

Redefining multiple sclerosis with CAR-T cell therapy

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Multiple sclerosis (MS) is a chronic autoimmune disorder of the central nervous system characterized by aberrant immune responses against myelin and neuronal antigens, resulting in demyelination, axonal injury, and progressive neurological impairment. Although current immunomodulatory therapies can reduce relapse frequency and slow disease progression, they rarely induce durable remission or reverse established pathology. Chimeric antigen receptor (CAR)-engineered T (CAR-T) cell therapy, initially developed for cancer treatment, has recently emerged as a promising strategy for autoimmune diseases. By engineering T cells to selectively eliminate autoreactive B cells or other pathogenic immune populations, CAR-T therapy holds the potential to achieve long-lasting disease control and even immune system reset. Preclinical studies and early-phase clinical trials targeting CD19⁺ B cells have shown encouraging efficacy in autoimmunity, including MS. Nonetheless, significant challenges remain, such as optimizing antigen targets, minimizing treatment-associated toxicities, sustaining therapeutic benefit, and advancing scalable, safe, and cost-effective clinical applications. In this review, we summarize recent advances in applying CAR-T cell therapy to MS, outline key lessons learned from oncology and other autoimmune diseases, and discuss future directions for establishing CAR-T cells as a transformative approach in neuroimmunology.

INTRODUCTION

Multiple sclerosis (MS) is a chronic, immune-mediated disorder of the central nervous system (CNS) characterized by heterogeneous neuroinflammation and progressive neurodegeneration.¹ Clinically, approximately 85%–90% of patients initially present with relapsing-remitting MS (RRMS), while 10%–15% exhibit primary progressive MS (PPMS). Over time, nearly 80% of RRMS patients transition into secondary PMS (SPMS) within 10–20 years of onset.^{2,3} The early immunopathology of MS is primarily driven by aberrant activation of autoreactive T cells in the periphery and their subsequent infiltration into the CNS, accompanied by waves of immune cell entry, including B cells, monocytes, macrophages, and dendritic cells (DCs).^{4,5} During progression, the disease shifts toward CNS-intrinsic, compartmentalized, and smoldering neuroinflammation,

characterized by expansion and persistence of CNS-resident microglia and astrocytes (Figure 1A).

A hallmark of PMS is the presence of meningeal B cell aggregates that resemble tertiary lymphoid structures, which are closely associated with cortical demyelination and neurodegeneration.⁶ These ectopic follicles secrete proinflammatory cytokines such as tumor necrosis factor- α , interleukin-6 (IL-6), and lymphotoxin- α , as well as pathogenic antibodies, which appear as oligoclonal bands (OCBs) in the cerebrospinal fluid (CSF). While current immunomodulatory therapies, particularly B cell-depleting strategies such as anti-CD20 monoclonal antibodies (mAbs), effectively reduce relapse frequency and control acute inflammatory activity, they do not prevent long-term progression.⁷ This therapeutic gap is likely attributable to the limited penetration of these agents into the CNS parenchyma and their insufficient impact on compartmentalized inflammation and neurodegeneration.⁸

In this context, chimeric antigen receptor-engineered T (CAR-T) cell therapy has recently emerged as a potential immune-resetting strategy for MS (Figure 1B). Unlike conventional immunomodulators that broadly suppress immune activity, CAR-T cells can be engineered to selectively eliminate autoreactive immune subsets implicated in disease pathology, most notably CD19⁺ or CD20⁺ B cells that contribute to intrathecal inflammation and formation of meningeal follicles.^{9,10} Early preclinical studies and, more recently, pioneering clinical investigations suggest that CAR-T therapy may achieve profound and durable depletion of pathogenic B cells, potentially exceeding the efficacy of antibody-based depletion strategies by accessing tissue-resident populations and promoting deeper immune reprogramming.^{9,10} Furthermore, CAR-T cells offer the

