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REVIEW

B cell targeted CAR-T therapy for autoimmune diseases

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Abstract **Chimeric antigen receptor T (CAR-T) cells demonstrate remarkable effectiveness in targeting and eliminating pathogenic B-cell lineages, showing significant specificity and efficacy against B cell malignancies. In addition, CAR-T cell-mediated B cell depletion and resetting, which showed great potential in treating autoimmune diseases, thereby extending the clinical applicability of adoptive cell therapy. In this review, we examine the progression of CAR-T targeted B cell therapy for autoimmune diseases, encompassing the development of new therapeutic strategies and reports on related clinical outcomes. Furthermore, the article delves into the challenges and potential avenues for enhancement related to the safety aspects and inherent limitations of current technological solutions.**

Keywords chimeric antigen receptor-T therapy; autoimmune diseases; clinical application; lymphodepletion; systemic lupus erythematosus; multiple sclerosis; rheumatoid arthritis; myasthenia gravis; immune-mediated necrotizing myopathy; systemic sclerosis

Introduction

The pathogenesis of autoimmune diseases is often diverse, involving not only B lymphocytes that produce autoantibodies and autoreactive T lymphocytes but also being associated with genetic and environmental factors [1]. Given the complexity of their pathological mechanisms, traditional treatments primarily focus on immunosuppressive drugs to alleviate symptoms. These include corticosteroids such as dexamethasone and methylprednisolone, as well as various immunosuppressants, including both targeted monoclonal antibodies (mAbs) and traditional agents such as cyclophosphamide, cyclosporine A, azathioprine, mycophenolate mofetil, methotrexate, and hydroxychloroquine. However, these drugs fail to cure the diseases, and long-term immunosuppressive therapy poses multiple risks to patients, such as increased susceptibility to infections and potential malignancies [2]. Therefore, finding a new method that can fundamentally solve the difficulties in treating autoimmune diseases is particularly important.

B cells are instrumental in the advancement of autoimmune disorders, with their aberrant activation and functional impairment being critical elements in the emergence and development of these pathologies. B cells contribute to the etiology of autoimmune diseases via two distinct mechanisms: direct engagement through the secretion of antibodies and indirect involvement via non-antibody-mediated pathways [3]. In the direct pathway, autoreactive B cells recognize self-antigens, differentiate into plasma cells, and produce large amounts of autoantibodies. These autoantibodies bind to self-antigens to form immune complexes, which are deposited in tissues and trigger chronic inflammatory responses [4]. For instance, patients with systemic lupus erythematosus (SLE) produce numerous autoantibodies targeting self-double-stranded DNA (dsDNA) and nuclear proteins. These autoantibodies induce chronic inflammation and organ damage mediated by immune complexes in various organs, such as the kidneys, heart, lungs, and skin [5]. On the other hand, B cells also participate in the disease process through non-antibody-dependent mechanisms. B cells can present antigens to T cells, promoting the activation and proliferation of T cells and exacerbating the immune response. B cells also secrete various cytokines, including interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α), which exert a direct stimulatory effect on inflammatory responses [4]. Therefore, B cells play a multifaceted role in the

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pathogenesis of autoimmune diseases and are a key target for the treatment of autoimmune diseases. Chimeric antigen receptor T (CAR-T) cell therapy was initially conceived for the treatment of hematological malignancies related to B cells. Currently, this therapy has not only demonstrated remarkable efficacy in treating blood cancers but also exhibited considerable potential in the treatment of autoimmune diseases, owing to its capability to target B cells, thereby offering fresh hope to patients [6].

This review systematically explores the research progress of CAR-T cell therapy targeting pathogenic B cell lineages in the treatment of autoimmune diseases. First, our study delves deeply into the selection of therapeutic strategies, encompassing the ontogeny of B cells, the meticulous screening of therapeutic targets, the sophisticated preparation techniques of CAR-T cells, and the crucial methods of lymphodepletion preceding treatment. Second, we investigated the preclinical and clinical application status of CAR-T cell therapy targeting pathogenic B cell lineages in autoimmune diseases (Fig. 1, Table 1), elucidating its great potential in the treatment of autoimmune diseases. Furthermore, this review discusses the safety and limitations of current technologies and offers insights into the future trajectory of this therapy's development.

CAR-T targeted B cell therapy strategies for autoimmune diseases

Phenotypic marker changes during B cell development

During the development of human B cells, cells progress through multiple stages, including pro-B cells, pre-B cells, immature B cells, transitional B cells, naïve B cells, and mature B cells [7]. Mature B cells further differentiate into germinal center (GC) B cells, memory B cells, and plasma cells. These distinct B cell populations can be accurately sorted and identified through the utilization of over a hundred cell surface molecules, such as CD19, CD20, IgD, CD27, CD38, and CD24. The different combinations of these molecular markers reflect various stages in the maturation process of B cells, which are significant for identifying developmental stages of B cell precursors, functional regulation, and the selection of therapeutic targets for B cell diseases (Fig. 2) [8].

At the pro-B cell stage, cells commence expressing an array of crucial markers such as CD19, CD45, CD24, and CD10. The expression of these markers marks the onset of B cell development [9]. Subsequently, during the late pre-B lymphocyte stage, the CD20 marker becomes continuously expressed [10]. Upon entering the immature B cell stage, the cell surface begins to express the complete B cell receptor (BCR), namely IgM [11], as well as the B cell activating factor of the TNF family receptor (BAFFR), which persists throughout the B cell's entire life cycle except for long-lived plasma cells [12]. Concurrently, the expression of CD19 and CD20 is maintained, while markers such as TdT and CD10 gradually disappear. When mature B cells are activated by antigens and transform into activated B cells, markers such as CD27 and CD30 appear or increase in expression on the cell surface [13]. B cells at this stage are in a highly active state, capable of rapidly responding to antigen stimulation and participating in immune responses. It is noteworthy that CD28 and CD40 could induce activated B cells to differentiate into memory B

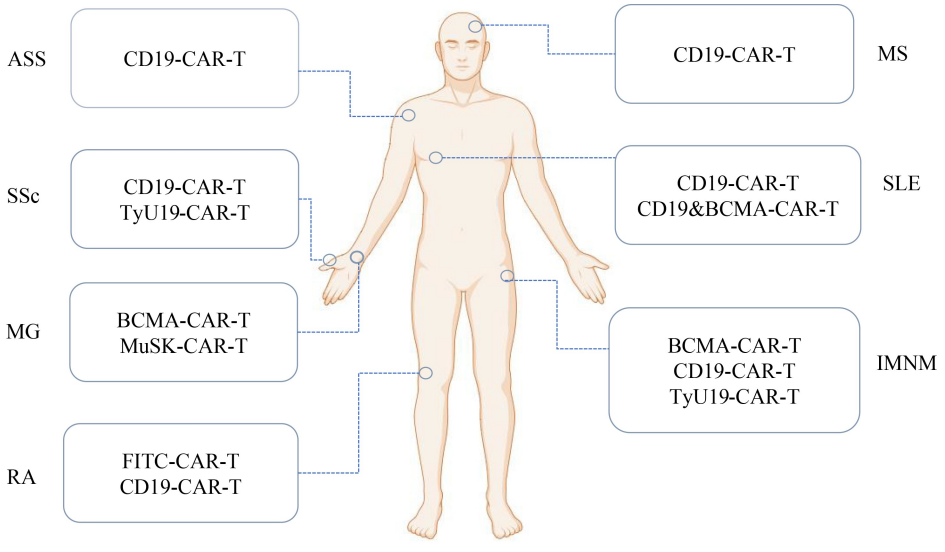

Fig. 1 Application of CAR-T cell therapy in autoimmune diseases. ASS, anti-synthetase syndrome; SSc, systemic sclerosis; MG, myasthenia gravis; RA, rheumatoid arthritis; MS, multiple sclerosis; SLE, systemic lupus erythematosus; IMNM, immune-mediated necrotizing myopathy.

