Review

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Beyond malignancies: Clinical advancements of CAR T-cell in the treatment of autoimmune diseases

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SUMMARY: Chimeric antigen receptor (CAR) T-cell therapy targeting B cells has emerged as a breakthrough treatment for hematological malignancies and shows promising potential in autoimmune diseases. While selective targeting of B-cell activation and autoantibody production represents an innovative therapeutic approach in autoimmune conditions, clinical responses remain suboptimal in many patients due to incomplete B-cell depletion in tissues and limitations in identifying ideal target antigens. Over the past four years, autologous or allogeneic CAR T-cell therapy has demonstrated remarkable efficacy in autoimmune diseases, achieving rapid and sustained B-cell depletion alongside complete clinical and serological remission. This review examines the current landscape of B cell-targeting CAR T-cell therapy, its therapeutic applications in autoimmune disorders, ongoing translational research, and future developments.

Keywords: CAR T-cell therapy, autoimmune disease, immunotherapy

1. Introduction

Autoimmune diseases constitute a diverse spectrum of disorders characterized by disrupted immune tolerance. In these conditions, autoreactive T and B cells, together with autoantibodies, trigger organ damage through multiple effector pathways (*1*). The cornerstone of autoimmune disease management lies in modulating dysregulated T-cell and B-cell responses. Current standard therapeutic approaches aim to inhibit autoreactive immune cell-mediated tissue damage, primarily through the administration of glucocorticoids, nonsteroidal anti-inflammatory drugs, and immunosuppressive agents (including azathioprine, mycophenolate, and tacrolimus). However, these conventional treatments typically require indefinite administration and often result in significant adverse effects while providing suboptimal disease control (*2*).

The selective targeting of B-cell activation and autoantibody production has emerged as a promising therapeutic strategy in autoimmune diseases. Rituximab, a CD20-targeted monoclonal antibody, has been utilized off-label for various autoimmune conditions for approximately two decades (*3,4*). More recent developments include next-generation anti-CD20 and anti-CD19 antibodies, such as ocrelizumab, obinutuzumab, and inebilizumab, which demonstrate enhanced antibody-dependent cellular cytotoxicity and have shown efficacy in reducing disease activity while maintaining favorable safety profiles (*5-7*). Despite these advances, a substantial proportion of patients fail to achieve adequate symptomatic improvement, primarily due to incomplete B-cell depletion within tissue compartments and challenges in identifying optimal target antigens (*8,9*).

The development of therapeutic strategies enabling permanent discontinuation of immunosuppressive medications addresses a major unmet medical need. This review presents a comprehensive analysis of B cell-targeting chimeric antigen receptor (CAR) T-cell therapy and its applications in autoimmune disorders. We examine the rapidly evolving landscape of translational research in CAR T-cell therapies (Table 1, Figure 1), and explore future developments in this field.

2. Therapy principle of CAR T-cells

CARs represent sophisticated synthetic receptors comprising multiple functional domains from distinct origins. Their structure includes: *i*) An extracellular antigen recognition domain derived from antibodies, *ii*) A flexible hinge region, *iii*) A transmembrane domain,

Table 1. Clinical trials of CAR T-cell therapy for autoimmune diseases

Autoimmune disease (*Ref.*)	Number of patients	CAR T-cell target antigen(s)	T cell source	CAR T-cells duration	Safety	Outcomes	Period of drug-free
SLE (*20*)	1	CD19	autologous	7 weeks	no CRS/ICANS	improvement in laboratory parameters and clinical disease activity	no report
SLE (*21*)	5	CD19	autologous	30 days	grade 1 CRS: 3; no ICANS	improvement in laboratory parameters and clinical disease activity in all patients	median of 8 months
SLE (*22*)	8	CD19	autologous	40 days (received rituximab); 58 days (no rituximab)	grade 1 CRS: 5; no ICANS	improvement in laboratory parameters and clinical disease activity	up to 29 months
SLE (*23*)	8	CD19	autologous	up to 60 days	grade 1 CRS: 7; grade 3 CRS: 1; no ICANS	improvement in laboratory parameters and clinical disease activity in all patients	up to 365 days
SLE (*24*)	1	CD19	autologous	6 months	grade 1 CRS:1; no ICANS	improvement in laboratory parameters and clinical disease activity	8 months (plus hydroxychloroquine and low-dose glucocorticoids)
SLE (*26*)	15	BCMA/CD19	autologous	exceeding 28 days	grade 1 CRS: 13; ICANS:1	improvement in laboratory parameters and clinical disease activity in 12 patients	up to 1134 days
SLE (*57*)	4	CD19	allogeneic	180 days	grade 1 CRS: 4; no ICANS or GVHD	improvement in laboratory parameters and clinical disease activity in all patients	during the 6-month follow-up period, 1 patient achieved a drug-free status
SLE (*58*)	3	CD19	allogeneic	Within 6–12 months	no CRS/ICANS/GVHD	improvement in laboratory parameters and clinical disease activity in all patients	patient 1 withdrew the study; 12 months (patient 2 plus prednisone for 6 months; patient 3 plus prednisone continuously
SLE (*71*)	5	CD19	*In Vivo*	within 2–3 days	grade 1 and 2 CRS: 3; no ICANS	improvement in laboratory parameters and clinical disease activity	no
ASS (*27*)	1	CD19	autologous	within 50 days	grade 1 CRS: 1; no ICANS	improvement in laboratory parameters and clinical disease activity	up to 180 days
ASS (*28*)	1	CD19	autologous	within 30 days	grade 1 CRS: 1; grade 1 ICANS	improvement in laboratory parameters and clinical disease activity	up to 150 days
ASS (*29*)	1	CD19	autologous	within 149 days	grade 1 CRS: 1; no ICANS	improvement in laboratory parameters and clinical disease activity	8 months (plus mycophenolate and nintedanib)