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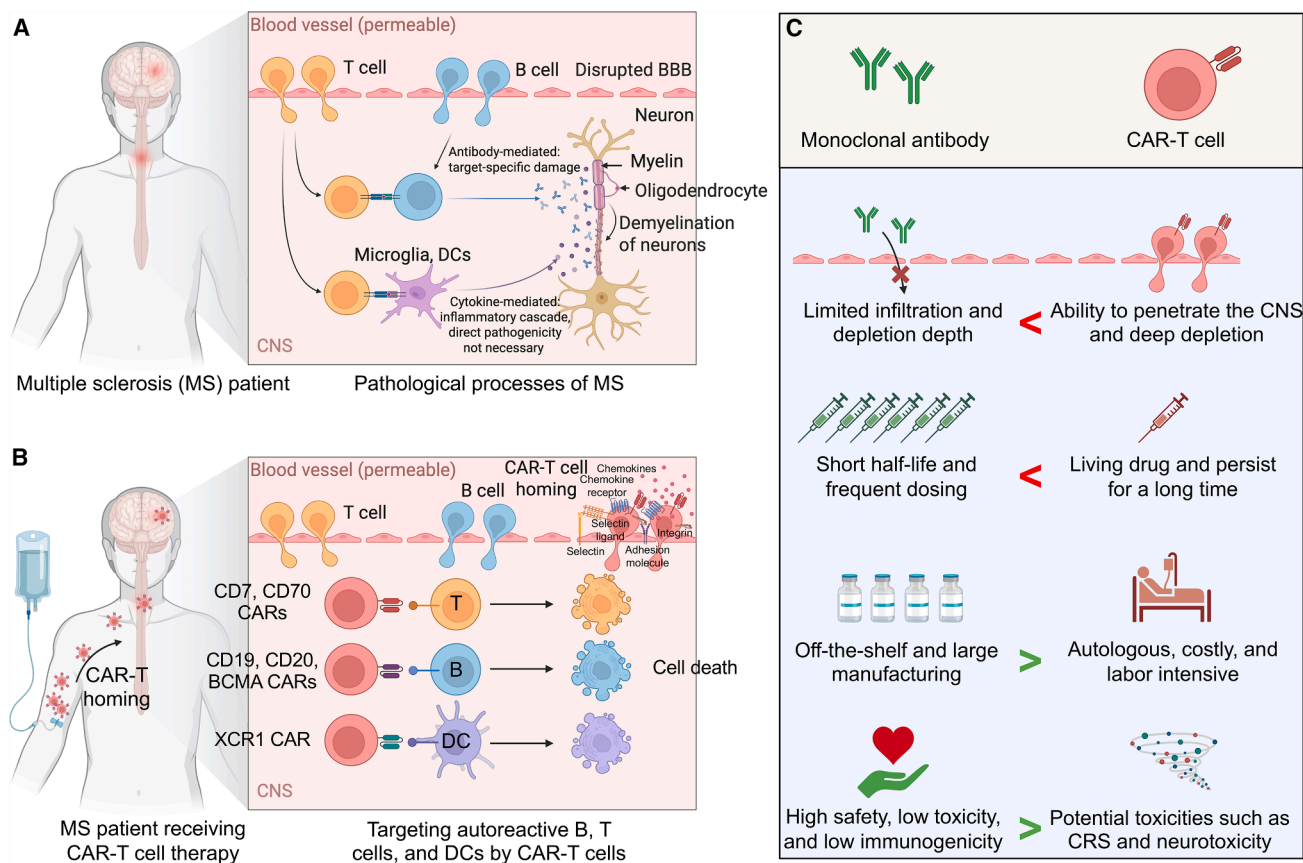


Figure 1. Development of CAR-T cell therapy for treating MS and comparison with monoclonal antibody therapy

