells specifically lyse Dsg3-reactive B cells while sparing B cells with other specificities [61]. In a humanized mouse model of pemphigus, Dsg3-CAAR T cells eliminated Dsg3-specific B cells and hybridomas, reduced circulating anti-Dsg3 antibodies, and prevented disease manifestations without affecting total B-cell numbers or responses to irrelevant antigens [62]. This selective approach preserves protective immunity while eliminating pathogenic B cells and represents an elegant solution for diseases with well-defined autoantibody targets.

5.3. Preclinical studies in other autoimmune models

Beyond lupus and pemphigus, CAR-T cell approaches have been explored in preclinical models of other autoimmune diseases. In experimental autoimmune encephalomyelitis (EAE), a model of multiple sclerosis, B-cell depletion with CD19-CAR-T cells reduced disease severity and demyelination, particularly when administered early in the disease course [63]. In collagen-induced arthritis, a model of rheumatoid arthritis, CD19-CAR-T cells suppressed joint inflammation and bone erosion, with effects comparable to or exceeding conventional B-cell-depleting antibodies [64].

Studies in NOD mice, a model of type 1 diabetes, have explored CAR-T cells targeting B cells or insulin-specific B cells [65]. These studies suggest potential for preventing or delaying autoimmune diabetes, though the complex pathophysiology involving B cells and T cells may limit efficacy of B-cell-directed approaches alone. Combination strategies incorporating B-cell depletion and T-cell modulation are under investigation in this model.

6. Clinical experience in autoimmune diseases

6.1. Systemic lupus erythematosus: Initial case series

The first clinical application of CAR-T cells in autoimmunity was reported by Mackensen and

colleagues at the University of Erlangen in 2022 [66]. Five patients with severe, treatment-refractory SLE received autologous CD19-CAR-T cells following lymphodepleting chemotherapy with fludarabine and cyclophosphamide. All patients had active disease despite multiple prior therapies, including glucocorticoids, hydroxychloroquine, mycophenolate mofetil, azathioprine, cyclophosphamide, and belimumab.

The results were remarkable and exceeded expectations based on prior experience with B-cell-depleting antibodies. All five patients achieved rapid clinical improvement, with SLE Disease Activity Index 2000 (SLEDAI-2K) scores declining to 0 within 3 months [67]. Following allogeneic anti-CD19 CAR-T cell therapy, complement C3 and C4 levels normalized within one month, while anti-dsDNA antibody levels decreased and proteinuria resolved in all treated patients. Importantly, one patient discontinued all immunomodulatory and immunosuppressive medications, including glucocorticoids, three months after CAR-T cell infusion and achieved drug-free remission [68].

CD19-CAR-T cell expansion was robust, peaking within the first 2 weeks post-infusion with peak expansion occurring at days 10–14. Complete B-cell aplasia was achieved in all patients and persisted for 3–7 months, with undetectable $CD19^+$ cells by flow cytometry in peripheral blood. B-cell reconstitution then occurred gradually, beginning with naive B-cell populations. Despite prolonged B-cell aplasia, no severe infections were observed, and protective antibody titers against tetanus and pneumococcus were maintained [69].

Cytokine release syndrome occurred in all patients but was mild (grade 1–2 by ASTCT criteria), characterized primarily by fever and transient hypotension managed with supportive care and tocilizumab in some cases. Peak cytokine levels (IL-6, IFN-γ, TNF-α) were substantially lower than typically observed in oncology patients receiving CAR-T therapy, consistent with the lower target B-cell burden. No immune effector cell-associated neurotoxicity syndrome (ICANS) was observed [70]. This favorable safety profile, in contrast to the more severe toxicity commonly seen in oncology patients, may reflect lower CAR-T cell doses used (1×10^6 cells/kg versus up to 6×10^8 total cells in some oncology protocols), lower B-cell tumor burden, or disease-specific factors in the autoimmune setting such as baseline immunosuppression reducing the inflammatory response.

6.2. Expanded cohort and extended follow-up

The Erlangen group subsequently reported an expanded cohort of 15 patients with severe autoimmune diseases treated with CD19-CAR-T cells, including 8 patients with SLE, 4 with idiopathic inflammatory myopathy (dermatomyositis or anti-synthetase syndrome), and 3 with systemic sclerosis [71]. All patients had failed multiple prior therapies and had active, progressive disease at enrollment.

Clinical responses were observed in all 15 patients (100% response rate). In SLE patients, SLEDAI-2K scores declined to 0, and all achieved drug-free remission. Specific disease manifestations showed dramatic improvement: Lupus nephritis resolved with normalization of proteinuria (from mean 3.2 g/day to <0.2 g/day); cytopenias corrected (platelets increasing from mean 42,000/μL to >150,000/μL; hemoglobin normalizing); and cutaneous manifestations cleared. In myositis patients, muscle strength improved substantially (measured by manual muscle testing and functional assessments), creatine kinase levels normalized (declining from mean 2,800 U/L to <200 U/L), and interstitial lung disease stabilized or improved as assessed by pulmonary function testing and high-resolution computed tomography [72]. In systemic sclerosis patients, modified Rodnan skin scores

improved substantially (from a mean of 20 to 4), representing clinically meaningful reduction in skin thickness, and pulmonary function stabilized with no further decline in forced vital capacity [73].

At median follow-up of 15 months, 14 of 15 patients remained in remission without immunosuppressive therapy. One SLE patient experienced mild disease flare 26 months after CAR-T therapy, coinciding with B-cell reconstitution, though the flare was manageable with low-dose hydroxychloroquine without requiring resumption of high-dose immunosuppression [74]. Extended follow-up data now available for the original cohort (up to 36 months) confirms durability of responses in the majority of patients, with no patient requiring return to baseline multi-drug immunosuppressive regimens [75]. Two additional patients have experienced mild flares responsive to single-agent maintenance therapy, suggesting that while CAR-T therapy induces profound disease remission, some patients may require low-level immune modulation long-term.

B-cell signaling plays a central role in the regulation of immune responses. In germinal center B cells, B-cell receptor (BCR) and CD40 signaling are functionally rewired compared with naïve B cells. BCR signaling promotes Akt-dependent phosphorylation of Foxo1, whereas CD40 signaling predominantly activates NF-κB. Importantly, both BCR and CD40 signals are required for strong induction of c-Myc, a critical mediator of germinal center B-cell survival and cell-cycle re-entry [76]. In the context of systemic lupus erythematosus, current cellular therapies, including CAR-T cell therapy, are being investigated as approaches to target pathogenic immune-cell populations and modify the underlying autoimmune response [77].

6.3. Other centers and ongoing trials

Following the Erlangen reports, additional centers have initiated CAR-T cell trials for autoimmune diseases, confirming and extending the initial observations. A Chinese group reported CD19-CAR-T cell treatment of 13 patients with refractory SLE, with similar results—100% response rate, normalization of disease activity scores, and resolution of autoantibodies [78]. Several patients with lupus nephritis showed complete renal responses, including normalization of proteinuria and serum creatinine. Importantly, this study employed a different CAR construct (CD28-based rather than 4-1BB-based) and demonstrated similar efficacy, suggesting that the therapeutic effect may be relatively independent of specific CAR design, though comparative data are lacking. The Chinese experience also included patients with more severe baseline disease, including some with neuropsychiatric lupus manifestations, which showed improvement following therapy.

Clinical trials are now underway or in development for a broader range of autoimmune indications, reflecting growing confidence in the approach. NCT03030976 is evaluating CD19-CAR-T cells in SLE at multiple US centers in a formal phase I/II trial with standardized eligibility criteria and outcome measures [78].

Moreover, additional clinical evidence has emerged from multicenter phase I/II studies, demonstrating that CD19-directed CAR-T cell therapy can induce rapid and sustained remission in refractory systemic lupus erythematosus. In an expanded cohort study, patients achieved deep clinical responses characterized by normalization of disease activity indices and marked reduction of autoantibody titers, with parallel improvement in renal involvement in cases of lupus nephritis. These findings further support the concept of CAR-T–mediated immune system reset as a reproducible therapeutic mechanism across independent clinical centers, extending beyond the initial Erlangen experience [79].

NCT05030779 is also testing BCMA-directed CAR-T cells in SLE, targeting plasma cells that

express B-cell maturation antigen with the hypothesis that combined depletion of B cells (via residual $CD19^+$ plasmablasts) and BCMA+ plasma cells will result in deeper and more durable suppression of autoantibody production than CD19 targeting alone [80]. Additional trials are planned or ongoing for rheumatoid arthritis, multiple sclerosis, immune thrombocytopenia, myasthenia gravis, and pemphigus, though most remain in early recruitment phases [81].

A phase I trial of DSG3-CAAR T cells for mucosal pemphigus vulgaris (NCT04422912) is evaluating the selective CAAR approach in humans [82]. This trial will provide critical data on the feasibility and safety of antigen-specific B-cell elimination without global B-cell depletion, potentially demonstrating whether selective targeting can achieve disease control while preserving protective immunity more completely than pan-B-cell approaches.