Abbreviations: SLE, systemic lupus erythematosus; ASS, antisynthetase syndrome; IMNM, immune-mediated necrotizing myopathy; NMOSD, neuromyelitis optica spectrum disorder.

Table 1. Clinical trials of CAR T-cell therapy for autoimmune diseases (continued)

Autoimmune disease (*Ref.*)	Number of patients	CAR T-cell target antigen(s)	T cell source	CAR T-cells duration	Safety	Outcomes	Period of drug-free
IMNM (*31*)	1	BCMA	autologous	within 2months	grade 1 CRS: 1; no ICANS	improvement in laboratory parameters and clinical disease activity	18 months
Systemic sclerosis (*32*)	1	CD19	autologous	11months	grade 1 CRS:1; no ICANS	improvement in laboratory parameters and clinical disease activity	11 month (plus mycophenolate and nintedanib)
Systemic sclerosis (*22,33*)	4	CD19	autologous	40 days (received rituximab); 58 days (no rituximab)	grade 1 CRS:3 no ICANS	improvement in laboratory parameters and clinical disease activity	up to 6 month
Systemic sclerosis (*56*)	2	CD19	allogeneic	6 months	no CRS; no ICANS; no GVHD	improvement in laboratory parameters and clinical disease activity in all patients	6 months
Generalised myasthenia gravis (*34*)	9	BCMA	autologous	no report	no CRS no ICANS	improvement in laboratory parameters and clinical disease activity in all patients	up to 9 months (most continued receiving corticosteroids)
Generalised myasthenia gravis (*35*)	2	BCMA	autologous	patient1:3 months patient2:6 months	grade 1 CRS: 1 no ICANS	improvement in laboratory parameters and clinical disease activity in all patients	18 months
Generalised myasthenia gravis (*36*)	1	CD19	autologous	still detectable after 62d	no CRS; no ICANS; no GVHD	improvement in laboratory parameters and clinical disease activity	62 days (plus low-dose glucocorticoids)
Myasthenia gravis / Lambert-Eaton syndrome (*37*)	2	CD19	autologous	154 and 94 days	patient 1: grade 1 CRS, grade 1 ICANS; patient 2: grade 2 CRS, no ICANS	improvement in laboratory parameters and clinical disease activity in all patients	up to 7 months
Generalised myasthenia gravis (*38*)	18	bispecific BCMA/ CD19	autologous	within 28days	grade 1 CRS: 7; ICANS:1	improvement in laboratory parameters and clinical disease activity in 17 patients	On day 180, 15 participants discontinued their glucocorticoid
NMOSD (*39*)	12	BCMA	autologous	6 months	all patients had grade 1 or 2 CRS; No ICANS	improvement in clinical disease activity	At a median 5.5-month follow-up, 11 patients attained drug-free remission
Multiple sclerosis (*41*)	2	CD19	autologous	Patient 1: remained detectable on day 100 patient 2: may detect at days 20	Patient 1: grade 1 CRS, no ICANS; Patient 2: no CRS, no ICANS	patient 1: improvement in clinical disease activity patient 2: neurological symptoms were stable	patient 1: up to 100days patient 2: last follow-up 28days
Progressive multiple sclerosis (*42*)	5	BCMA	autologous	continued detection over the subsequent 3 months	grade 1 CRS: 4; ICANS: no report	improvement in laboratory parameters and clinical disease activity in all patients	up to 9 months

Abbreviations: SLE, systemic lupus erythematosus; ASS, antisynthetase syndrome; IMNM, immune-mediated necrotizing myopathy; NMOSD, neuromyelitis optica spectrum disorder.