Table 1 Published studies or registered clinical trials of CAR-T cell therapy for autoimmune diseases

Target		Research type	Outcome/current status	Safety	Reference/NCT
SLE	CD19	Case report	$CD19^+$ CAR-T cell therapy results in complete and sustained depletion of B cells and leads to decreased levels of dsDNA autoantibodies	No adverse events related to CAR-T cell therapy	[58]
	CD19		symptoms of SLE remitted quickly, and anti-dsDNA antibodies disappeared and remained negative over 29 months	No adverse events related to CAR-T cell therapy	[59]
	CD19		CAR-T cell therapy resulted in deep B cell depletion and improved clinical symptoms, including normalization of laboratory parameters for serological conversion of anti-dsDNA antibodies	Mild cytokine release syndrome, CRS grade1	[106]
	CD19, BCMA		CAR-T treatment resulted in all autoantibodies being negative, including those from long-lived plasma cells, and complement levels returning to normal	The efficacy and safety of cCARs are good	[33]
	CD19, BCMA		CAR-T cell therapy resulted in patients with stable SLE after 23 months, with various antinuclear antibody (ANA) titers reduced to undetectable levels	Not provided	[60]
MS	CD19	Case report	$CD19^+$ CAR-T cell therapy could rapidly decrease in the number of antibodies in the cerebrospinal fluid (CSF)	CAR-T cell enrichment in the CSF was observed without clinical signs of early neurotoxicity	[69]
	CD19	Clinical trial	Phase I, recruiting	Not provided	NCT06138132
	CD19		Phase I, recruiting	Not provided	NCT06384976
RA	FITC	Basic research	Anti-FITC CAR-T could clear autoreactive B cells from RA patients with high levels of auto-antibodies against the peptides	Further efficacy and safety studies remain to be performed	[76]
	CD19	Case report	In patients treated with CD19/anti-IL-6/anti-TNF-α CAR-T cells, $CD19^+$ B cells in peripheral blood were cleared and the number of tender and swollen joints decreased at 3 and 7 days	The efficacy and safety of CD19/aIL-6/ATNF-α CAR-T therapy are good	[77]
ASS	CD19	Case report	Creatinine kinase and myoglobin concentrations were significantly reduced, alanine aminotransferase also returned to normal concentrations, and lung function was significantly improved in patients with normalized and sustained serum CK levels, $CD19^+$ CAR-T cell therapy could induce rapid remission of refractory ASS	No evidence of CRS, neurotoxic effects, or prolonged cytopenia	[80]
SSc	CD19	Clinical trial	Phase I, II, recruiting	No evidence of CRS,neurotoxic effects,or prolonged cytopenia	NCT06347718
	CD19		TyU19 CAR-T celltherapy achieved antigen-specific B cell depletion and induced rapid remission of refractory SSc, disease scores were achieved in patients and persisted throughout the 6-month monitoring period, with a very desirable safety profile	No evidence of CRS,neurotoxic effects,or prolonged cytopenia	NCT05859997
MG	BCMA	Clinical trial	Phase I, II, recruiting	Common adverse events were headache, nausea, vomiting, and fever, which resolved within 24 h after infusion. Fever was not associated with elevated levels of CRS markers (IL-6, IL-2, and tumor necrosis factor-α)	NCT04146051
	MuSK	Basic research	CD137-based CAAR-T celltherapy achieved antigen-specific B cell depletion.	No evidence of CRS,neurotoxic effects,or prolonged cytopenia	[97]
IMNM	BCMA	Case report	BCMA-CAR-T cell therapy could induce rapid remission of refractory ACNA	The patient experienced a brief grade 1 CRS, which quickly resolved	[102]
	CD19	Clinical trial	Phase I, II, recruiting	No evidence of CRS, neurotoxic effects, or prolonged cytopenia	[103]
	CD19		TyU19 CAR-T cell therapy achieved antigen-specific B cell depletion	It has very ideal security characteristics	[92]

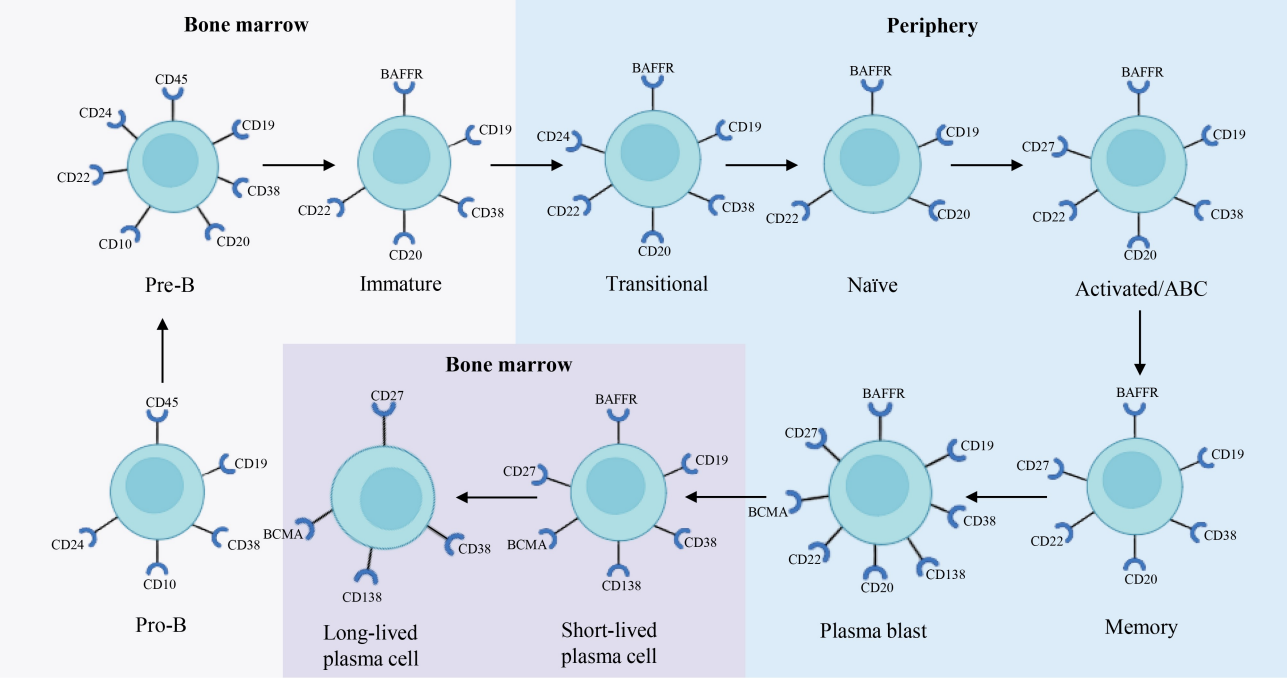

Fig. 2 Changes in surface marker expression during B cell development.