The geographic diversity of clinical CAR-T experience in autoimmune diseases provides important insights into the generalizability and reproducibility of outcomes across healthcare systems and patient populations. The initial European experience, primarily from Germany (Erlangen group), has now been complemented by independent validation from Asian centers, particularly in China, where different CAR constructs (CD28-based versus 4-1BB-based costimulation) have demonstrated similar efficacy profiles [78,79]. This cross-continental reproducibility strengthens confidence in the therapeutic mechanism and suggests that outcomes are not dependent on specific geographic, genetic, or environmental factors. However, subtle differences in patient selection criteria, supportive care practices, and follow-up protocols across centers highlight the need for international standardization efforts to enable robust comparative analyses. Ongoing multicenter trials in North America (NCT03030976) and planned international registry studies will further clarify whether regional variations in disease phenotype, treatment history, or healthcare delivery impact CAR-T efficacy and safety. The absence of published data from Latin America, Africa, and other underrepresented regions represents an important gap that should be addressed in future clinical development to ensure equitable access and applicability across all populations. Table 1 describes main clinical studies evaluating CAR-T cell therapy in autoimmune diseases.

6.4. Comparison with conventional therapies

The emerging clinical data suggest that CAR-T cell therapy may offer substantial advantages over conventional treatments for severe autoimmune diseases, though important caveats regarding the evidence base must be acknowledged. Complete responses (defined as disease activity index of 0) and drug-free remissions are rarely achieved with standard immunosuppressive regimens, which typically require ongoing therapy to maintain disease control [83]. Even with optimal use of contemporary therapies including biologic agents, complete remission rates in SLE typically range from 10–30%, and most patients require continued immunosuppression indefinitely. Autologous hematopoietic stem cell transplantation (AHSCT) can induce sustained remissions in some patients but requires intensive conditioning chemotherapy, carries significant morbidity and mortality (treatment-related mortality 2–10% in autoimmune disease registries), and is limited to specialized centers with extensive transplant experience [84].

Table 1. Summary of main clinical studies evaluating CAR-T cell therapy in autoimmune diseases.

References	Year	Study design	Disease	n	CAR Target	CAR Construct	Lymphodepletion	Cell Dose ($\times 10^6$/kg)	Response Rate (%)	Median Follow-up (months)	CRS (Max Grade)	ICANS	Drug-Free Remission	Key Outcomes
Mougiakakos et al. [45]	2021	Case report	SLE	1	CD19	2nd generation (4-1BB/CD3ζ)	Fludarabine/Cyclophosphamide	1.0	100	6	Grade 1	None	Yes	SLEDAI-2K = 0; anti-dsDNA negative; first proof-of-concept case
Mackensen et al. [66]	2022	Clinical case series	SLE	5	CD19	2nd generation (4-1BB/CD3ζ)	Fludarabine/Cyclophosphamide	1.0	100	17	Grade 1–2	None	Yes (5/5)	Complete B-cell aplasia 3–7 months; disappearance of autoantibodies; complement normalization; drug-free remission all patients
Taubmann et al. [72]	2023	Clinical case series	Antisynthetase syndrome (IIM)	2	CD19	2nd generation (4-1BB/CD3ζ)	Fludarabine/Cyclophosphamide	1.0	100	12	Grade 1	None	Yes	CK normalization; stabilization of interstitial lung disease; reduced anti-Jo-1 levels; improved muscle strength
Bergmann et al. [73]	2023	Clinical case series	Systemic sclerosis	3	CD19	2nd generation (4-1BB/CD3ζ)	Fludarabine/Cyclophosphamide	1.0	100	9	Grade 1	None	Yes	Modified Rodnan Skin Score (mRSS) reduced from mean 20→4; improved lung function; resolution of autoantibodies
Müller et al. [71]	2024	Clinical case series	SLE, IIM, SSc	15	CD19	2nd generation (4-1BB/CD3ζ)	Fludarabine/Cyclophosphamide	1.0	100	15	Grade 1–2	None	Yes (14/15)	Discontinuation of immunosuppressants; durable remission; naive B-cell reconstitution; one mild relapse at 26 months
Taubmann et al. [74]	2024	Clinical case series	SLE (retreatment)	1	CD19	2nd generation (4-1BB/CD3ζ)	Fludarabine/Cyclophosphamide	1.0	100	8 (post-retreatment)	Grade 1	None	Yes	Successful retreatment after mild relapse; demonstrates feasibility of repeat dosing
Merkt et al. [75]	2025	Clinical case series	SLE	8	CD19	2nd generation (4-1BB/CD3ζ)	Fludarabine/Cyclophosphamide	1.0	100	36	Grade 1–2	None	Yes (7/8)	Extended 3-year follow-up confirms durability; sustained B-cell reconstitution with normal phenotype; preserved vaccine responses

Continued on next page

References	Year	Study design	Disease	n	CAR Target	CAR Construct	Lymphodepletion	Cell Dose (× 10^6/kg)	Response Rate (%)	Median Follow-up (months)	CRS (Max Grade)	ICANS	Drug-Free Remission	Key Outcomes
Zhang et al. [78]	2023–2024	Case report (retreatment)	SLE	13	CD19	2nd generation (CD28/CD3ζ)	Fludarabine/Cyclophosphamide	1.0–1.5	100	12	Grade 1–2	None	Yes (12/13)	Complete renal response in lupus nephritis; anti-dsDNA undetectable; normalization of proteinuria and serum creatinine; Chinese multicenter data
Yang et al. [68]	2025	Single-center pilot study (NCT05988216)	SLE	4	CD19	2nd generation (4-1BB/CD3ζ)	Fludarabine/Cyclophosphamide	1.0	100		Grade 1	None	Yes (majority)	C3/C4 normalized within 1 month; anti-dsDNA decreased; proteinuria resolved in all patients; all patients achieved SRI-4; 1 patient achieved drug-free remission
NCT04422912 [82]	Ongoing (Phase I)	Phase I clinical trial (ongoing)	Pemphigus vulgaris	Enrolling	DSG3-CAAR	CAAR (Dsg3/CD137/CD3ζ)	Fludarabine/Cyclophosphamide	TBD						First-in-human trial of antigen-specific CAAR approach; selective B-cell depletion without global immunosuppression
NCT05030779 [80]	Ongoing (Phase I)	Phase I clinical trial (ongoing)	SLE	Enrolling	BCMA	2nd generation (4-1BB/CD3ζ)	Fludarabine/Cyclophosphamide	TBD						Targeting plasma cells expressing BCMA; complementary to CD19 targeting; aims for deeper autoantibody suppression
NCT03030976 [79]	Ongoing (Phase I/II)	Phase I/II clinical trial (ongoing)	SLE	Enrolling	CD19	2nd generation (4-1BB/CD3ζ)	Fludarabine/Cyclophosphamide	TBD						US multicenter trial; enrollment ongoing; results anticipated 2025–2026

Study Design Classifications: Case report = single patient or n < 5; Clinical case series = n = 5–30 patients with systematic data collection; Clinical trial = prospective interventional study with predefined protocol; Review article = synthesis of existing literature; Phase I = safety/feasibility study; Phase I/II = combined safety and preliminary efficacy evaluation.

Geographic origins: Mougiakakos et al., Mackensen et al., Taubmann et al., Bergmann et al., Müller et al., Merkt et al. (Germany, University Hospital Erlangen); Zhang et al. (China, multiple centers); NCT trials (USA/international, multiple sites).

Evidence levels: Clinical case series with n ≥ 5 = Moderate-High; Case reports n < 5 = Moderate; Ongoing trials without results = N/A pending publication.

Abbreviations: CRS, Cytokine Release Syndrome (graded by ASTCT criteria); ICANS, Immune Effector Cell-Associated Neurotoxicity Syndrome; SLE, Systemic Lupus Erythematosus; IIM, Idiopathic Inflammatory Myopathy; SSc, Systemic Sclerosis; CK, Creatine Kinase; mRSS, Modified Rodnan Skin Score; SLEDAI-2K, SLE Disease Activity Index 2000; TBD, To Be Determined.

In contrast, CAR-T cell therapy, as currently administered, involves less intensive lymphodepletion than conventional AHSCT conditioning (fludarabine/cyclophosphamide at doses well below myeloablative levels), appears to have a favorable safety profile in autoimmune patients based on published series, and does not require the prolonged hospitalization and supportive care (including hematopoietic growth factor support, prolonged neutropenic precautions) associated with AHSCT [85]. The vein-to-vein timeline for CAR-T therapy (approximately 4–6 weeks) is comparable to AHSCT but involves less intensive inpatient treatment. If long-term follow-up confirms durability of responses extending 5–10 years or longer, CAR-T cells could represent a superior therapeutic option for selected patients with severe, refractory autoimmune disease.