Table 1. Clinical trials of CAR T-cell therapy for autoimmune diseases (continued)

Autoimmune disease (*Ref.*)	Number of patients	CAR T-cell target antigen(s)	T cell source	CAR T-cells duration	Safety	Outcomes	Period of drug-free
CIDP (*43*)	2	BCMA	autologous	6 months	grade 1 CRS: 2; ICANS: no report	improvement in laboratory parameters and clinical disease activity in all patient	patient 1: up to 12 months, relapse following COVID-19 infection patient 2: up to 24 months

Abbreviations: SLE, systemic lupus erythematosus; ASS, antisynthetase syndrome; IMNM, immune-mediated necrotizing myopathy; NMOSD, neuromyelitis optica spectrum disorder.

and *iv*) An intracellular activation domain derived from T cells (Figure 2).

The antigen-binding domain, typically constructed as a single-chain variable fragment, facilitates MHC-independent target antigen recognition. The hinge region and transmembrane domain serve as a structural bridge, connecting the extracellular antigen-binding component to the intracellular signaling machinery. The intracellular domain incorporates T-cell receptor (TCR) components essential for initiating T-cell activation upon antigen engagement (*10,11*).

Second-generation and later CAR designs incorporate one or two co-stimulatory domains (predominantly CD28 and/or 4-1BB) alongside the activation domain, enhancing T-cell activation, proliferation, and survival capabilities. Through genetic engineering, CAR-encoding DNA is integrated into T cells, generating CAR T-cells capable of antigen recognition, activation, and target cell elimination upon host infusion (*12*). Current clinical research focuses primarily on CARs targeting CD19 or B-cell maturation antigen (BCMA) expressed on B-cell surfaces (*13,14*).

3. Clinical implementation of CAR T-cell therapy

The therapeutic protocol for CAR T-cell treatment involves utilizing autologous T cells and requires preliminary lymphodepletion chemotherapy (*15*). This preparative regimen, typically employing cyclophosphamide and fludarabine, creates an optimal microenvironment for CAR T-cell proliferation and activation. The manufacturing process encompasses: *i*) Leukopheresis to collect sufficient functional lymphocytes, *ii*) T-cell modification using viral vectors, and *iii*) *In vitro* expansion under stringent quality control measures (Figure 3).

CAR T-cell therapy has demonstrated remarkable efficacy in B-cell malignancies, including B-cell acute lymphoblastic leukemia and large B-cell lymphoma (*16,17*). Notably, in refractory and relapsed disease settings, CAR T-cells have shown the potential to induce sustained and potentially curative responses, highlighting their therapeutic promise (*18*).

3.1. CAR T-cell therapy in systemic immune-mediated disease

3.1.1. Systemic lupus erythematosus (SLE)

SLE is a severe autoimmune condition predominantly affecting young women and has historically shown limited response to conventional B-cell depleting antibody therapies. Nevertheless, it has emerged as the autoimmune disease with the most prolific and advanced CAR T-cell research. Preclinical studies by Jin *et al.* demonstrated that anti-CD19 CAR T-cell therapy effectively eliminated circulating CD19+ B cells in