cells, providing long-term immune memory for the body [14]. The terminal differentiation stage of B cells is the plasma cell stage, which is primarily responsible for the massive secretion of antibodies. At this stage, the expression of CD19 on the cell surface decreases, CD20 disappears, and high expression of CD38 becomes a typical marker of plasma cells [15,16]. Surface markers expressed at various developmental stages of B cells play a pivotal role not only in identifying and functionally regulating these cells, but also in furnishing an abundance of targets for the treatment of related diseases, thereby enabling more precise and efficient therapeutic strategies.

Target selection of CAR-T therapy for autoimmune diseases

In CAR-T therapy, the precise selection of targets holds decisive significance for achieving optimal therapeutic effects. CD20, as a marker of early B cell development and differentiation, amplifies calcium signals through the BCR signaling pathway during B cell antigen recognition [17]. Since the 1990s, anti-CD20 mAbs have been utilized to treat CD20-positive B cell malignancies, with notable success [18]. Subsequent advancements have led to the development of targeted CD20 mAbs such as ofatumumab, ocrelizumab, and obinutuzumab, which have expanded the therapeutic arsenal for managing these conditions and have shown significant therapeutic effects in the treatment of SLE and multiple sclerosis (MS), effectively reducing the number of B cells and decreasing disease activity [19,20]. However, in the realm of CAR-T targeted therapy, research has predominantly concentrated on CD19, with relatively less attention paid to CD20. As mentioned earlier, the expression of CD19 spans the entire process of B cell differentiation, while the expression pattern of CD20 in the B cell lineage is relatively limited, especially with the absence of CD20 expression in most plasma cells and plasmablasts. Thus, CAR-T cells that target CD19 are capable of more efficiently eradicating a range of B cell precursors, such as immature B cells, memory B cells, and plasmablasts. It is important to note that, as some cells of the central nervous system (CNS) also express CD19, CAR-T cell therapy directed at CD19 may result in the depletion of these cells and alterations in blood-brain barrier permeability, which may ultimately cause neurotoxicity [21–23]. Therefore, to enhance the accuracy of treatment for autoimmune diseases, additional therapeutic targets are being explored and developed.

B cell maturation antigen (BCMA), a member of the tumor necrosis factor receptor (TNFR) superfamily, is predominantly expressed by mature B cell populations such as memory B cells, plasmablasts, and plasma cells [24]. Previous studies have revealed that BCMA, in collaboration with BAFFR, jointly regulates the proliferation and maturation of B cells, while simultaneously enhancing the survival of plasma cells and facilitating the secretion of antibodies. This has positioned BCMA as a pivotal target for the treatment of autoimmune diseases [25–27]. A recent study has elucidated the underlying mechanism of anti-BCMA CAR-T cell therapy in the treatment of recurrent and

refractory neuromyelitis optica spectrum disorder (NMOSD) [28].

In the field of CAR-T cell therapy aimed at autoimmune diseases, a multitude of potential targets are under rigorous development and investigation. For instance, CD38, also known as cluster of differentiation 38, is a glycoprotein present on the surface of many immune cells, including B lymphocytes. It plays roles in cell adhesion, signal transduction, and calcium signaling. Under normal physiological conditions, CD38 expression is low in lymphocytes and myeloid cells, but it is highly expressed on plasma cells and certain tumor cells, such as those in multiple myeloma (MM). CD38's expression in B cells is particularly significant in the context of inflammation, as it is involved in the regulation of immune responses and can be induced to express in an inflammatory environment [29]. CD22, a type I transmembrane glycoprotein expressed on B lymphocytes, acts as a B cell surface inhibitory co-receptor. It plays a crucial role in preventing autoimmune diseases by regulating B cell signaling and inhibiting BCR signal transduction. This helps prevent immune system overactivation. The development of immunotherapeutic drugs targeting CD22 includes mAbs, antibody-drug conjugates (ADCs), and CAR-T therapies, which have shown promise in treating autoimmune diseases and B cell malignancies [30]. CD27 is expressed on activated B cells and memory B cells following antigen induction [31]. Additionally, CD138 is highly expressed on antibody-secreting plasma cells and plasmablasts [32].

To enhance the efficacy of CAR-T cell therapy, the "dual-targeting" approach has been widely adopted. This approach targets two distinct B cell antigens to prevent antigen escape. In some autoimmune diseases, a portion of autoantibodies are produced by CD19-negative cells. Consequently, CAR-T cell therapy targeting solely CD19 cannot completely eradicate these autoantibodies, thereby precluding the complete control of the disease. Thus, dual-specific CAR-T cell therapy targeting both CD19 and BCMA recognize and attack B cells expressing both CD19 and BCMA, thereby expanding the range of target cells for treatment. Its efficacy has been corroborated in the treatment of SLE [33]. However, the application of this dual-targeting strategy in the treatment of autoimmune diseases still confronts several challenges and issues that warrant consideration. On one hand, it is imperative to ensure that CAR-T cells can accurately recognize and attack target cells, thereby circumventing unnecessary damage to normal tissues and cells. On the other hand, a greater volume of clinical data are required to verify the safety of potential side effects and safety issues that may arise during the treatment process, such as cytokine release syndrome (CRS), neurotoxicity, and infection-related complications.

Particularly, the extensive B cell depletion induced by CD19/CD22 dual-targeting CAR-T therapy may result in prolonged hypogammaglobulinemia, markedly elevating the susceptibility to opportunistic infections. Consequently, in the treatment of autoimmune diseases, it is imperative to administer patients with certain prophylactic interventions to circumvent infections by pathogenic microorganisms, which may arise from diminished immune resistance during immune reconstitution.

Manufacturing of CAR-T cells

The engineering of CAR-T cells involves a series of complex and sophisticated biotechnological processes. In the traditional autologous CAR-T cell preparation, T cells are harvested from the patient and then undergo customized modifications. This process must overcome several key technical challenges, including the repeated use of apheresis machines to separate and enrich T cells from the patient's peripheral blood, activation of these cells with anti-CD3/anti-CD28 antibodies, production of clinical-grade viral vectors, and introduction of the chimeric antigen receptor gene carried by these vectors into the T cells. Finally, the modified CAR-T cells are expanded *in vitro* to reach the required cell count for treatment [34,35]. These technical limitations have further increased the price of CAR-T cell therapy, making it unaffordable for many patients [36].