However, important caveats apply that must be emphasized. Experience is limited to small case series and early-phase trials from a limited number of specialized centers, without randomized controlled comparisons to either conventional therapy or AHSCT. Patient selection has focused on severe, refractory disease with multiple prior treatment failures, and efficacy in earlier disease stages or in less severe presentations is unknown [86]. The relatively short follow-up (maximum 36 months for most patients) precludes definitive assessment of long-term durability; longer observation periods extending to 10+ years will be essential to determine whether CAR-T therapy truly provides curative outcomes or whether late relapses occur. Long-term safety data beyond 3 years are limited, and potential late complications, including secondary malignancies, chronic immunodeficiency, or other unexpected toxicities, cannot be excluded. The absence of control groups in published case series introduces potential for bias, as natural disease variability and concurrent interventions (bridging therapies, supportive care optimization) could contribute to observed responses. Larger trials with longer follow-up and ideally randomized comparisons are needed before definitive conclusions can be drawn regarding the role of CAR-T therapy in the treatment algorithm for autoimmune diseases.

7. CAR-T cell approaches in allergic diseases

7.1. Rationale for targeting IgE-producing B cells

Allergic diseases are characterized by inappropriate type 2 immune responses to innocuous environmental proteins (allergens), leading to IgE antibody production, mast cell and basophil sensitization, and immediate hypersensitivity reactions upon allergen re-exposure [87]. The central role of IgE in allergic pathophysiology is well-established, as demonstrated by the efficacy of omalizumab, a humanized anti-IgE monoclonal antibody, in allergic asthma and chronic urticaria [88].

However, omalizumab neutralizes only circulating IgE and does not eliminate IgE-producing B cells, requiring continuous therapy to maintain efficacy with rebound of IgE levels and potential symptom recurrence upon discontinuation [89]. Moreover, long-lived IgE-secreting plasma cells in bone marrow survival niches continue to produce allergen-specific IgE and perpetuate allergic sensitization even during anti-IgE therapy [90]. A therapeutic strategy that eliminates IgE-producing B cells and their precursors could potentially provide durable suppression of allergen-specific IgE and long-term tolerance, fundamentally altering the natural history of allergic disease rather than providing symptomatic control.

7.2. IgE-targeted CAR-T cells

Preclinical studies have explored CAR-T cells engineered to target membrane-bound IgE on B

cells that have undergone class switching to the epsilon heavy chain [91]. Unlike secreted IgE, membrane IgE contains a unique membrane-proximal domain (M1' segment) that distinguishes it from secreted IgE and provides a potential target for selective elimination of IgE-producing cells without affecting other B cells or neutralizing circulating IgE [92]. This approach theoretically offers advantages over pan-B-cell depletion by preserving B cells producing protective antibodies (IgG, IgM, IgA) while selectively eliminating the pathogenic IgE-committed population.

In a murine model of allergic asthma employing ovalbumin sensitization and challenge, CAR-T cells targeting the M1' epitope of membrane IgE eliminated IgE-positive B cells and plasma cells, resulting in sustained reduction in allergen-specific serum IgE levels [93]. Treated mice showed diminished airway hyperresponsiveness (measured by methacholine challenge), reduced eosinophilic airway inflammation (assessed by bronchoalveolar lavage differential counts), and attenuated late-phase allergic responses upon allergen challenge. Importantly, total serum immunoglobulin levels (IgG, IgM, IgA) were preserved, indicating selective depletion of IgE-committed B cells without affecting other B-cell lineages [94]. Histological examination of treated animals demonstrated reduction in tissue-resident IgE^+ cells in lungs and lymphoid organs, supporting effective targeting of the IgE^+ compartment.

These preclinical results suggest that IgE-targeted CAR-T cells could provide a disease-modifying approach for allergic diseases by eliminating the cellular source of pathogenic IgE rather than simply neutralizing the antibody. Potential applications include severe allergic asthma uncontrolled on conventional therapy, life-threatening food allergy (particularly peanut, tree nut, and shellfish allergies with risk of fatal anaphylaxis), and anaphylaxis-prone venom allergy [95]. However, translation to human application faces several challenges, including the need to demonstrate adequate safety margins, particularly given that most allergic diseases are not immediately life-threatening and thus the risk-benefit calculation differs substantially from cancer or severe autoimmune disease indications.

7.3. Regulatory CAR-T cells for tolerance induction

An alternative approach employs regulatory T cells (Tregs) engineered with chimeric antigen receptors to suppress allergic inflammation and potentially induce long-term tolerance [96]. Tregs play a critical role in maintaining immunological tolerance and suppressing inappropriate immune responses, and defects in Treg number or function contribute to allergic sensitization and disease severity [97]. Successful allergen-specific immunotherapy is associated with induction of allergen-specific Tregs, suggesting that enhancing this regulatory population could provide therapeutic benefit.

CAR-Tregs can be engineered to recognize allergens or tissue-specific markers, directing their suppressive activity to sites of allergic inflammation with high specificity [98]. In a mouse model of peanut allergy, Tregs engineered with a CAR specific for peanut allergen components (Ara h 1, Ara h 2) trafficked to gut-associated lymphoid tissues and suppressed peanut-induced anaphylaxis upon oral challenge [99]. CAR-Tregs produced immunosuppressive cytokines (IL-10, TGF-β) that created a local tolerogenic environment and induced bystander suppression of allergen-specific effector T cells through antigen-presenting cell modulation. Protection persisted even after CAR-Treg levels declined, suggesting induction of durable tolerance mechanisms [100].

Similar approaches are being developed for allergic asthma, where lung-targeted CAR-Tregs could suppress airway inflammation and remodel the local immune environment, and for atopic dermatitis, where skin-homing CAR-Tregs could modulate local immune responses and reduce chronic inflammation [101]. CAR-Tregs offer the potential advantage of inducing tolerance without

eliminating B cells or causing global immunosuppression, potentially providing a safer approach for non-life-threatening allergic conditions. However, significant technical challenges remain, including ensuring stable FOXP3 expression and suppressive function of engineered Tregs, achieving adequate homing to relevant tissue sites, and generating sufficient cell numbers given the lower proliferative capacity of Tregs compared to conventional T cells.

7.4. Challenges specific to allergic applications

Several challenges must be addressed before CAR-T cell approaches can be translated to clinical allergy treatment, and these differ in important ways from challenges in autoimmune or oncology applications. First, the risk-benefit calculation differs substantially from severe autoimmune diseases or cancer; allergic conditions, while burdensome and sometimes severe, are rarely immediately life-threatening with the exception of anaphylaxis, and exposing patients to potential CAR-T cell toxicities requires careful justification [102]. Regulatory pathways and ethical frameworks for testing cellular therapies in pediatric populations (where many allergic diseases manifest) are more stringent than for adult indications. The high prevalence of allergic diseases means that any approved therapy would need to be scalable to treat large patient populations, creating manufacturing and cost challenges.

Second, allergen-specific IgE represents a small fraction of total IgE (often < 1–5% of total IgE is specific for any single allergen), and targeting all IgE-producing cells may have unintended consequences for parasite immunity, particularly in endemic regions where helminth infections remain common [103]. IgE plays important roles in anti-parasitic immunity, and complete elimination of IgE-producing capacity could theoretically increase susceptibility to parasitic infections. Geographic stratification of potential patient populations and careful post-treatment monitoring would be essential. Additionally, the functional importance of low-level IgE responses to environmental allergens in maintaining barrier immunity and limiting allergen penetration remains incompletely understood.

Third, the durability of IgE suppression following CAR-T cell therapy is uncertain; if IgE-committed B cells regenerate from precursors or if residual IgE^+ plasma cells persist in protected niches, allergic sensitization could recur over time [104]. Long-lived plasma cells residing in bone marrow survival niches may not express sufficient membrane IgE for CAR-T recognition, potentially enabling persistent low-level IgE production. The kinetics of re-sensitization upon allergen re-exposure following successful IgE depletion are unknown, as are the factors that might promote or prevent generation of new IgE responses.

Fourth, for CAR-Treg approaches, ensuring long-term persistence and stability of the regulatory phenotype is challenging, as Tregs can lose FOXP3 expression and suppressive function under inflammatory conditions, potentially converting to effector cells [105]. Engineering stable CAR-Tregs that maintain their regulatory program, even in pro-inflammatory environments, is an active area of research, with strategies, including forced FOXP3 expression, deletion of genes that promote effector differentiation, and incorporation of domains, that enhance suppressive function. Whether engineered Tregs can be manufactured at sufficient scale and purity to achieve therapeutic efficacy in humans remains to be demonstrated.

8. Safety considerations and toxicity management

8.1. Cytokine release syndrome

Cytokine release syndrome (CRS) is the most common acute toxicity associated with CAR-T cell therapy, resulting from massive cytokine release by activated CAR-T cells and bystander immune cells following rapid target cell lysis and CAR-T expansion [106]. CRS manifests as fever, hypotension, hypoxia, and in severe cases, multi-organ dysfunction including cardiac dysfunction, acute respiratory distress syndrome, and coagulopathy. The severity of CRS correlates with CAR-T cell expansion kinetics, disease burden (in oncology), baseline inflammatory state, and potentially with specific CAR design features [107]. Grading scales developed by ASTCT provide standardized classification: Grade 1 (fever only); Grade 2 (fever with hypotension not requiring vasopressors and/or hypoxia requiring low-flow oxygen); Grade 3 (fever with hypotension requiring vasopressor support and/or hypoxia requiring high-flow oxygen); and Grade 4 (life-threatening symptoms requiring ventilator support or multiple vasopressors) [70].