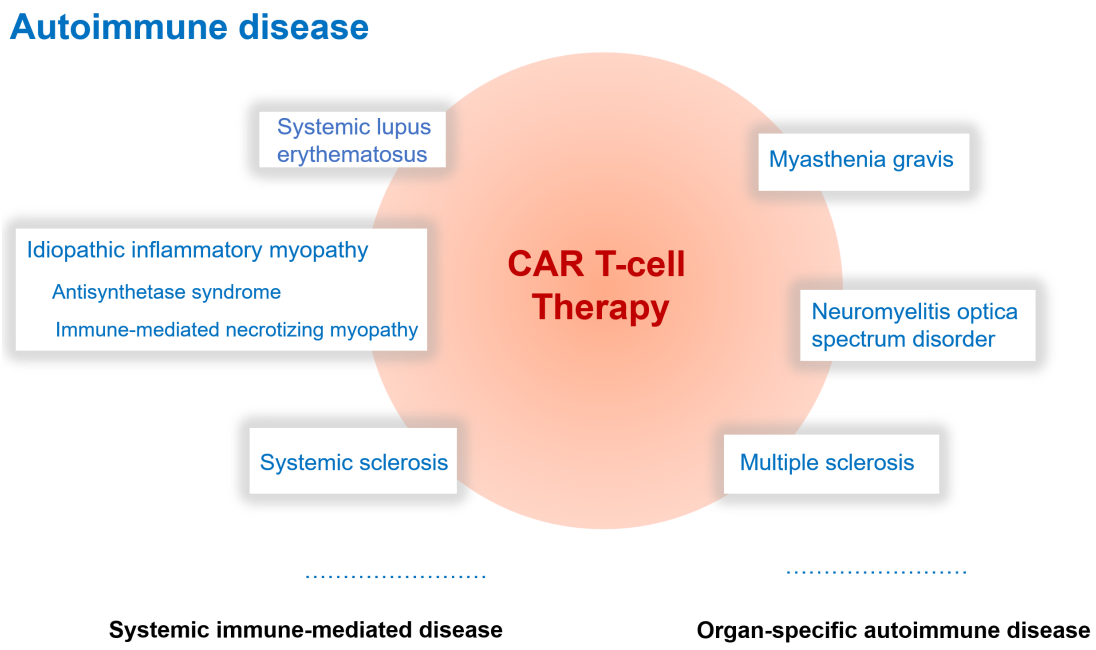

Figure 1. The therapeutic spectrum of CAR T-cells treatment in autoimmune disease.

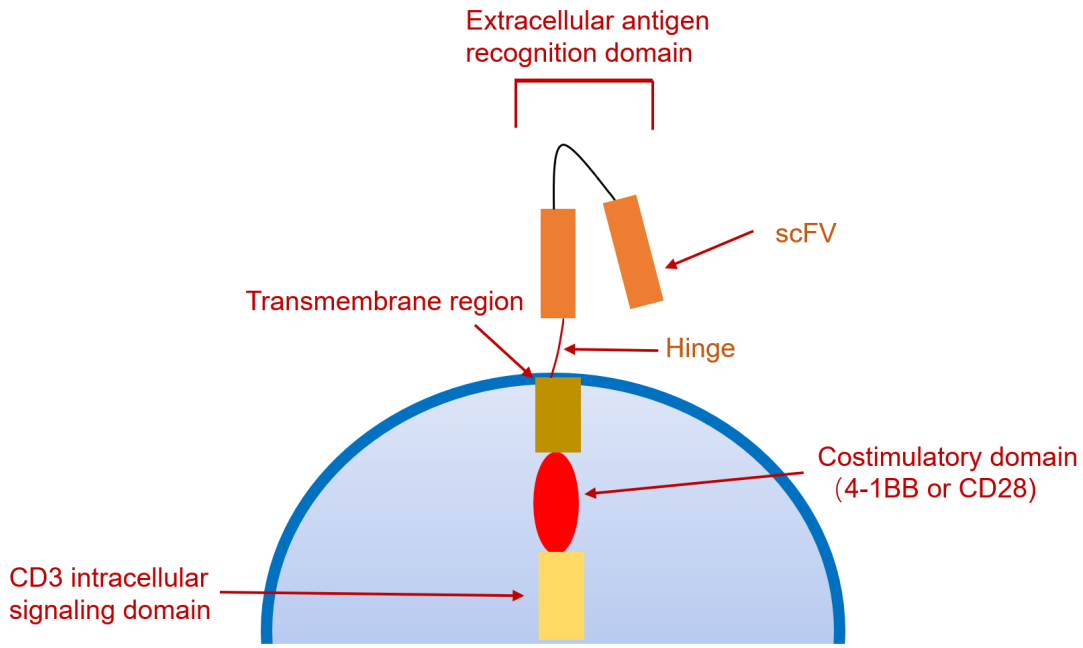

Figure 2. Schematic representation of the CAR T structure. The CAR contains a single-chain variable fragment (scFv), a transmembrane region, an intracytoplasmic costimulatory domain (usually 4-1BB or CD28 in 2nd-generation constructs), and a CD3 intracellular signaling domain.

murine SLE models, resulting in improved survival rates and attenuated manifestations of skin lesions and glomerulonephritis (*19*). These findings also suggested potential prevenative applications of CAR T-cell therapy in SLE.

A breakthrough in clinical application occurred in 2021 when Mougiakakos *et al.* reported the first case of CD19-targeted CAR T-cell therapy in autoimmune disease: a 21-year-old woman with refractory SLE. The therapy demonstrated robust *in vivo* expansion of CAR T-cells followed by a characteristic decline, with persistent detection of circulating CAR T-cells for seven weeks. Notably, the patient experienced no adverse events such as cytokine release syndrome (CRS), neurotoxicity, or prolonged cytopenia, while maintaining sustained B-cell depletion. Within five weeks, double-stranded DNA autoantibody levels decreased significantly, accompanied by clinical remission