(A) Pathological processes of MS. The disease is initiated in the periphery, where autoreactive lymphocytes, including T and B cells, infiltrate the central nervous system (CNS) through a compromised blood-brain barrier (BBB). These cells recognize myelin-derived antigens and trigger an inflammatory cascade by secreting proinflammatory cytokines and recruiting additional immune cells to the lesion sites. Autoreactive B cells contribute to disease progression by producing autoantibodies, releasing inflammatory mediators, and acting as antigen-presenting cells (APCs). Dendritic cells (DCs) and other APCs present autoantigens to T cells, leading to further activation of autoreactive lymphocytes. Activated T cells then promote B cell activation and directly mediate tissue-specific injury, culminating in demyelination, axonal loss, and neurodegeneration. (B) CAR-T cell therapy for MS. Autologous CAR-T cells are engineered *ex vivo* and reinfused into patients, where they home to sites of inflammation within the CNS. Preclinical and early clinical studies have explored various CAR-T cell strategies, including CD7- or CD70-targeting CAR-T cells to eliminate autoreactive T cells; CD19-, CD20-, or BCMA-targeting CAR-T cells to deplete pathogenic B cells; and XCR1-targeting CAR-T cells to selectively target type 1 DCs. These CAR-T products exert therapeutic activity by lysing disease-driving immune cells, thereby ameliorating MS pathology. (C) Comparison between CAR-T and monoclonal antibody therapies for MS. CAR-T cells offer several advantages over monoclonal antibodies, including the ability to deeply infiltrate the CNS, achieve sustained and profound depletion of pathogenic B cells, and function as “living drugs” capable of long-term persistence without the need for frequent dosing. However, CAR-T therapies also present disadvantages, such as reliance on autologous manufacturing, high production costs, limited scalability for multiple patients, and risks of adverse events, including cytokine release syndrome (CRS) and neurotoxicity.

possibility of tailoring specificity beyond B cells, such as targeting autoreactive T cell populations or modulating myeloid and antigen-presenting cell subsets.¹¹ These advances position CAR-T therapy as a promising next-generation approach aimed not only at controlling relapses but also at fundamentally altering the course of PMS by addressing compartmentalized inflammation within the CNS.

In this review, we summarize recent advances in the application of CAR-T cell therapy to MS, with a particular emphasis on how this emerging approach could overcome the limitations of current immunomodulatory treatments. We also highlight key insights gained from the development of CAR-T therapy in oncology and

its expanding use in other autoimmune diseases, which together provide critical guidance for adapting this strategy to neuroimmunology. Finally, we discuss outstanding challenges and future directions, including antigen selection, safety optimization, and strategies to enhance CNS penetration, with the ultimate goal of positioning CAR-T cells as a transformative modality for the treatment of MS.

RATIONALE FOR CAR-T CELL THERAPY IN MS

Over the past decade, CAR-T cell therapy has expanded beyond oncology and is now being actively investigated for several autoimmune diseases, including systemic lupus erythematosus (SLE), refractory systemic sclerosis, Sjögren’s syndrome, antisynthetase

syndrome, and MS.^{12–19} Most of these early trials have employed CAR-T cells targeting pan-B cell antigens such as CD19, with some strategies exploring B cell maturation antigen (BCMA) to target plasma cells. The rationale for this approach stems from the central role of B cells in sustaining autoimmunity.

B cells contribute to MS pathogenesis through multiple mechanisms: (1) differentiation into plasma cells that produce autoantibodies, which bind to CNS self-antigens or form pathogenic immune complexes; (2) secretion of inflammatory cytokines, such as IL-6 and granulocyte-macrophage colony-stimulating factor, which enhance CD4⁺ T cell activation and promote a proinflammatory milieu; and (3) serving as highly effective antigen-presenting cells that capture self-proteins through their B cell receptors, process them, and present self-peptides to autoreactive T cells.^{1,6,20,21} PMS is often characterized by the accumulation of ectopic B cell-rich aggregates within the meninges, resembling tertiary lymphoid structures, which are strongly linked to cortical gray matter demyelination and ongoing neurodegeneration.⁶ These structures not only sustain local inflammation but they also act as chronic reservoirs of pathogenic B cells. Therefore, selectively eliminating autoreactive B cells represents a rational therapeutic strategy.