In autoimmune patients treated to date, CRS has been remarkably mild compared to oncology experience, with most experiencing only grade 1–2 toxicity (fever, mild hypotension) manageable with supportive care including antipyretics, intravenous fluids, and supplemental oxygen [108]. Across published series totaling over 30 patients, no grade 4 CRS has been reported, and grade 3 CRS occurred in fewer than 10% of patients. This favorable profile may reflect multiple factors: Lower CAR-T cell doses used in autoimmune trials (typically 1×10^6 cells/kg versus $1–2 \times 10^8$ total cells in some oncology protocols); lower B-cell burden compared to B-cell malignancies (estimated <1% of total body cell mass versus up to 50% in some leukemias); or disease-specific factors such as baseline immunosuppression reducing cytokine production capacity [109]. However, caution is warranted, as the inflammatory milieu of active autoimmune disease could theoretically amplify CAR-T cell activation and cytokine production in some patients, and larger experience may reveal heterogeneity in toxicity profiles.

Management of CRS follows established algorithms developed in oncology and adapted for the autoimmune setting. Tocilizumab, an IL-6 receptor antagonist, is the cornerstone of CRS treatment and can rapidly reverse symptoms in most cases [110]. Dosing is typically 8 mg/kg IV (maximum 800 mg) given as a single dose, which can be repeated after 8–12 hours if symptoms persist or recur. Tocilizumab acts by blocking IL-6 signaling, interrupting the cytokine cascade while generally preserving CAR-T cell function. Corticosteroids (typically dexamethasone 10 mg IV every 6 hours or methylprednisolone 1–2 mg/kg/day) are reserved for tocilizumab-refractory cases but are used cautiously given potential effects on CAR-T cell function and expansion [111]. Some centers have evaluated prophylactic or preemptive tocilizumab strategies administered at the first sign of fever or elevated inflammatory markers, potentially preventing progression to severe CRS, though this approach may not be necessary in the autoimmune setting given the generally mild toxicity observed. Supportive care measures including aggressive fluid resuscitation, supplemental oxygen, and ICU-level monitoring for patients with grade ≥2 symptoms remain essential components of management.

8.2. Immune effector cell-associated neurotoxicity syndrome

Immune effector cell-associated neurotoxicity syndrome (ICANS) is a potentially serious complication characterized by encephalopathy, aphasia, decreased level of consciousness, motor

deficits, seizures, and in severe cases, cerebral edema with risk of herniation [112]. ICANS typically occurs after CRS onset (though can occur without preceding CRS) and is associated with blood-brain barrier disruption, elevated cytokines in cerebrospinal fluid (particularly IL-6, IL-1, and IFN-γ), endothelial activation, and potentially direct CAR-T cell trafficking to the central nervous system [113]. Grading employs the ICE (Immune Effector Cell-Associated Encephalopathy) score assessing orientation, ability to follow commands, writing ability, and attention, with additional consideration of motor findings and seizures. Pathophysiology may involve cytokine-mediated endothelial activation, pericyte dysfunction, and breakdown of blood-brain barrier integrity, enabling cytokine and potentially cellular infiltration into the CNS.

Notably, no cases of ICANS have been reported in autoimmune CAR-T cell trials to date across all published series and conference presentations, consistent with the lower CAR-T cell doses and milder CRS observed [114]. This represents a substantial difference from oncology experience where ICANS occurs in 20–64% of patients in some series, with grade 3–4 ICANS in 10–30%. The absence of ICANS in autoimmune applications may reflect the lower overall inflammatory burden and reduced CAR-T expansion, though vigilance remains necessary particularly as CAR-T cell therapy expands to broader autoimmune populations and different CAR constructs are tested. Standard monitoring protocols include serial neurological assessments using the ICE scoring system performed at least daily for the first 7–10 days post-infusion, with more frequent assessment if any neurological symptoms develop [115]. Early recognition and aggressive management with corticosteroids (dexamethasone 10 mg IV every 6–8 hours) are essential, as ICANS can progress rapidly and may not respond to tocilizumab alone.

8.3. B-cell aplasia and infection risk

Prolonged B-cell aplasia following CD19-CAR-T cell therapy raises theoretical concerns about infection risk due to impaired humoral immunity, particularly susceptibility to encapsulated bacteria (Streptococcus pneumoniae, Haemophilus influenzae) and respiratory viruses [116]. In oncology patients, hypogammaglobulinemia (IgG < 400 mg/dL) occurs frequently during prolonged B-cell aplasia and is associated with increased risk of sinopulmonary infections, with some series reporting infection rates of 0.4–1.2 infections per patient-year during B-cell aplasia [117]. Management in oncology typically includes intravenous immunoglobulin (IVIG) replacement for patients with recurrent infections or severe hypogammaglobulinemia, antimicrobial prophylaxis (particularly against Pneumocystis jirovecii), and vaccination strategies timed to coincide with B-cell recovery.

Surprisingly, severe infections have been rare in autoimmune CAR-T cell recipients despite B-cell aplasia lasting 6–12 months or longer [118]. Across published series, the infection rate during B-cell aplasia has been approximately 0.1–0.3 infections per patient-year, substantially lower than in oncology populations and comparable to infection rates in autoimmune patients on conventional immunosuppression. No opportunistic infections have been reported in the autoimmune series. Several factors may explain this favorable observation. First, autoimmune patients are often on baseline immunosuppression that is discontinued after CAR-T therapy, potentially offsetting infection risk from B-cell aplasia as T-cell function and neutrophil counts improve with cessation of conventional immunosuppressants [119]. Second, pre-existing protective antibodies produced by long-lived CD19-negative plasma cells appear to be preserved, maintaining protective titers against common bacterial and viral pathogens [120]. Longitudinal measurement of vaccine titers shows stable levels of tetanus, diphtheria, and pneumococcal antibodies in most patients during B-cell aplasia. Third, careful patient

selection, excluding those with baseline severe immunodeficiency or recent severe infections, and monitoring protocols enabling early detection and treatment of infections may have contributed to the favorable safety record [121].

Nevertheless, infection risk remains a concern for long-term CAR-T cell recipients, particularly those with prolonged B-cell aplasia extending beyond 12–18 months. IVIG replacement should be considered for patients with recurrent infections (≥2 significant infections within 12 months) or severe hypogammaglobulinemia (IgG < 400 mg/dL with evidence of impaired vaccine responses), though prophylactic IVIG for all patients with B-cell aplasia is probably not warranted given the low infection rates observed [122]. Vaccination strategies for CAR-T recipients are being developed, with current recommendations suggesting administration of inactivated vaccines (pneumococcal, influenza, COVID-19) beginning approximately 6 months post-CAR-T to coincide with B-cell reconstitution, though optimal timing relative to B-cell reconstitution remains uncertain [123]. Live vaccines are generally contraindicated during B-cell aplasia but may be considered after documented B-cell recovery and normalization of immunoglobulin levels.

8.4. Long-term safety considerations

Long-term safety data for CAR-T cells in autoimmunity remain limited, as the longest follow-up extends only 3–4 years in the initial case series [30]. Potential late complications requiring ongoing surveillance include: Chronic infections as the immune system reconstitutes with altered B-cell repertoire; secondary malignancies, a rare but documented complication of CAR-T therapy in oncology possibly related to insertional mutagenesis from viral vector integration into proto-oncogenes or tumor suppressors; prolonged effects of B-cell depletion on vaccine responses and protective immunity requiring booster vaccinations; and potential unexpected toxicities not apparent in short-term follow-up [124].

In oncology, rare cases of T-cell lymphoma arising from CAR-T cells have been reported, with viral integration into the TET2 gene or other loci leading to clonal T-cell expansion, prompting FDA investigation and enhanced monitoring requirements [125]. Moreover, while the absolute risk appears very low (estimated <0.1% based on denominators of treated patients), the potential for this serious late complication emphasizes the need for lifelong follow-up. In the autoimmune setting with younger patient populations and longer life expectancy compared to oncology patients, even rare late events could have substantial impact. Registry studies and collaborative monitoring efforts coordinated across treating centers are essential to capture rare events and ensure early detection of potential late complications [126]. Current monitoring recommendations include annual complete blood counts, flow cytometry for detection of clonal T-cell populations, and clinical assessment for evidence of lymphoproliferation or secondary malignancy, though the optimal duration and intensity of monitoring remain to be defined.

9. Next-generation approaches and future directions

The clinical success of CD19-CAR-T cells in autoimmune diseases and the promising preclinical results in allergic conditions have stimulated the development of diverse next-generation CAR-T cell strategies. These approaches aim to improve selectivity, reduce toxicity, broaden disease applicability, and enhance accessibility. Figure 2 provides a comparative visual overview of the five principal CAR-T cell strategies under development for autoimmune and allergic diseases, illustrating the differences in target antigen, mechanism of action, selectivity, and anticipated therapeutic outcomes.