To simplify the production process and reduce costs, the use of allogeneic CAR-T cells derived from healthy allogeneic donors is considered a potential solution. The essence of this approach lies in employing gene editing technology to knockout the *TCR* gene and *HLA* gene loci within allogeneic T cells, thereby effectively mitigating the risk of graft-versus-host disease (GVHD) [37]. This methodology has demonstrated effectiveness in clinical trials for cancer treatment [38] as well as for autoimmune disorders.

During the manufacturing of CAR-T cells from autologous T cells, there is a risk that autoreactive clones may be inadvertently activated or expanded *ex vivo*. These T cells may retain or even enhance their pathogenic potential after reinfusion, possibly exacerbating the autoimmune condition [39,40]. Moreover, CAR constructs often promote T cell proliferation and survival, which could further support the persistence of harmful autoreactive subsets. As a precaution, researchers are exploring strategies to either selectively deplete autoreactive clones or use gene-edited allogeneic donor T cells to reduce this risk [41].

Another treatment strategy considered to have potential is the *in vivo* programming of *CAR* genes. Engineered viral vectors, bioengineered materials, and nanomaterials are utilized to deliver *CAR* genes into the body, enabling

efficient T cell transduction [42,43]. While this method significantly streamlines the preparation of CAR-T cells, the *in vivo* environment poses greater complexity and uncontrollability, introducing challenges like cell toxicity, gene off-targeting, and over-editing [44].

Lymphodepletion prior to CAR-T cell therapy

In the clinical application of CAR-T technology for the treatment of B cell malignancies, lymphodepletion serves as a pivotal prelude to therapy [45]. This step aims primarily at eradicating lymphocytes in the patient's body via chemotherapy or radiotherapy, consequently creating a more conducive immune microenvironment for the proliferation and sustained efficacy of CAR-T cells, while eliminating immunosuppressive factors. Currently, the combination of cyclophosphamide and fludarabine is the mainstream method for lymphocyte depletion [46]. Other commonly used pre-treatment drugs include pentostatin [47], bendamustine [48], cytarabine [49]; total body irradiation (TBI) is also one of the lymphodepletion regimens for CAR-T therapy [50]. Although there is currently a lack of scientific evidence regarding the necessity of lymphocyte depletion therapy for autoimmune diseases, this pre-treatment has been administered to all such patients who have undergone CAR-T cell therapy to date. This practice aims to guarantee the stable proliferation of CAR-T cells and may also facilitate the resetting and functional recovery of the immune system [51].

Prior to the implementation of the lymphodepletion pre-treatment procedure, a comprehensive assessment of the patient must be conducted, including their general condition, laboratory test results, and imaging findings, to ensure the safety and tolerability of the patient for lymphodepletion therapy and subsequent CAR-T cell infusion [52]. Lymphodepletion treatment is typically scheduled to be performed within 1 week prior to the infusion of CAR-T cells. After completing lymphodepletion treatment, patients are required to rest for at least 2 days. It is crucial to prevent the potential inhibitory effects of chemotherapy on CAR-T cell infusion. If the patient's absolute lymphocyte count falls below 200 cells/μL, pre-treatment regimens are not advisable [53]. When the interval between lymphodepletion and CAR-T cell infusion exceeds 3 weeks and the white blood cell count exceeds 1.0×10^9/L, it may be necessary to reconsider lymphodepletion before CAR-T cell infusion, depending on the patient's bone marrow suppression status. For elderly patients, patients with a creatinine clearance rate < 30 mL/min, patients with poor performance status, or patients with multiple comorbidities, the lymphodepletion regimen and dosage should be adjusted [54]. In addition, before lymphodepletion treatment, it is essential to exclude or control active infections to prevent an increased risk of infection during the period of immune system suppression [55,56].

Clinical application of CAR-T therapy in autoimmune diseases

SLE

SLE is a typical systemic autoimmune disease characterized by high circulating autoantibody titers and immune complex deposition, which can cause inflammatory damage in multiple organs and/or organ systems [57]. The current targets for CAR-T therapy mainly include CD19 and BCMA.

A 20-year-old woman with SLE, refractory to targeted B cell antibody therapy, was treated with CD19-directed CAR-T cells and experienced no therapy-related adverse events, such as CRS, neurotoxicity, or prolonged cytopenia. The infused CAR-T cells underwent rapid expansion, peaking within 10 days before contracting. This was followed by the complete and sustained depletion of circulating B cells, which led to a dramatic reduction in anti-dsDNA autoantibody levels from > 5000 U/mL to 4 U/mL within 5 weeks. Complement C3 and C4 levels normalized, culminating in the rapid remission of her refractory SLE [58]. Another set of clinical data from 8 SLE patients indicated that after the injection of CD19 CAR-T cells, symptoms of SLE remitted quickly, and anti-dsDNA antibodies disappeared and remained negative over 29 months, with complement C3 levels normalizing [59]. In addition, the CD19-BCMA composite CAR (abbreviated as cCAR) capable of dual targeting CD19 on B cells and BCMA on plasma cells, significantly reduces donor-specific antibody levels. In the cCAR clinical trial (NCT04162353), a lupus patient received an injection of cCAR, and 23 months after the injection of cCAR, the patient's SLE symptoms remitted, and various antinuclear antibody (ANA) titers decreased to undetectable levels [60].

Currently, there are new strategies for treating SLE, such as CAR-Tregs, which confer antigen specificity by transducing Tregs cells with recombinant TCRs and then suppress autoimmune responses through Tregs to achieve the goal of treating SLE. A study on CAR-Tregs overexpressing Foxp3 with anti-CD19 CAR showed that in a humanized SLE mouse model, infusion of Fox19 CAR-Tregs reduced the formation of anti-dsDNA and reduced inflammation in SLE target organs, demonstrating good safety and therapeutic effects [61]. At the same time, chimeric autoantigen receptor (CAAR) modified T cells can specifically kill autoreactive B cells targeted by the extracellular domain of CAAR. The authors constructed a C1q protein fused with a CD19-CD3 signal transduction domain. *In vitro*, these T cells

completely consumed B cells within 48 h, suggesting the therapeutic potential of CAAR-T (Fig. 3). However, it is necessary to complete translational research to explore its feasibility in clinical treatment simultaneously [62]. Moreover, a recent study by researchers at East China Normal University has developed a novel allogeneic CD19-targeted CAR-T cell therapy, TyU19, which employs CRISPR-Cas9 gene editing to knockout *TRAC*, *HLA-A*, *HLA-B*, *CIITA*, and *PD-1* genes, achieving significant advancements in the treatment of autoimmune diseases. Compared to conventional CAR-T cell therapies, TyU19 requires only an extremely low-intensity lymphodepletion regimen and has even successfully trialed a "lymphodepletion-free infusion" model in clinical trials, while still demonstrating remarkable therapeutic efficacy. This advancement not only provides a new pathway for the treatment of refractory SLE but also highlights the substantial clinical translation potential of this approach [63].