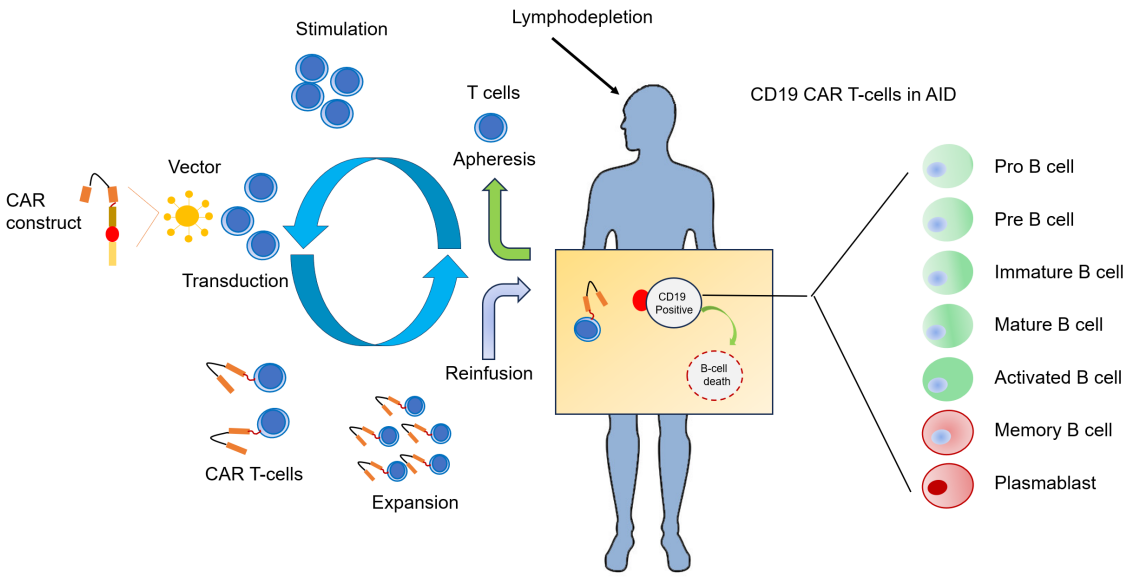

Figure 3. Illustration of autologous CAR T-cells treatment. T cells are collected from the patients' peripheral blood by apheresis. Next, T cells are genetically modified to include a CAR and finally expanded to obtain millions of CAR T-cells. After lymphodepleting chemotherapy, CAR T-cells are reinfused into the patients. Anti-CD19 CAR T-cells, for example, recognise CD19 expressed at various stages of the B-cell lineage, become activated, and destroy the target cell. *Abbreviations*: AID, autoimmune disease. CAR, chimeric antigen receptor.

evidenced by improved proteinuria and SLE Disease Activity Index scores. The rapid reduction in dsDNA autoantibodies suggested CD19-expressing plasmablasts as their primary source (*20*).

Building on these initial successes, subsequent studies have evaluated the safety and clinical efficacy of CD19-targeted CAR T-cell therapy in patients with treatment-resistant or moderate-to-severe SLE. Despite variations in dosing regimens and follow-up durations (up to 29 months), the findings collectively confirm the therapy's transformative potential. Most patients achieved either disease remission or a low disease activity state, accompanied by normalized serologic parameters, while long-term safety was characterized by only mild infections. These results position CAR T-cell therapy as a groundbreaking advancement for refractory SLE, particularly for severe clinical phenotypes including lupus nephritis and immune thrombocytopenia (*21-24*). Furthermore, its efficacy in penetrating sanctuary sites may be key to its success in complex manifestations such as neuropsychiatric lupus (*25*).

Feng *et al.* found that peripheral $CD19^+$ B cells and bone marrow $CD19^-BCMA^+$ long-lived plasma cells (LLPCs) are dominant autoantibody sources, indicating that successful CAR T-cell therapy for SLE must target both cell populations. Indeed, dual anti-CD19/anti-BCMA CAR T-cell therapy has demonstrated good safety and promising efficacy in treatment-refractory SLE. Multi-omic analyses confirmed the elimination of autoreactive $CD19^+BCMA^+$ clones, along with reconstitution of naïve B cells and downregulation of pathogenic immune signatures—findings that point to improved immune homeostasis. Longitudinal monitoring of three patients for one year revealed sustained eradication of pathogenic clones, hinting at a potential cure (*26*).

3.1.2. Idiopathic inflammatory myopathy: Antisynthetase syndrome (ASS)

Müller *et al.* documented remarkable therapeutic success with CD19 CAR T-cell therapy in ASS. By day 180 post-administration, the patient demonstrated near-complete recovery of muscle strength and endurance, accompanied by significant improvements in biochemical markers and imaging studies (*27*). Extended observations from other studies confirmed that patients maintained major clinical responses without the need for glucocorticoids or other immunosuppressive agents for up to 12 months (*28,29*).