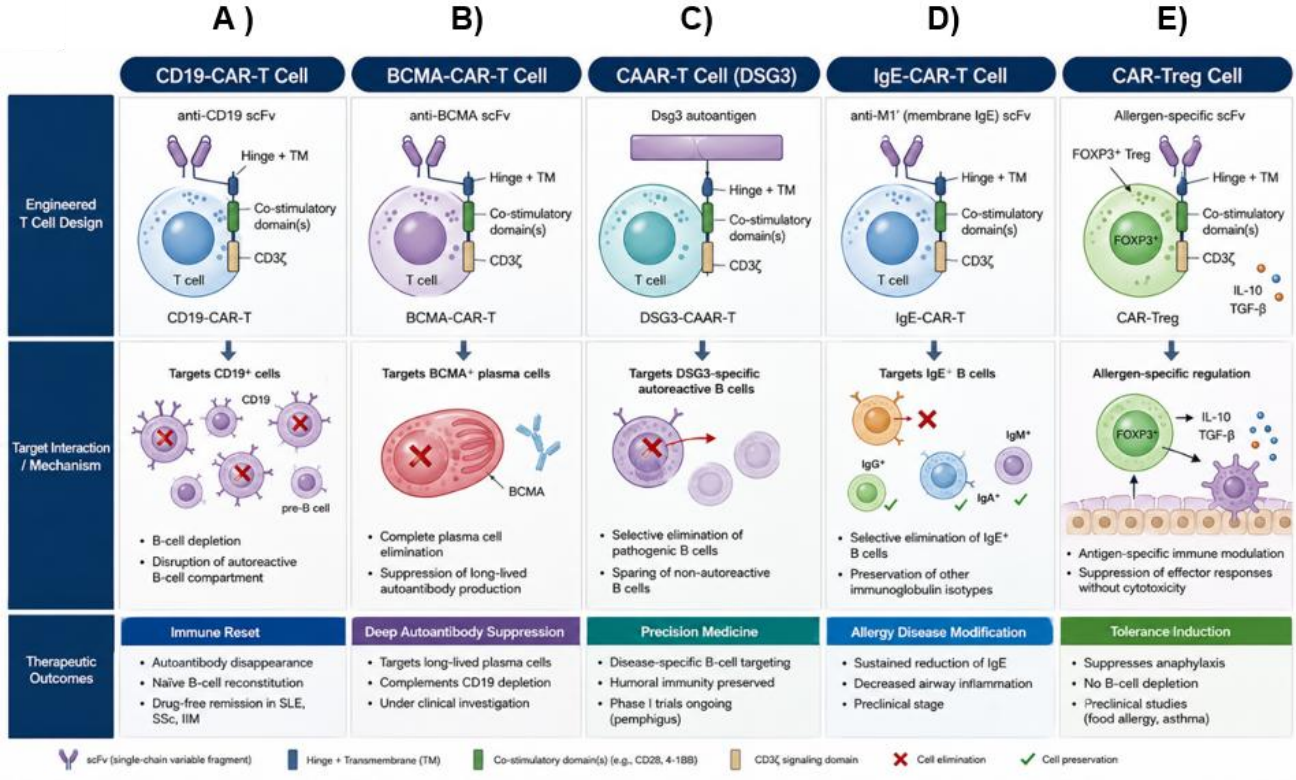


Figure 2. Comparative schematic of five chimeric antigen receptor (CAR) T-cell strategies for autoimmune and allergic diseases. The figure illustrates the engineered T-cell design (top row), the target cell interaction and selectivity (middle row), and the anticipated therapeutic outcome (bottom row) for each approach. (A) CD19-CAR-T cells eliminate all CD19-expressing B cells, achieving complete B-lineage depletion and immune reset, with proven clinical efficacy in systemic lupus erythematosus (SLE), idiopathic inflammatory myopathy (IIM), and systemic sclerosis (SSc). (B) BCMA-CAR-T cells target B-cell maturation antigen on plasma cells and mature B cells, providing complementary depletion of autoantibody-secreting cells. (C) Chimeric autoantibody receptor (CAAR) T cells display the autoantigen (e.g., desmoglein 3) to selectively eliminate only autoreactive B cells bearing the cognate B-cell receptor, preserving protective humoral immunity. (D) IgE-targeted CAR-T cells recognize membrane-bound IgE (M1' segment) and selectively eliminate IgE class-switched B cells while preserving other immunoglobulin isotype-producing cells. (E) CAR-regulatory T cells (CAR-Tregs) engineered with allergen-specific receptors traffic to sites of allergic inflammation and suppress effector immune responses through secretion of immunosuppressive cytokines (IL-10, TGF-β) without eliminating any cell population. scFv, single-chain variable fragment; TM, transmembrane domain; FOXP3, forkhead box P3; PC, plasma cell; BCR, B-cell receptor.

To facilitate detailed comparison, Table 2 summarizes the key characteristics of each strategy, including target antigens, target cell populations, mechanisms of action, disease applicability, clinical development stage, advantages, limitations, and safety considerations.

9.1. Alternative targets beyond CD19

While CD19 remains the most extensively studied target, alternative targets are being explored to optimize B-cell depletion or enable selective elimination of pathogenic B-cell subsets [127]. B-cell maturation antigen (BCMA), expressed on mature B cells and particularly highly on plasma cells, is an attractive target for diseases driven by autoantibody-producing plasma cells that may escape CD19-directed therapy [128]. BCMA is a member of the TNF receptor superfamily that binds APRIL and BAFF, cytokines important for plasma cell survival. Its expression increases as B cells differentiate into plasma cells, with highest expression on long-lived bone marrow plasma cells. BCMA-CAR-T cells have shown remarkable efficacy in multiple myeloma, achieving deep responses in heavily pretreated patients, and are now being tested in SLE (NCT05030779) with the goal of achieving deeper plasma cell depletion and more complete suppression of autoantibody production than CD19-targeting alone [129]. Early safety data suggest acceptable toxicity profiles, though CRS rates may be higher than with CD19 CARs.

CD20-targeted CAR-T cells are under development and may offer similar efficacy to CD19 CARs with potentially different kinetics of B-cell depletion and reconstitution [130]. CD20 expression is more restricted than CD19 (absent on early precursors and plasma cells), which could result in faster B-cell reconstitution and reduced duration of immunosuppression, potentially favorable for patients requiring only transient B-cell depletion to achieve disease control. CD22, another pan-B cell marker, is being explored as a target for dual-targeting strategies and for patients who relapse with CD19-negative B cells, a phenomenon observed in some oncology patients that could theoretically occur in autoimmune settings [131].

9.2. Dual-targeting and multi-specific CARs

Dual-targeting approaches aim to prevent antigen escape, achieve more complete target cell elimination across B-cell developmental stages, and potentially enhance efficacy through complementary mechanisms [132]. Bispecific CARs that recognize two antigens simultaneously through tandem scFv domains or separate CAR molecules expressed on the same cell (e.g., CD19 and BCMA) are being developed for autoimmune indications [133]. These constructs can be designed with "AND-gate" logic (requiring both antigens for full activation, enhancing specificity) or "OR-gate" logic (responding to either antigen, broadening target range). Sequential or tandem CAR designs enable targeting of multiple B-cell populations, CD19 for broad B-cell depletion and BCMA for plasma cell targeting, and may be particularly valuable for autoimmune diseases where B cells and plasma cells contribute to pathogenesis [134].

In SLE, dual CD19/BCMA-CAR-T cells have been tested in small pilot studies with the hypothesis that combined B-cell and plasma cell depletion will result in more durable autoantibody suppression than CD19 targeting alone [135]. Early results suggest feasibility and acceptable safety, with no evidence of additive toxicity compared to single-targeted approaches, though comparative efficacy data versus CD19-alone are not available. Theoretical advantages include more complete depletion of antibody-secreting cells and potentially longer duration of autoantibody suppression, though these benefits remain to be definitively demonstrated in controlled comparisons.

Table 2. Comparative overview of CAR-T cell strategies under development for autoimmune and allergic diseases.