MS

MS is a CNS inflammatory disease characterized by autoimmune-mediated demyelination and neurodegeneration [64]. The disease is initiated by the aberrant response of autoreactive lymphocytes to autoantigens in the CNS. Current evidence highlights the dominant role of $CD4^+$ T cells in disease pathogenesis [65], particularly interferon-γ (IFN-γ)-producing Th1 cells and interleukin-17 (IL-17)-secreting Th17 cells, which are prominently found in active MS lesions and critically contribute to disease progression [64,66]. However, whether the immune infiltration of B cells occurs inside CNS or in peripheral tissues is unclear. Currently, characterization of B cell clonality in peripheral compartments and cerebrospinal fluid (CSF) in patients with MS using sequencing techniques demonstrates that B cells are able to freely migrate between tissue barriers, and the maturation of most B cells occurs outside the CNS in secondary lymphoid tissues [67,68]. This discovery has important implications for immunomodulatory treatment of MS, especially for B cell-targeted strategies. Currently effective B cell therapeutic strategies for MS focus on circulating B cell depletion (anti-CD20 mAbs; rituximab, ocrelizumab, and ofatumumab), but all with limited efficacy and partial patient responsiveness [69].

The results of the clinical treatment for CD19 CAR-T showed that in two patients with MS treated with CD19 CAR-T cells, expansion of CD19 CAR-T cells was observed in the CSF of the patients, but no CAR-T cell-related neurotoxicity was observed, especially in cases where CAR-T cells expanded substantially in the CSF. Moreover, it also demonstrated the possible effect of CD19 CAR-T cells on antibody-producing B cells in the CSF, as shown by a rapid decrease in the number of antibodies in the CSF of the patient after 14 days of treatment that persisted until 64 days. At the same time, the Expanded Disability Status Scale (EDSS) test indicated an increase in walking distance and remission of the disease after infusion of CD19 CAR-T. This shows good safety and promising disease-specific target cell effects [70]. Currently, Bristol Myers Squibb (BMS) is recruiting more patients to participate in the phase I clinical trial of anti-CD19 CAR-T for MS [71], and Stanford University is conducting a phase I clinical trial (NCT06138132) examining the therapeutic effect of this anti-CD19 CAR-T named KYV-101 in patients with non-relapsing and progressive MS [72].

RA

RA is a chronic autoimmune disease, its main characteristics are joint inflammation and osteochondral injury, among many pathogenic factors, B cells play a role through antibody-dependent and non-dependent pathways, and anti-cyclic peptide antibody (ACPA) and rheumatoid factor (RF) in RA, Immune complexes containing RF or ACPA activate the complement pathway, leading to the production of C5a and membrane attack complexes, both of which cause joint damage [73]. At the same time, in RA, B cells increase the autoimmune

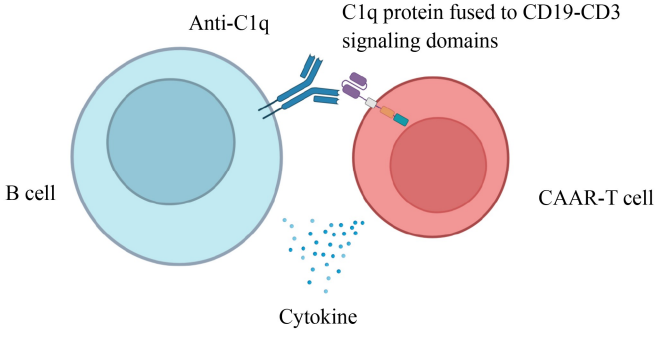

Fig. 3 CAAR-T cell strategy for antigen-specific B cell depletion.

response through antigen presentation and cytokine secretion, and autoreactive B cells may initiate or aggravate the disease by activating autoreactive T cells, and B cells in the peripheral blood of patients with RA can secrete a variety of cytokines to participate in bone destruction, including: TNF-α, IFN-γ, IL-6, IL-1β, IL-17, and IL-10 [74]. At present, targeted B cell antibody therapy, such as anti-CD20 monoclonal antibody rituximab, has been proved to be effective in the treatment of RA, RA patients treated with rituximab show positive clinical responses, such as reduction of synovial B cells, plasma cells and IgG levels [75]. However, pathogenic B cells and protective B cells have been eliminated by rituximab treatment, which will cause a huge immunosuppressive effect in RA patients [76].

The potential of CAR-T cell therapy for RA has been proven by specifically eliminating various autoreactive B cells using universal anti-fluorescein isothiocyanate FITC CAR-T cells combined with FITC-labeled RA autoantigen peptides. The results showed that anti-FITC CAR-T cells could specifically target and kill antigen peptide-producing hybridoma cells and autoreactive B cell subsets from RA patients by recognizing the corresponding FITC-labeled citrullinated peptide epitopes, demonstrating the potential of CAR-T cells in treating RA [77]. Clinically, a novel, autologous, fourth-generation CD19-targeted CAR-T cells secreting anti-IL-6 and TNF-α antibodies (CD19/aIL-6/aTNF-α) was recently used to treat three RA patients refractory to conventional drugs. After treatment with these CAR-T cells, the patients showed rapid improvement. Specifically, after infusion of CAR-T cells, patients exhibited clearance of $CD19^+$ B cells in peripheral blood at 3 and 7 days, and a decrease in the number of tender and swollen joints. RA-related autoantibodies decreased significantly within 6 months, and RF disappeared in all 3 patients and a significant decrease in anti-citrullinated peptide (CCP) antibodies was observed. Additionally, the erythrocyte sedimentation rate (ESR) values also significantly decreased, supporting the therapeutic effect of CAR-T therapy in RA [78].

ASS

ASS is a common subtype of autoimmune rheumatic diseases and falls within the category of idiopathic inflammatory myopathies [79]. Patients exhibit abnormal adaptive immune responses, producing autoantibodies against aminoacyl-tRNA synthetases. These antibodies interfere with normal protein synthesis, leading to a series of inflammatory reactions and tissue damage. The clinical manifestations of this disease are diverse, involving multiple organs, with common symptoms including interstitial lung disease (ILD), myositis, non-erosive arthritis, fever, mechanic's hands, and Raynaud's phenomenon [80]. Histological studies have revealed that the sites of disease onset in ASS primarily involve B cells and plasmablasts located near T cells, and are associated with changes in the peripheral B cell spectrum. Current treatment options include corticosteroids, intravenous immunoglobulin (IVIG), and B cell- and T cell-targeted therapies. However, these treatments are generally limited in efficacy and may be accompanied by severe side effects, potentially increasing mortality [81].