Müller *et al.* demonstrated that BCMA CAR T-cell therapy can restore drug-free remission after relapse of ASS after the first CD19 CAR T-cell treatment. This case highlights the challenges in CAR T-cell reinfusion, underscores the potential of alternative targets and therapeutic products, and suggests that plasma cell depletion may enhance therapeutic outcomes in treatment-refractory patients (*30*).

3.1.3. Immune-mediated necrotizing myopathy (IMNM)

Qin *et al.* reported significant therapeutic success with BCMA CAR T-cell therapy in IMNM, documenting improved limb strength by month three and near-normal neurological function at nine months. Clinical and radiological improvements persisted beyond 18 months without additional immunomodulatory intervention. The study revealed comprehensive immune system

modulation, demonstrated through longitudinal single-cell RNA analysis and detailed receptor sequencing. Notable findings included specific CD8+ CAR T-cell characteristics, featuring enhanced NK-like phenotype patterns and distinct cell death tendencies compared to malignancy applications (*31*).

3.1.4. Systemic sclerosis

Third-generation CD19 CAR T-cell combination therapy demonstrated significant efficacy in systemic sclerosis, as reported by Merkt *et al.* (*32*). Treatment resulted in improved skin fibrosis and lung function, with dramatic regression visible on imaging studies. Eleven-month follow-up confirmed sustained improvement through normalized inflammatory markers (CRP and hsTNT) and declining autoantibody levels. In a cohort of four patients, marked reductions in global disease and skin activity were observed six months post-treatment, enabling complete discontinuation of glucocorticoids and other immunosuppressive medications (*22,33*).

3.2. CAR T-cell therapy in organ-specific autoimmune disease

3.2.1. Myasthenia gravis

Granit *et al.* demonstrated significant therapeutic potential of BCMA-directed mRNA CAR-T cell therapy in generalized myasthenia gravis, with symptom improvement emerging after 5–8 weeks and persisting up to 12 months. This approach notably eliminated the requirement for lymphodepletion chemotherapy while avoiding common complications such as CRS, neurotoxicity, and hematological toxicities (*34*). Tian *et al.* demonstrated that proliferating cytotoxic-like $CD8^+$ T cell clones were identified as primary effectors in autoimmunity, whereas pre-infusion cytotoxic/proliferation impairment and profound mitochondrial dysfunction in $CD8^+$ T cells—along with subsequent generation of defective CAR T-cell products—may explain patient-specific therapeutic outcomes (*35*). Additional studies demonstrated that CD19 CAR T-cell infusion improved muscle strength, correlating with improved antibody profiles (*36,37*). Dual-target CAR T-cell (*e.g.*, BCMA-CD19) showed promise in Zhang *et al.*'s cohort, where refractory generalized MG patients achieved remission, suggesting broader antigen targeting may reduce relapse risk (*38*).

3.2.2. Neuromyelitis optica spectrum disorder (NMOSD)

Qin *et al*.'s research revealed promising outcomes for BCMA CAR T-cell therapy in relapsed/refractory AQP4-IgG seropositive NMOSD patients. During a median 5.5-month follow-up, all eleven patients maintained relapse-free status with improved disability measures and quality-of-life outcomes, accompanied by declining serum AQP-4 antibody levels. Mechanistic studies identified proliferating cytotoxic-like CD8+ CAR T-cell clones as primary autoimmunity effectors. The enhanced chemotactic properties of anti-BCMA CAR T-cells facilitated blood-CSF barrier crossing, enabling effective elimination of CSF plasmablasts and plasma cells while suppressing neuroinflammation. Notably, CD44-expressing early memory phenotype correlated with sustained CAR T-cell persistence (*39,40*).

3.2.3. Multiple sclerosis (MS)

Fischbach *et al.* reported pioneering treatment of progressive MS using fully human CD19 CAR T-cell therapy (KYV-101) in two patients. The therapy demonstrated favorable safety profiles with evidence of CAR T-cell presence and expansion in cerebrospinal fluid, notably without neurotoxicity. The observed intrathecal antibody reduction, coupled with CAR T-cell expansion, suggested effective targeting of CNS CD19+ cells (*41*). Qin *et al.* demonstrated that anti-BCMA CAR-T cells could not only enter CNS but also reduce oligoclonal bands (OCBs) and kappa free light chains (KFLC), leading to significant functional improvement in the progressive multiple sclerosis (PMS) cohort, with follow-up of up to 9 months. Notably, CAR T-cells in the cerebrospinal fluid (CSF) exhibited a delayed peak and longer persistence compared with those in peripheral blood and bone marrow. Critically, TSPO-PET imaging revealed that this clinical improvement was likely mediated by alleviation of microglia-mediated neuroinflammation (*42*).