Feature	CD19-CAR-T Cells	BCMA-CAR-T Cells	CAAR-T Cells (e.g., DSG3-CAAR)	IgE-Targeted CAR-T Cells	CAR-Treg Cells
Target antigen	CD19 (pan–B cell marker) [48]	BCMA (plasma cells, mature B cells) [128,129]	Autoantigen-specific BCR (e.g., anti-Dsg3) [58,60]	Membrane IgE (M1' segment) on IgE^+ B cells [91,92]	Allergen or tissue-specific antigen [96,98]
Target cell population	All $CD19^+$ B cells (pro-B to plasmablast) [48]	Plasma cells and late-stage B cells [128]	Only autoreactive B cells bearing target-specific BCR [58]	IgE class-switched B cells and IgE^+ plasmablasts [91]	None eliminated; suppression of effector cells [96]
Mechanism of action	Cytotoxic elimination of all B cells [19,37]	Cytotoxic elimination of plasma cells [128,129]	Selective cytotoxic elimination of autoreactive B cells [60,61]	Cytotoxic elimination of IgE-producing cells [93]	Immunosuppression via IL-10, TGF-β; bystander suppression [100,101]
Selectivity	Non-selective (all B cells depleted) [49]	Semi-selective (plasma cells and mature B cells) [129]	Highly selective (only disease-specific B cells) [62]	Isotype-selective (only IgE^+ B cells) [93,94]	Antigen-directed suppression without cell killing [98,99]
Preservation of humoral immunity	No (global B-cell aplasia; vaccine titers preserved via long-lived PCs) [53,120]	Partial (other B-cell subsets preserved) [129]	Yes (non-autoreactive B cells spared) [62]	Yes (IgG, IgM, IgA B cells spared) [94]	Yes (no B-cell depletion) [100]
Disease applicability	SLE [49,71,75], SSc [73], IIM [72], RA, MS, MG [81]	SLE (plasma cell–driven) [80], myeloma (approved) [129]	Pemphigus vulgaris [82], MG, ITP (antigen-defined diseases) [58,61]	Allergic asthma [93], food allergy [95], venom allergy	Food allergy [99,100], allergic asthma, atopic dermatitis, transplant tolerance [98]
Clinical stage	Phase I/II (multiple trials; published case series) [49,68,71,74,75,78]	Phase I (autoimmune) [80]; approved (oncology) [129]	Phase I (pemphigus) [82]	Preclinical [93,94]	Preclinical (advancing toward Phase I) [99,100]
Advantages	Proven clinical efficacy [71,75]; deep immune reset [77]; durable remissions [74,75]	Targets antibody-secreting plasma cells missed by CD19 [128,129]	Preserves protective immunity [62]; minimal immunosuppression	Selective IgE suppression [93]; preserves other Ig classes [94]	Induces tolerance [100]; no cell depletion; potential for long-term regulation [101]
Limitations	Global immunosuppression [116,117]; infection risk [118,121]; hypogammaglobulinemia [122]	Does not eliminate B-cell precursors; may need combination with CD19 [129]	Applicable only to diseases with well-defined autoantigen [58]; limited repertoire coverage	Long-lived IgE^+ PCs may lack membrane IgE [90]; durability uncertain [104]	Treg instability (loss of FOXP3) [105]; limited persistence; manufacturing complexity [101]
Safety concerns	CRS (mild in autoimmune) [108,109]; prolonged B-cell aplasia [118]; infection [116,117,121]	CRS; cytopenias; infection [129]	Theoretical off-target toxicity if autoantigen expressed on non-B cells	Potential loss of anti-parasite IgE [103]; unknown long-term effects	Risk of Treg conversion to effector phenotype [105]; insufficient suppression

9.3. Safety switches and controllable CARs

Incorporating safety switches into CAR designs enables rapid elimination of CAR-T cells if severe toxicity develops or if prolonged B-cell depletion is no longer desired, providing an important safety mechanism particularly for non-malignant indications where the risk-benefit calculation may be more marginal [136]. The inducible caspase-9 (iCasp9) suicide gene system enables rapid CAR-T cell elimination (>90% within 24–48 hours) upon administration of a small molecule dimerizer drug (AP1903/rimiducid) that activates the caspase pathway [137]. This approach has been validated in clinical trials of conventional T-cell therapies for GVHD prevention, demonstrating effective CAR-T elimination and resolution of toxicity. Alternative approaches include incorporation of truncated epidermal growth factor receptor (tEGFR), which serves as a detection marker and a target for cetuximab-mediated antibody-dependent cellular cytotoxicity, enabling antibody-mediated CAR-T elimination [138].

Controllable CARs (also termed "ON-switch" CARs) require a small molecule or second signal to activate, enabling external control of CAR-T cell function and titration of therapeutic activity [139]. These sophisticated designs employ split CAR constructs that only form functional receptors in the presence of a bridging molecule, or incorporate drug-responsive domains that control CAR expression. Such systems could enable titration of B-cell depletion to achieve desired therapeutic effect while minimizing over-immunosuppression, with the potential to "tune" the degree of depletion to match disease requirements. For autoimmune diseases, this might enable initial deep depletion followed by controlled reconstitution, or maintenance of partial B-cell depletion tailored to individual disease activity.

9.4. Transient CAR expression

mRNA-encoded CARs provide transient receptor expression, with CAR protein levels declining over days to weeks as mRNA is degraded and not replaced, offering temporal control over CAR activity [140]. This approach could be advantageous in autoimmunity, where permanent B-cell depletion may not be necessary or desirable. Transient CAR expression could achieve initial B-cell depletion sufficient to reset the immune system, with subsequent B-cell reconstitution occurring once CAR expression wanes and target elimination ceases [141]. This "pulse" of CAR-T activity might reduce long-term safety concerns while achieving therapeutic benefit, though efficacy of transient versus sustained CAR expression has not been compared.

Several groups are developing mRNA CAR-T cell platforms for autoimmune indications, with potential advantages including: Faster manufacturing (mRNA transfection can be accomplished in 24–48 hours versus 10–14 days for viral transduction); reduced risk of insertional mutagenesis since genetic material is not permanently integrated; and ability to administer repeat dosing to achieve desired degrees of B-cell depletion with cumulative control [142]. A challenge is achieving sufficient CAR expression duration to enable effective target elimination, as B cells in lymphoid tissues and bone marrow may require sustained CAR-T presence for complete depletion. Optimization of mRNA stability and delivery methods to enhance transfection efficiency are ongoing.

9.5. Allogeneic and off-the-shelf products

Allogeneic CAR-T cells derived from healthy donors could overcome many limitations of autologous manufacturing, including impaired T-cell quality in immunocompromised patients, manufacturing time delays that can extend 4–6 weeks from apheresis to infusion, and high costs associated with individualized production [143]. Healthy donor T cells may have superior fitness and expansion capacity compared to T cells from patients with active autoimmune disease on

immunosuppression. However, allogeneic cells pose risks of graft-versus-host disease (GVHD) if they contain functional endogenous TCRs that recognize host alloantigens, and rejection by the host immune system reducing persistence and efficacy.

Gene editing technologies (CRISPR-Cas9, TALEN, zinc finger nucleases) enable disruption of endogenous T-cell receptor (TCRA and TCRB genes) and HLA molecules (particularly HLA-A, minimizing recognition by host T cells) in allogeneic CAR-T cells, reducing GVHD risk and potentially prolonging persistence [144]. Multiple allogeneic CD19-CAR-T products with TCR and HLA knockout are in clinical development for oncology indications and could potentially be adapted for autoimmune applications [145]. Early clinical data suggest acceptable safety with manageable GVHD rates and reasonable persistence despite host immune responses, though efficacy appears somewhat reduced compared to autologous products in some studies. Additional engineering to disrupt other immune recognition pathways (CD52 knockout to enable alemtuzumab-based host conditioning while sparing CAR-T cells; PD-1 incorporation to reduce rejection) may further optimize allogeneic platforms.

9.6. Manufacturing innovations

Point-of-care manufacturing platforms that enable CAR-T cell production at the treatment center rather than centralized facilities could reduce manufacturing time from 3–4 weeks to 3–7 days, eliminate logistical challenges and costs of shipping cells to manufacturing sites and back, reduce risk of product mix-ups or shipping failures, and lower overall costs through reduced infrastructure requirements [146]. Automated, closed manufacturing systems currently in development could democratize access to CAR-T cell therapy beyond specialized academic centers, enabling community hospitals to offer treatment. Several platforms, including CliniMACS Prodigy and Cocoon systems, provide integrated apheresis, T-cell selection, viral transduction, expansion, and formulation in a single device [147].

Shortened manufacturing protocols employing "rapid manufacturing" approaches that reduce *ex vivo* culture time from 10–14 days to 2–5 days may preserve T-cell stemness characteristics associated with improved *in vivo* expansion and persistence, reduce differentiation and exhaustion that can occur during prolonged culture, and enable faster treatment delivery [148]. These innovations are particularly relevant for autoimmune applications, where patient T cells may have reduced fitness due to disease activity or prior therapy, and where rapid treatment may be important for patients with aggressive disease. Trade-offs between shorter manufacturing (preserving T-cell quality) and achieving sufficient cell numbers for dosing must be optimized for each indication.

10. Practical considerations for clinical implementation

10.1. Patient selection and eligibility

Current CAR-T cell trials in autoimmunity have focused on patients with severe, treatment-refractory disease who have failed multiple conventional therapies, reflecting the risk-benefit balance of an investigational therapy with potential serious toxicities [149]. Typical inclusion criteria have required: Failure of ≥2–3 conventional disease-modifying therapies (often including both traditional immunosuppressants and biologic agents); active disease despite therapy as defined by validated disease activity indices (e.g., SLEDAI ≥6 for SLE, active organ involvement requiring intensification of therapy); and ability to tolerate lymphodepleting chemotherapy. This conservative selection reflects appropriate caution in early-phase studies and limits the study population to those with greatest medical need and favorable risk-benefit profiles.