Due to the difficulty in reaching inflamed tissues and lymphoid organs, mAbs drugs targeting pathogenic B cell lineages, such as rituximab, cannot completely eliminate abnormal B cells [81]. CAR-T cell therapy, with its strong tissue penetration and targeting ability against plasmablasts, can achieve deep B cell depletion and has thus been introduced into the treatment of ASS. Recently, a clinical trial was conducted using CD19 CAR-T cells in ASS patients who were refractory to existing treatments. During the 18-month follow-up period after treatment, 3 ASS patients who received CD19 CAR-T cell therapy achieved major clinical responses according to ACR-EULAR criteria, with normalization of muscle function based on MMT-8 assessment and improvement in extramuscular symptoms. Specifically, creatine kinase (CK) levels decreased from 13 600 U/L to 102 U/L, and myoglobin levels dropped from 2148 μg/L to 70 μg/L. Alanine aminotransferase levels also returned to normal. Serum CK levels were normalized and sustained, and high titer anti-Jo-1 antibodies (331 U/L) completely disappeared after CAR-T cell treatment. Pulmonary function also showed significant improvement. These results demonstrate that CAR-T cell therapy is highly effective in treating anti-synthetase syndrome [81,83,84].

SSc

SSc is a classic chronic autoimmune rheumatic disease, characterized by an abnormal response of autoreactive antibodies to self-antigens, leading to attacks on the body's organs and tissues [85]. The pathophysiology of SSc involves progressive fibrosis, inflammatory reactions, vascular damage, and immune dysfunction [86]. Symptoms of SSc widely affect multiple organs, including the skin, kidneys, lungs, heart, gastrointestinal tract, and musculoskeletal system [87]. Numerous studies have indicated that the pathogenesis of SSc is closely related to the imbalance of B cell homeostasis. Therefore, immune therapy targeting pathogenic B cell lineages is considered one of the effective treatment strategies for SSc [88,89].

Although autologous hematopoietic stem cell transplantation has shown some efficacy in improving symptoms in patients with SSc, the multiple side effects associated with this therapy limit its widespread application [90]. CAR-T cell therapy, with its potential

for deep B cell clearance and immune reconstitution in patients, is considered a viable option for achieving long-term drug-free remission in patients with SSc. Bergmann and colleagues conducted a clinical trial (NCT06347718) using CD19 CAR-T cells to treat patients with severe refractory SSc. After 13 months of treatment and follow-up, four patients showed significant improvements in the EUSTAR activity index (a median change of −2.3 points (IQR, −4.5 to −2.1) post-treatment) and Rodnan skin score (a decrease of −9 points (IQR, −19.5 to −7.5) post-treatment). Disease manifestations in the heart, skin, and joints also improved significantly [83,91,92]. Additionally, a novel, multi-gene-edited, allogeneic CD19-targeted CAR-T product has been proven effective in treating two patients with refractory dcSSc (NCT05859997). According to the revised CRISS assessment, patient S0103 showed improvement of at least 25%, 50%, and 75% in three out of the five core items (including modified Rodnan skin score, FVC, HAQ-DI, PGA score, and PtGA score) at the M3 and M6 follow-up visits. This treatment achieved deep B cell depletion and significant clinical improvement in disease scores in all patients, with these benefits persisting throughout the 6-month monitoring period and demonstrating an excellent safety profile [92]. These results highlight the great potential of off-the-shelf allogeneic CAR-T products in treating refractory autoimmune diseases.

MG

MG is a chronic autoimmune disorder characterized by impaired neuromuscular junction transmission. Its primary clinical manifestations of muscle weakness and fatigability, with severe cases may lead to respiratory dysfunction [94]. The pathogenesis of this disease primarily involves the specific attack of the immune system on acetylcholine receptors (AChR) at the neuromuscular junction; in some patients, abnormal antibodies against muscle-specific kinase (MuSK) can also be detected [95].

Currently, clinical treatment mainly relies on anticholinesterase drugs (such as pyridostigmine), glucocorticoids, mAb targeting pathogenic B cell lineages (such as telitacicept), and complement inhibitors (such as eculizumab) to suppress the abnormal immune attack in patients. However, during long-term treatment, patients often develop varying degrees of drug resistance and chronic immunosuppression [96]. In recent years, CAR-T cell therapy targeting BCMA has been applied to the treatment of highly relapsed and refractory MG patients, showing significant efficacy in patients with AChR-IgG and MuSK-IgG, with some patients achieving sustained clinical improvement for over 18 months [97]. Additionally, a MuSK chimeric autoantibody receptor (MuSK-CAAR) T cell therapy targeting CD19 is under preclinical validation. This therapy has demonstrated good efficacy in experimental autoimmune MG mouse models, specifically clearing B cells that secrete MuSK antibodies without reducing the overall B cell or IgG levels [98].

A novel RNA-engineered chimeric antigen receptor T (rCAR-T) cell therapy has been developed for the treatment of generalized myasthenia gravis (gMG). Unlike conventional DNA-integrated CAR-T cells, this approach utilizes transient mRNA-modified *CAR* genes targeting BCMA to selectively deplete autoantibody-producing plasma cells. The mRNA-based modification eliminates risks associated with genomic integration while maintaining therapeutic efficacy. In this clinical study, 14 gMG patients received rCAR-T therapy and were followed for 9 months. Results demonstrated significant improvement in Myasthenia Gravis-Activities of Daily Living (MG-ADL) scores without incidence of CRS or neurotoxicity. The transient nature of mRNA-mediated CAR expression reduced signal amplification and enabled safer outpatient administration [99].

IMNM

IMNM is a subtype of idiopathic inflammatory myopathies characterized by severe proximal muscle weakness, markedly elevated CK levels, and necrosis of muscle fibers, typically in the absence of inflammatory infiltrates [100,101]. A hallmark of IMNM is the presence of specific autoantibodies, most notably anti-signal recognition particle (SRP) and anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR), which are believed to initiate complement-mediated cytotoxicity and drive chronic muscle damage [101]. These autoantibodies are produced by long-lived plasma cells and persist despite conventional immunosuppressive treatments such as corticosteroids, methotrexate, or IVIG, which often fail to induce durable remission and are associated with side effects including myelosuppression, infection, and organ toxicity [100,102].

Given this pathogenesis, therapies that selectively eliminate autoantibody-producing plasma cells have attracted increasing interest. CAR-T cell therapy targeting the BCMA provides the potential for achieving deep, antigen-specific immune clearance. Early clinical data have shown that BCMA-targeted CAR-T therapy in patients with refractory IMNM leads to significant improvements in muscle strength, reductions in CK and autoantibody levels, and long-term immune resetting. Therefore, BCMA CAR-T represents a promising therapeutic strategy that directly addresses the pathogenic mechanism of IMNM, especially in treatment-resistant cases.