3.2.4. Chronic inflammatory demyelinating polyneuropathy

Dong *et al.* reported two patients had no severe adverse events and achieved drug-free remission within 6 months post–CAR T-cell therapy. One patient experienced relapse 12 months post-infusion following severe COVID-19 infection, and the other patient had achieved sustained symptom remission for 24 months post-infusion. Disease relapse coincided with pathogenic B cell reactivation and recurrence of axon/myelin-targeting autoantibodies or pathogenic peptides, while B cell metabolic reprogramming featuring hyperglycolysis constituted a mechanistic driver of relapse (*43*).

4. CAR T-cell toxicity in autoimmune diseases

CAR T-cell therapies are associated with significant adverse events, including CRS, immune effector cell-associated neurotoxicity syndrome (ICANS), and hemophagocytic lymphohistiocytosis, all of which present complex clinical management challenges (*44*). CRS manifests as an acute systemic inflammatory syndrome characterized by sepsis-like symptoms,

including fever and hypotension. The underlying mechanism involves activated CAR T-cells interacting with myeloid cells, leading to substantial cytokine release. The standard therapeutic approach includes tocilizumab (anti-interleukin-6) administration and steroid therapy (*45*).

ICANS typically develops within days to weeks following CAR T-cell administration. While its precise mechanisms remain incompletely understood, current evidence suggests that CAR T-cells secrete pro-inflammatory cytokines into the circulation, leading to blood-brain barrier disruption. This disruption results in cytokine accumulation within the central nervous system and subsequent activation of resident microglial cells (*46*). Initial manifestations include dysgraphia, word-finding difficulties, tremor, cognitive impairment, and fatigue, necessitating consistent monitoring. More severe cases may present with epileptic seizures, increased intracranial pressure, and potentially, coma (*47*). Treatment protocols typically involve dexamethasone administration, with high-dose methylprednisolone reserved for grade 4 ICANS (*48*). Cytopenia represents another significant adverse effect, attributed to either haematotoxic lymphodepletion or underlying immunological processes (*49*). Extended cytopenia particularly warrants attention due to increased susceptibility to infectious complications.

However, a notable distinction exists between cancer and autoimmune disease applications of CAR T-cell therapy. A meta-analysis indicates that CRS occurs in approximately 55.3% of patients, with about 18.5% being severe (*50*). Additionally, while incidence of ICANS ranges from 2% to 64% (severe: 0–50%) (*51*), two Phase I trials reported hemophagocytic lymphohistiocytosis in 32.7% and 35.6% of patients, respectively—a complication with a mortality rate that can reach 80% (*52*). Patients with autoimmune diseases generally demonstrate superior tolerability, experiencing either no or mild manifestations of CRS or ICANS (approximately 61% and 3%, respectively) (Table 1). This markedly improved safety profile may be attributed to the substantially lower antigen burden present in autoimmune conditions compared to B-cell malignancies (*39*). This differential toxicity profile highlights the potential advantages of CAR T-cell therapy in autoimmune disease applications, though continued vigilance and monitoring remain essential components of clinical management.

5. Future in CAR

5.1. Current limitations and allogeneic approaches

Hundreds of studies involving CAR T-cell therapy for autoimmune diseases are registered on *ClinicalTrials.gov*, predominantly in the United States and China, with BCMA and CD19 being the main targets. However, to date, FDA-approved CAR T-cell therapies remain exclusively autologous, involving complex multistep processes. This approach presents significant challenges, including manufacturing and transit delays, elevated costs, and dependence on patient T-cell fitness, collectively limiting therapeutic accessibility (*53*). Several challenging stages—including scale-up, cell source selection, gene delivery, purification, storage, and quality control—can compromise the quality of CAR immune cells and increase cost per dose. Therefore, it is critical to select an appropriate manufacturing strategy (*e.g.*, centralized, point-of-care, next-day, or *in vivo* generation) and to integrate innovations like novel gene transfer methods, alternative cell sources, automation, and artificial intelligence to overcome these bottlenecks and ensure success (*54*).