As safety and efficacy data accumulate demonstrating favorable outcomes and acceptable toxicity,

eligibility criteria may expand to include patients earlier in their disease course, potentially improving outcomes by intervening before irreversible organ damage occurs [150]. Arguments for earlier intervention include: Greater likelihood of achieving complete disease control before structural damage; potentially better T-cell quality for manufacturing in patients with less prior immunosuppression; and ability to prevent rather than only reverse organ dysfunction. However, expanding to less severe disease raises important ethical and practical questions about exposing patients with manageable disease to risks of an invasive cellular therapy, and the appropriate threshold for treatment remains to be defined through clinical experience and shared decision-making.

Optimal candidate characteristics based on current experience include: Active disease despite standard therapy (defined by validated disease activity measures showing inadequate control); absence of severe organ dysfunction that would preclude safe administration of lymphodepleting chemotherapy (severe renal insufficiency, significant cardiac dysfunction, severe hepatic impairment); adequate T-cell numbers for apheresis (typically absolute lymphocyte count ≥500–1000/μL); and absence of active uncontrolled infection; and ability to undergo close post-infusion monitoring [151]. Patients with severe cytopenias (platelets <50,000/μL, neutrophils <500/μL), recent high-dose immunosuppression (cyclophosphamide within 3 months, rituximab within 6 months), or very low T-cell counts may require modified protocols, temporizing therapies to improve counts, or alternative conditioning regimens [152]. Pregnancy and active malignancy represent absolute contraindications in current protocols.

10.2. Lymphodepleting chemotherapy

Lymphodepleting conditioning prior to CAR-T cell infusion serves multiple important purposes: Creating "space" for CAR-T cell expansion by reducing competing lymphocytes (homeostatic proliferation signals); eliminating regulatory T cells and myeloid-derived suppressor cells that might suppress CAR-T function; inducing cytokine release (particularly IL-7 and IL-15) that promotes CAR-T cell proliferation and survival; and potentially depleting some autoreactive lymphocytes contributing to disease [153]. Standard regimens employed in autoimmune trials consist of fludarabine 25–30 mg/m^2 daily for 3 days plus cyclophosphamide 250–500 mg/m^2 daily for 3 days, completed 2–7 days before CAR-T infusion [154]. This represents moderate-intensity conditioning, substantially less aggressive than myeloablative conditioning used in hematopoietic stem cell transplantation.

The optimal lymphodepletion intensity for autoimmune patients remains an important open question without definitive answer. Some investigators have used reduced-intensity regimens (fludarabine 25 mg/m^2, cyclophosphamide 250 mg/m^2) to minimize toxicity and accommodate patients with organ dysfunction, while others have adopted more intensive protocols (fludarabine 30 mg/m^2, cyclophosphamide 500 mg/m^2 or higher) to maximize CAR-T expansion [155]. Comparative studies are needed to determine whether conditioning intensity affects efficacy (degree and duration of B-cell depletion, clinical response rates, relapse risk) or safety (infection risk, organ toxicity) in the autoimmune setting. Theoretical considerations suggest that deeper lymphodepletion might enhance CAR-T expansion and efficacy but could increase infection risk and other toxicities, while lighter conditioning might be safer but potentially less effective. Individualization based on patient characteristics (weight, organ function, disease severity, prior treatment) may be required.

10.3. Monitoring and follow-up

Post-infusion monitoring protocols include intensive early surveillance followed by long-term follow-up to assess efficacy, safety, and disease outcomes. During the acute post-infusion period (days 0–14), daily assessment for cytokine release syndrome and ICANS using standardized grading systems is

essential, with particular attention to fever (may indicate CRS onset), vital signs (hypotension, hypoxia), mental status (orientation, ability to follow commands, signs of encephalopathy), and symptoms of organ dysfunction [156]. Serial measurement of inflammatory markers, including ferritin, C-reactive protein, and IL-6, can help predict CRS severity and guide intervention thresholds, with marked elevations (ferritin > 10,000 ng/mL, CRP > 100 mg/L) suggesting higher risk of progression to severe CRS. Regular blood counts detect CAR-T expansion (often manifested as transient lymphocytosis or lymphopenia, cytopenias from marrow toxicity), and assessment of B-cell aplasia (flow cytometry for $CD19^+$ cells) confirms on-target effect [157].

Long-term follow-up extending beyond the initial post-infusion period includes systematic immune reconstitution and disease-activity surveillance to evaluate durability of response and detect early relapse. Monitoring typically involves flow cytometry for $CD19^+$ B cells and detailed B-cell subset profiling (naïve, memory, plasmablast compartments), performed monthly in early follow-up and then spaced to every 2–3 months as clinically stable, consistent with emerging autoimmune CAR-T long-term surveillance protocols [158]. Parallel monitoring of serum immunoglobulins (IgG, IgA, IgM) is required to evaluate humoral recovery and determine need for IVIG replacement due to persistent hypogammaglobulinemia. Infection surveillance is maintained through clinical assessment and targeted diagnostics when indicated, as infection risk correlates with duration of B-cell aplasia and IgG suppression. Ongoing disease activity scoring (e.g., SLEDAI, myositis activity indices, modified Rodnan skin score) is used to quantify therapeutic durability and detect relapse, while autoantibody titers provide complementary serologic markers that may precede clinical recurrence and track immunologic remission over time [153,159]. Given the potential for late complications including secondary malignancies and clonal T-cell disorders, some experts recommend lifelong annual follow-up with complete blood counts, peripheral blood flow cytometry for clonal T-cell populations, and clinical assessment, though optimal duration and intensity of monitoring remain to be defined based on accumulating experience.

10.4. Cost and access considerations

CAR-T cell therapy is among the most expensive medical treatments available, with approved oncology products priced at $373,000–$475,000 per infusion in the United States, excluding costs of hospitalization, supportive care, and toxicity management which can add $100,000–$300,000 or more [160]. These costs present significant barriers to access and healthcare system sustainability, particularly if indications expand to include prevalent autoimmune diseases affecting millions of patients. Current pricing reflects the complex individualized manufacturing process, extensive quality control requirements, substantial development costs, and limited competition.

However, several factors may reduce costs for autoimmune applications, potentially improving access and cost-effectiveness. First, lower CAR-T cell doses used in autoimmune trials (approximately 5–10-fold lower than typical oncology doses) could reduce manufacturing costs through shorter expansion times and reduced reagent use [161]. Second, reduced toxicity requiring less intensive care with lower rates of ICU admission, shorter hospitalizations (3–5 days versus 2–3 weeks in some oncology series), and fewer interventions for toxicity management could substantially reduce total episode costs. Third, potential for outpatient administration in selected low-risk patients could further reduce costs, with early experience suggesting feasibility of outpatient CAR-T delivery with close monitoring. Fourth, simplified manufacturing platforms and point-of-care production could decrease production costs by reducing shipping, testing, and facilities expenses.

Most importantly, if CAR-T cells achieve durable drug-free remission extending years or decades, cost-effectiveness analyses may favor this approach over decades of conventional immunosuppressive

therapy with associated medication costs (biologics costing $30,000–$100,000 annually), monitoring costs, frequent medical visits, hospitalizations for disease flares, management of treatment complications (infections, malignancies), and indirect costs from work disability and reduced quality of life [162]. Preliminary modeling studies suggest that a single CAR-T intervention achieving 10-year disease control could be cost-effective compared to lifetime conventional therapy, though definitive analyses require longer follow-up data and incorporation of quality-of-life metrics. Value-based pricing models linking reimbursement to achievement of defined outcomes (disease remission at 1–2 years, drug-free status) are being explored by payers and manufacturers.

11. Comparative analysis with other advanced therapies

11.1. Autologous hematopoietic stem cell transplantation

Autologous hematopoietic stem cell transplantation (AHSCT) has been used for severe autoimmune diseases for over two decades, with documented efficacy in systemic sclerosis, multiple sclerosis, systemic lupus erythematosus, and other conditions [163]. AHSCT achieves profound immune reconstitution through intensive conditioning chemotherapy (typically cyclophosphamide ± fludarabine ± ATG), stem cell mobilization, collection and reinfusion, potentially eliminating autoreactive lymphocyte clones and restoring tolerance through regeneration of the immune system from hematopoietic stem cells [85]. Registry data demonstrate that approximately 50–80% of patients achieve sustained disease control (≥5 years) depending on disease and conditioning intensity, with some patients experiencing apparent cure.

Compared to AHSCT, CAR-T cell therapy has several potential advantages and some theoretical disadvantages. Advantages include substantially less intensive conditioning chemotherapy (fludarabine/cyclophosphamide at non-myeloablative doses versus high-dose cyclophosphamide ± TBI ± ATG), resulting in reduced acute toxicity, lower treatment-related mortality (0% in published autoimmune CAR-T series versus 2–10% for AHSCT in registry data), and shorter hospitalization (typically 3–7 days versus 3–4 weeks). In addition, there is no requirement for growth factor mobilization and stem cell collection, simplifying the treatment process and avoiding mobilization-related complications. It also potentially more targeted B-cell elimination without affecting other immune compartments as extensively, which could reduce infection risk and preserve some protective immunity [164].