In clinical application, BCMA CAR-T therapy was

used to treat a patient with highly refractory IMNM. After 18 months of treatment and follow-up, the patient's neurological examination results nearly returned to normal. Muscle strength in the proximal lower limbs, neck, distal lower limbs, and upper limbs reached normal levels according to the Medical Research Council (MRC) grade 5. Serum CK levels decreased from 4778 IU/L to 260 IU/L, and myoglobin levels dropped from 837 ng/mL to 66.2 ng/mL. Pathogenic autoantibodies were continuously reduced, and B cell lineage reconstitution was induced in the patient [103]. Furthermore, clinical data from the RESET-Myositis Phase I/II trial (NCT06154252) showed that CD19 CAR-T cell therapy (CABA-201) was used to treat a patient with refractory IMNM. Over a 4-month treatment and follow-up period, the patient's CK levels decreased, muscle strength improved, and peripheral B cells were depleted. Compared with pre-treatment levels, autoantibodies such as SRP-9, SRP-72, SRP-54, and Ro-52 significantly decreased, with no significant cytotoxic reactions observed. This indicates that CD19 CAR-T therapy for IMNM is effective and safe [104].

Additionally, the allogeneic CAR-T cells TyU19 was also applied in treating IMNM (NCT05859997). Over a 6-month treatment and follow-up period, the patient's CK concentration decreased from 2295 U/L to 255 U/L. Both the Physician Global Assessment (PGA) and Patient Global Assessment (PtGA) scores significantly improved. The MMT-8 test score increased from 75/150 to 143/150, and the Health Assessment Questionnaire Disability Index (HAQ-DI) decreased from 2 to 0.25. This study demonstrated that allogeneic CD19-targeted CAR-T therapy achieved deep B cell depletion, significantly relieved patient symptoms, and maintained these benefits throughout the 6-month monitoring period, with excellent safety characteristics. These results highlight the great potential of off-the-shelf allogeneic CAR-T products in treating refractory autoimmune diseases [93].

Current limitations and challenges in CAR-T cell therapy

Recent clinical trials underscore the promising efficacy and tolerability of CAR-T therapy in autoimmune diseases including SLE, MS, and RA. However, its clinical translation remains constrained by limited patient cohorts and unresolved biological challenges. Beyond the need for expanded validation, intrinsic limitations of B cell targeting impede universal success: tissue-resident plasma cells within immune-sanctuary sites such as bone marrow persistently evade CAR-T recognition through absence of surface targets like CD19/20, sustaining autoantibody production. Furthermore, in T cell-driven pathologies exemplified by MS, B cell depletion exhibits incomplete efficacy against core neuroinflammatory mechanisms. Compounding this, non-selective depletion risks eliminating regulatory B cells that maintain immune tolerance via interleukin-10 secretion, potentially disrupting homeostatic balance. These collective mechanisms underlie cases of therapeutic non-response despite successful peripheral B cell eradication

The necessity of lymphocyte depletion

Whether patients with autoimmune diseases should undergo lymphocyte depletion therapy before receiving CAR-T therapy remains a matter of debate. Some researchers argue that lymphocyte depletion therapy was originally designed for patients with hematologic malignancies, primarily to facilitate the expansion and persistence of CAR-T cells, as well as to reduce tumor burden and eliminate malignant cells in the bone marrow and lymph nodes. However, for patients with autoimmune diseases, the necessity of lymphocyte depletion is not clear, as there are no tumor cells to eliminate. Instead, the burden that lymphocyte depletion places on patients must be considered. In physically weakened or immunocompromised patients, lymphocyte depletion may exacerbate their health conditions, and several cases of infections following lymphocyte depletion have been reported [56].

Nevertheless, some studies have revealed the potential necessity of lymphocyte depletion therapy. In patients with SLE and IMNM, pharmacokinetic studies of CD19-targeted CAR-T cells have been conducted [59,104]. The results showed that CAR-T cells peaked at days 8 and 15 post-treatment, followed by a rapid decline. Subsequently, B cells re-emerged on average after 3 months. This indicates that a competitive environment is formed between the patient's T cell system and the infused CAR-T cells, leading to a gradual reduction in the CAR-T cell population. Therefore, lymphocyte depletion therapy can provide a stable proliferative environment for CAR-T cells. Additionally, the depletion of the patient's original B and T cells by lymphocyte depletion helps reduce immune rejection and assists allogeneic CAR-T cells in achieving deep B cell depletion, which may contribute to the resetting of the patient's immune system.

Low-dose chemotherapy drugs may enhance the safety of CAR-T cell therapy, especially for elderly, frail, or metabolically compromised patients. Preliminary studies have shown that low-dose chemotherapy agents (e.g., cyclophosphamide and fludarabine at doses of 500 mg/m^2 and 37.5 mg/m^2, respectively) used for lymphodepletion prior to CAR-T targeting therapy for SLE did not significantly reduce therapeutic efficacy [105]. However, due to the close association of individualized low-dose (LD) regimens with specific CAR-T products and the significant variability in patients' immune capabilities, standardization of LD regimens and dosages becomes complex.

Safety

At the current stage, the challenges faced by CAR-T cell therapy are primarily concentrated in three core areas: CAR-T cell-related toxicities, infection risks due to immune suppression, and inflammatory reactions and potential tumor risks triggered by "off-target effects."

It is worth noting that cytotoxic reactions observed in patients with autoimmune diseases treated with CAR-T cell therapy have so far been mostly mild, and can be cured with a small dose of tocilizumab [33,81,91,106,107]. There have been occasional reports of moderate CRS, for example, fever caused by moderate CRS has been reported to exacerbate existing dyspnea in patients with ILD [82]. However, there have been no reports of severe CRS and ICANS to date.

Second, there is a potential risk of infection due to immune suppression. Both lymphocyte depletion and CAR-T cell therapy can weaken the patient's immune system. In particular, after deep B cell depletion caused by CAR-T cell therapy, it usually takes about 3 months to restore B cell function. Therefore, patients with autoimmune diseases receiving CAR-T cell therapy should immediately discontinue the use of immunosuppressive agents after treatment to avoid increasing the risk of infection. Although there is no statistical data on the risk of infection in patients with autoimmune diseases receiving CAR-T cell therapy, approximately 25% of cancer patients may suffer from bacterial, viral, or fungal infections [108]. Therefore, regular testing of various physiological indicators, such as serum immunoglobulin levels, T cell, and NK-cell levels, should be conducted in patients after CAR-T cell therapy, and appropriate prophylactic medications should be administered.

When CAR-T cells attack healthy cells or tissues expressing the same antigen, unintended adverse reactions may be triggered, a phenomenon known as "on-target off-disease toxicity" [82]. Although there have been no reports of off-target effects causing inflammatory reactions and potential tumor risks to date, ensuring the precise targeting and toxicity control of CAR-T cell therapy remains crucial. Currently, several strategies have been developed to enhance the biosafety of CAR-T cell therapy. For example, switchable CAR (sCAR) cells [109,110], CAR-TSCM cells with suicide genes (iCasp9) to regulate survival [111,112], and mRNA-based mCAR cells can all achieve dose-controllable regulation of CAR-T cell activity [113].