Allogeneic or "off-the-shelf" CAR T-cells derived from healthy donors offer several advantages: immediate availability of cryopreserved products, standardized production, opportunities for multiple modifications, potential for redosing or combining CAR T-cells targeting different antigens, and reduced costs. However, these cells risk triggering life-threatening graft-versus-host disease and may face rapid host immune elimination. Recent advances in gene editing, particularly TRAC and/or B2M knockout to reduce TCR or MHC class I expression, show promise in addressing these challenges (*55,56*). Wang *et al.* demonstrated the first successful application of off-the-shelf allogeneic CD19-targeted CAR T-cell in treating one relapsing SRP-IMNM case and two relapsing diffuse cutaneous systemic sclerosis cases. The engineered cells persisted beyond three months, achieving complete B-cell depletion within two weeks. Six-month follow-up revealed deep remission without significant adverse events, evidenced by improved clinical response indices and reversed inflammation and fibrosis (*56*). Recently, Yang *et al.* reports the first clinical application of allogeneic anti CD19 CAR T-cell therapy in patients with refractory SLE, demonstrating significant clinical remission and a favorable safety profile. No patients developed immune ICANS or GVHD during treatment (*57*). Wang *et al.* also got favorable results with the allogeneic CD19-targeted CAR T-cell therapy (*58*).

5.2. CAR T-cell innovation

Chimeric autoantibody receptor (CAAR) T cell technology represents a significant advancement, potentially enabling selective elimination of pathogenic B cells while preserving healthy B cells. Oh *et al.* developed a MuSK-CAAR system comprising the MuSK autoantigen linked to CD137-CD3ζ signaling domains, demonstrating specific cytotoxicity against B cells expressing anti-MuSK surface autoantibodies (*59*). In an MG mouse model, MuSK-CAART reduced anti-MuSK IgG without decreasing B cells or total

IgG levels, reflecting MuSK-specific B cell depletion. Specific off-target interactions of MuSK-CAART were not identified *in vivo*, in primary human cell screens or by high-throughput human membrane proteome array. This technology has progressed to phase 1 clinical trials for MuSK autoantibody-positive MG treatment (*59*).

Recent developments include DNA-CAART cells specifically targeting anti-dsDNA autoantibody-expressing B cells, showing promising results in lupus nephritis treatment (*60*). Similarly, DSG3-CAART has demonstrated efficacy in mucosal pemphigus vulgaris, with successful preclinical studies enabling first-in-human trials (*61*). Additional applications are being explored in NMDAR encephalitis (*62*) and experimental autoimmune encephalomyelitis (*63*).

5.3. Alternative cell therapy approaches

CAR-NK cells present distinct advantages over CAR T-cells, offering enhanced tumor-specific targeting and cytotoxicity through co-stimulatory molecules like NKG2D and CD244. These cells demonstrate reduced adverse effects and lower production costs, though challenges persist regarding persistence and transduction efficiency (*64*). Gao *et al.* firstly showed that allogeneic CD19-targeted CAR NK cells were tolerable, with minimal treatment-related adverse events that have burdened other effective immunotherapies, and showed encouraging preliminary efficacy in patients with relapsed or refractory SLE who had been systematically pretreated (*65*). iPSC-derived CD19/BCMA dual-targeting CAR NK cells also demonstrated its treatment effect in systemic sclerosis (*66*).

Regulatory T cells (Tregs) represent another promising approach, functioning through direct cellular interactions and immunosuppressive cytokine production (*67*). CD19-CAR Tregs have demonstrated efficacy in suppressing antibody production and B-cell differentiation *via* TGF-β-dependent mechanisms, with reduced GvHD risk compared to conventional CAR T-cells (*68*). In SLE models, Fox19CAR-Tregs have shown ability to restrict autoantibody generation and restore immune system composition without significant toxicity (*69*).

In vivo CAR T-cell engineering aims to generate CAR T-cells directly within the patient's body. This approach seeks to overcome the limitations of conventional *ex vivo* manufacturing—such as its labour-intensive processes and limited production capacity—by eliminating need for complex external cell processing and logistics. It also holds the potential to enhance clinical outcomes. Driven by recent advances in virology, RNA therapeutics, and nanotechnology, the field is undergoing a radical transformation. The current strategy employs targeted delivery systems, including lentiviral vectors and lipid nanoparticles, to introduce CAR-encoding genetic material into the body's endogenous T cells (*70*). In their preliminary study, Wang *et al.* found that cell-targeted LNP technology can successfully generate functionally active CD19 CAR T-cells *in vivo* in patients with SLE. These CD19 CAR T-cells were capable of depleting B cells, modulating disease-associated autoantibodies, and reducing disease activity. The treatment was associated with only low-grade CRS and no other major toxic effects (*71*).

6. Conclusions

CAR T-cell therapy signifies a pivotal paradigm shift from chronic immunosuppression toward a potential "one-time curative" strategy in autoimmune diseases. To fully realize this transformative potential, rigorous long-term immune monitoring and expansive multicenter trials are essential to confirm durable efficacy and safety.

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