However, AHSCT has important advantages including much longer follow-up data demonstrating durability extending more than 10–20 years in selected patients, whereas CAR-T autoimmune data currently remain limited to early mid-term follow-up (generally up to ~3–4 years); established integration into treatment algorithms with consensus indications, referral pathways, and reimbursement frameworks supported by long-standing EBMT/consortium guidelines and registry data; and a broader immune ablation and reconstitution effect involving B- and T-cell compartments, which may be particularly relevant in diseases with substantial T-cell–mediated pathology and complex immune dysregulation [165]. Whether CAR-T cells can achieve equivalent long-term disease control compared to AHSCT remains to be established through head-to-head comparisons or longer follow-up of CAR-T cohorts. The optimal role of each approach (CAR-T as less toxic first-line cellular therapy, AHSCT reserved for CAR-T failures or diseases requiring broader immune reconstitution) requires definition through clinical experience.

11.2. Bispecific antibodies and other B-cell-targeted therapies

Bispecific T-cell engagers (BiTEs) such as blinatumomab (CD19 × CD3) recruit endogenous patient

T cells to eliminate B cells without requiring *ex vivo* T-cell engineering or manufacturing [166]. These off-the-shelf antibody constructs bind CD19 on target B cells and CD3 on T cells, creating a transient immunological synapse that triggers T-cell-mediated cytotoxicity. BiTEs have shown efficacy in B-cell malignancies (blinatumomab approved for relapsed/refractory acute lymphoblastic leukemia) and might theoretically be applicable to autoimmune diseases [167]. However, BiTE therapy (e.g., blinatumomab) is limited by the need for continuous IV infusion over ~28-day cycles due to a very short ~2-hour half-life, requiring specialized infusion systems or hospitalization. It also lacks CAR-T–like *in vivo* expansion and long-term immune memory, so B-cell depletion depends on ongoing drug delivery rather than a durable one-time effect. Additionally, BiTEs are associated with significant toxicity, including cytokine release syndrome and neurotoxicity (ICANS-like events), with neurologic adverse events occurring in ~65% of patients and grade ≥3 events in a clinically meaningful subset, sometimes approaching CAR-T toxicity levels depending on context and study design [168]. The convenience advantage of avoiding manufacturing is offset by the inconvenience of prolonged infusions.

Other emerging B-cell–targeted strategies aim to improve the specificity, durability, or depth of B-cell depletion. These include engineered CD19/CD20 bispecific antibodies with modified Fc domains designed to enhance Fc-mediated effector functions and promote more effective depletion of B cells [169]. In autoimmune diseases, alternative targeted approaches are also being investigated, including BiTEs and other T-cell-engaging platforms for selective elimination of pathogenic B-cell populations [166,168].

BCMA-directed strategies provide an additional approach for targeting antibody-secreting plasma cells that may persist after CD19-directed B-cell depletion. CD19/BCMA dual-targeted CAR-T and BCMA-CD19 armored CAR-T approaches have shown potential for achieving profound depletion of B-cell and plasma-cell compartments and inducing sustained clinical remission in refractory systemic lupus erythematosus [158,159]. This strategy is particularly relevant because long-lived plasma cells can persist independently of conventional CD19-positive B-cell populations and contribute to continued autoantibody production [120]. Together, these approaches expand the therapeutic landscape beyond conventional CD19 CAR-T therapy by targeting complementary B-cell and plasma-cell compartments [153,161].

12. Limitations and interpretation of the evidence

While we synthesize a substantial body of literature, findings should be interpreted with appropriate consideration of the evidence composition and its inherent limitations. The clinical evidence for CAR-T therapy in autoimmune diseases currently consists predominantly of case reports and small case series (n = 28 clinical publications, representing 46 total patients across all published studies as of March 2026), with the majority originating from a single center (University Hospital Erlangen, Germany). This geographic concentration, while reflecting genuine pioneering clinical innovation, limits the ability to assess generalizability across different healthcare settings, practice patterns, and patient populations. The longest follow-up duration currently available is 36 months, which, though encouraging, remains insufficient to definitively establish long-term durability of remission or to exclude late toxicities that may emerge over decades.

The evidence base is further characterized by reliance on observational designs without randomized comparisons to either conventional therapies or alternative cellular interventions such as autologous hematopoietic stem cell transplantation. This absence of controlled comparative data precludes definitive conclusions regarding the relative efficacy, safety, or cost-effectiveness of CAR-T therapy versus established treatment approaches. Patient selection in published series has uniformly

focused on severe, refractory disease with multiple prior treatment failures, representing a highly selected population that may not reflect the broader spectrum of autoimmune disease severity or treatment responsiveness. Consequently, the impressive response rates observed (approaching 100% in published series) may not be reproducible in less selected populations or in earlier disease stages.

Regarding preclinical evidence (n = 25 studies, 14.6% of included literature), most mechanistic insights derive from murine models that, while informative, they have well-recognized limitations in recapitulating human autoimmune disease complexity, including differences in immune system organization, disease kinetics, and response to immunotherapy. Translation of promising preclinical findings to clinical efficacy remains uncertain, particularly for allergic disease applications where no human clinical data yet exist. The review articles cited (n = 45, 26.3% of literature) provide valuable synthesis and expert perspective but inherently reflect the opinions and potential biases of their authors rather than primary evidence generation.

Publication bias represents another important consideration, as the uniformly positive outcomes reported in published CAR-T case series may reflect selective reporting of successes, with negative results or treatment failures potentially underreported. The novelty and high profile of CAR-T therapy may incentivize publication of favorable outcomes while discouraging reporting of adverse events or treatment failures. Additionally, the rapid evolution of the field means that some cited evidence, particularly from conference presentations and trial registries (n = 5, 2.9%), represents preliminary or incomplete data subject to revision upon final publication.

Despite these limitations, the convergent findings across independent centers, the mechanistic plausibility supported by preclinical studies, the consistency of outcomes across different autoimmune diseases, and the biological rationale for immune reset all provide substantial, though not definitive, support for the therapeutic potential of CAR-T cells in carefully selected patients with refractory autoimmune disease. The evidence base is evolving rapidly, with multiple ongoing trials that will provide higher-quality comparative data in the coming years. Readers are encouraged to consult Table S1 (Supplementary Material) to assess the specific evidence type and quality supporting particular claims throughout this review, and to weight their interpretation accordingly.

13. Conclusions

Chimeric antigen receptor T-cell (CAR-T) therapy is rapidly emerging as a transformative treatment strategy beyond oncology, particularly for severe autoimmune and potentially allergic diseases. Clinical studies have demonstrated remarkable efficacy in patients with treatment-refractory autoimmune disorders such as systemic lupus erythematosus, idiopathic inflammatory myopathies, and systemic sclerosis, with many patients achieving complete, drug-free remission. Follow-up data extending up to three years suggest that these responses are durable and may exceed the long-term benefits achieved with conventional immunosuppressive therapies. Such findings raise the possibility that CART therapy may not only control disease activity but also induce profound immune resetting capable of producing long-lasting remission and, in selected cases, a functional cure.

The application of CAR-T technology to allergic diseases represents another promising frontier. Preclinical studies have shown that targeting IgE-producing B cells or employing regulatory CAR-T cells can suppress allergic responses and promote immune tolerance. Although clinical evidence in humans is lacking, these approaches could eventually transform the management of severe allergic conditions by addressing the underlying causes of disease rather than merely alleviating symptoms.

Despite these encouraging advances, several challenges remain. Long-term safety and efficacy beyond a few years are still uncertain, and optimal patient selection criteria have yet to be established.

In addition, the high cost, complex manufacturing process, and limited availability of specialized treatment centers currently restrict widespread implementation. Further mechanistic studies are needed to understand how durable remission is maintained after immune reconstitution and to identify biomarkers predictive of treatment success.

Future innovations, including CAAR-T cells, dual-targeting CAR designs, safety switches, allogeneic "off-the-shelf" products, and streamlined manufacturing platforms, are expected to enhance efficacy, safety, accessibility, and affordability. As clinical experience grows and technological barriers are overcome, CAR-T therapy is poised to become an important therapeutic option for patients with refractory autoimmune and allergic diseases.

Overall, the field stands at a critical transition from proof-of-concept studies to large-scale clinical validation. Continued investment in clinical trials, long-term registries, and mechanistic research will be essential to fully realize the potential of CAR-T therapy and move closer to the goal of durable remission and cure for patients suffering from chronic immune-mediated diseases.

Use of AI tools declaration

During the production of this work, the authors employed ChatGPT to enhance language and readability. After utilizing this tool/service, the authors examined and edited the text as needed, and they accept full responsibility for the publication's contents.

Conflicts of interest

The authors declare no conflicts of interest.

Author contributions

C.T.Z. Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Validation, Visualization, Supervision, Resources, Writing—original draft, Writing—review & editing. R.N. Data curation, Formal analysis, Investigation, Methodology, Software, Validation, Visualization, Writing—original draft, Writing—review & editing. All the authors read and approved the submitted version.

Availability of data and materials

All data generated or analyzed during this study are included in the present article and its supplementary materials.

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