Cost, risk, and benefit

However, for patients, facing the high cost of treatment and potential risks, whether the cost and benefits can be balanced, and whether CAR-T treatment is really worth choosing, is a question that deserves in-depth discussion.

CAR-T therapy is expensive, mainly due to the complexity of its production process and the highly personalized nature of treatment protocols. The prices of CAR-T cell therapy products currently approved for sale in the Chinese and U.S. markets are summarized in Table 2. The selling prices of CAR-T cell therapy products vary greatly depending on the type of CAR-T product and the manufacturer, with the single-treatment price of CAR-T cell therapy products produced in China ranging from \$150 000 to \$465 000 per infusion, while those manufactured in the U.S. range from \$373 000 to \$475 000 per infusion. In addition to the above costs, patients also need to bear additional cumulative costs, including leukapheresis, patient monitoring and management of complications, as well as long-term follow-up and physiological indicator testing after treatment to assess efficacy and potential late-onset side effects [51,114,115]. Due to the complex and time-consuming process, there is an inherent risk of production failure [37].

In current reports, there is significant variation in the efficacy and durability of different CAR-T cells. Although CAR-T therapy has demonstrated significant efficacy in some diseases, there is still a risk of treatment failure and disease recurrence. A recent study reported the clinical outcomes of 449 patients who received commercial CAR-T therapy for relapsed/refractory B cell non-Hodgkin lymphoma (NHL), MM, and acute lymphoblastic leukemia (ALL). Within 10 months after treatment, 3.6% of patients developed secondary primary malignancies [116]. In multiple reports on anti-CD19 CAR-T cell therapy for relapsed/refractory aggressive B cell lymphoma, the overall probability of disease recurrence or progression within six months was greater than 50% [117]. Although there have been no reports of disease recurrence and secondary primary malignancies in the treatment of autoimmune diseases, patients should be aware of the potential risks.

When evaluating cost-benefit trade-offs, bispecific antibodies represent a clinically relevant alternative to CAR-T cell therapy. These agents offer significantly lower initial costs (approximately \$50 000/year vs. \$150 000–\$475 000 for a single CAR-T dose) and shorter manufacturing times (approximately 2 weeks vs. 3–4 weeks). However, their requirement for chronic administration contributes to progressive T cell exhaustion and limits deep tissue penetration. Consequently, while bispecific antibodies may serve effectively as bridging therapies, CAR-T cell therapy often remains superior for achieving sustained remission in refractory cases, despite its higher initial resource investment. Therefore, a careful balance is needed between the substantial upfront costs and potential risks of CAR-T therapy and its significant therapeutic benefits.

Table 2 CAR-T cell therapy products and prices marketed in China and the USA

Product name	Generic name	Indications	Price (USD)	Approval date	Approval authority	Country of production
Kymriah	Tisagenlecleucel	Recurrent or refractory B cell acute lymphoblastic leukemia (ALL), Recurrent or refractory large B cell lymphoma, Follicular lymphoma	$475 000 per dose	August 2017	US FDA	USA/Switzerland
Yescarta	Axicabtagene ciloleucel	Recurrent or refractory large B cell lymphoma, follicular lymphoma	$373 000 per dose	October 2017	US FDA	USA
Tecartus	Brexucabtagene autoleucel	Recurrent or refractory mantle cell lymphoma, recurrent or refractory B cell ALL	$373 000 per dose	July 2020	US FDA	USA
Abecma	Idecabtagene vicleucel	Recurrent or refractory multiple myeloma (MM)	$438 000 per dose	March 2021	US FDA	USA
Breyanzi	Lisocabtagene maraleucel	Recurrent or refractory large B cell lymphoma	$410 000 per dose	February 2021	US FDA	USA
Carvykti	Ciltacabtagene autoleucel	Recurrent or refractory MM	$465 000 per dose	February 2022	US FDA	USA
Yescarta (Yikaida®)	Axicabtagene ciloleucel	Recurrent or refractory large B cell lymphoma, B cell ALL	$175 000 per dose	June 2021	China NMPA	China
Rejimabtagene Autoleucel Injection (Bainoda®)	Relmacabtagene autoleucel	Recurrent or refractory large B cell lymphoma, Follicular lymphoma	$195 000 per dose	September 2021	China NMPA	China
Equecabtagene Autoleucel Injection (Fukusu®)	Equecabtagene autoleucel	Recurrent or refractory MM	$175 000 per dose	June 2023	China NMPA	China
Inaticabtagene Autoleucel Injection (Yuanruida®)	Inaticabtagene autoleucel	Recurrent or refractory B cell ALL	$150 000 per dose	November 2023	China NMPA	China
Zevorcabtagene Injection (Saikaize®)	Zevorcabtagene autoleucel	Recurrent or refractory MM	$172 000 per dose	March 2024	China NMPA	China
Carvykti (Kaweidi®)	Ciltacabtagene autoleucel	Recurrent or refractory MM	$465 000 per dose	August 2024	China NMPA	China

Conclusions

In summary, CAR-T cell therapy targeting pathogenic B cell lineages has emerged as a highly promising approach for treating a wide range of autoimmune diseases. By specifically targeting and depleting B cells, which play a pivotal role in the pathogenesis of these conditions, CAR-T cells offer the potential for a cure, rather than merely managing symptoms. Clinical applications in diseases such as SLE, MS, RA, and others have demonstrated not only significant therapeutic efficacy and safety but also led to long-term remission in numerous patients. However, several challenges persist, encompassing the necessity and safety concerns surrounding lymphodepletion, potential off-target effects, as well as the significant cost of treatment.

The trajectory of CAR-T cell therapy for autoimmune diseases hinges on strategically addressing persistent translational challenges. Key priorities center on advancing switchable CAR architectures to enable tunable control over T cell activation kinetics, thereby enhancing safety profiles for chronic autoimmune conditions. Concurrently, robust development of off-the-shelf allogeneic products through precision gene editing offers a viable pathway to circumvent the manufacturing constraints, temporal delays, and economic burdens intrinsic to autologous platforms. Equally pivotal is pioneering efficient *in vivo* generation platforms — leveraging targeted viral vectors or non-viral systems (e.g., lipid nanoparticles/mRNA) —to redirect T cell specificity directly within patients, potentially revolutionizing production scalability and cost structures. Complementary exploration of dual-antigen targeting strategies to refine specificity, alongside prospective multicenter trials establishing durable efficacy and safety across heterogeneous autoimmune indications, remains fundamentally important. Through integrated multidisciplinary innovation, these converging fronts hold significant potential to overcome existing barriers, positioning CAR-T therapy as an accessible, well-tolerated, and transformative pillar in autoimmune disease management.

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Compliance with ethics guidelines

Conflicts of interest Qi Li, Ning Zhao, Ruitao Hou, Juliang Qin, Jiqin Zhang, Mingyao Liu, and Bing Du declare no conflicts of interest.

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