Indeed, mAbs targeting CD20 or CD19, such as rituximab, ocrelizumab, ofatumumab, and inebilizumab, have demonstrated substantial clinical benefit in MS and other autoimmune diseases by depleting B cells and reducing relapse rates.^{20,22–25} However, B cell-depleting mAbs are associated with important limitations (Figure 1C). First, their activity is often incomplete, sparing long-lived plasma cells that reside in bone marrow or CNS niches and continue to produce pathogenic autoantibodies.²⁶ Second, these antibodies have a restricted ability to penetrate the blood-brain barrier (BBB) and reach B cell aggregates sequestered within the CNS such as meningeal follicle-like structures, limiting their efficacy in PMS, where inflammation becomes compartmentalized in the CNS.^{8,27,28} In progressive disease stages, ectopic B cell follicles in the meninges drive cortical injury, but peripherally administered anti-CD20 mAbs only weakly affect these entrenched CNS reservoirs, consistent with modest slowing, rather than halting, of progression observed clinically.^{6,29–31} Third, mAbs typically persist for only weeks in the body, so repeated infusions are required to maintain their therapeutic effect.^{32,33} This need for continuous dosing can be burdensome and leaves gaps when B cells can re-emerge. In contrast, CAR-T cells function as a living drug capable of self-expansion and long-term persistence within the patient, thereby providing sustained therapeutic activity.¹¹ These challenges underscore the need for more durable and targeted approaches.

CAR-T cell therapy offers a promising solution by providing deeper and potentially more comprehensive depletion of pathogenic B cell populations. Unlike antibodies, CAR-T cells can migrate into inflamed tissues, including the CNS, and exert cytotoxic effects against B cells residing in ectopic lymphoid structures. Mechanistically, adoptively transferred CAR-T cells are expected to use the same trafficking modules as activated autoreactive T cells that drive MS pa-

thology.^{34–36} Encephalitogenic T helper 1 (Th1) and Th17 cells upregulate integrins such as VLA-4 and LFA-1; selectin ligands such as PSGL-1; chemokine receptors, including CXCR3 and CCR6, which interact with VCAM-1, ICAM-1, and P-selectin; and chemokines such as CXCL9/10/11 and CCL20 expressed by inflamed CNS endothelium, leptomeninges, and choroid plexus.^{36–38} These coordinated adhesion and chemokine cues mediate rolling, firm adhesion, and diapedesis across the BBB and blood-CSF barriers, allowing T cells to enter perivascular and meningeal spaces and cluster near aggregates of B cells.^{39,40} Clinical experience with CD19 CAR-T cells in PMS and other autoimmune settings where CAR-T cells are detectable and can expand in CSF relative to blood supports the view that activated CAR-T products exploit these same pathways to access intrathecal and meningeal compartments.^{9,10,41} Furthermore, the self-expanding and persistent nature of CAR-T cells allows for sustained immunomodulation, which may not only control relapsing disease activity but also interrupt the compartmentalized inflammation that drives progression.^{9,10} Collectively, these features provide a strong rationale for exploring CAR-T cell therapy as a transformative approach for MS.

Beyond relying on endogenous trafficking programs, CAR-T therapies can be engineered to enhance CNS homing.⁴² Preclinical studies in CNS malignancies have shown that the overexpression of chemokine receptors such as CXCR3 or CXCR3A can improve CAR-T migration along CXCL9/10/11 gradients into brain tumors, while CCR2b or CXCR4 can be used to follow CCL2- or CXCL12-rich niches at the neurovascular unit and within perivascular spaces.^{43–46} Similar principles could be applied in MS to direct CAR-T cells toward leptomeningeal and perivascular regions enriched for B cell aggregates. In parallel, selecting or enforcing central memory or stem cell-like phenotypes such as CD62L⁺ and CCR7⁺ preserves S1P-dependent recirculation and may support repeated surveillance of CNS barriers.^{47,48} These natural and engineered homing programs provide a mechanistic rationale for how CAR-T cells can cross CNS barriers, localize to disease-relevant compartments, and function within the inflammatory microenvironment in MS.

Beyond the elimination of autoreactive B cells, targeting pathogenic T cells represents another critical opportunity for CAR-T cell therapy in MS. Autoreactive CD4⁺ and CD8⁺ T cells are central drivers of disease pathogenesis, mediating CNS infiltration, demyelination, and neuronal injury.^{5,6,49} While clinical application of T cell-directed CAR-T therapies in autoimmunity remains limited, preclinical studies have demonstrated the feasibility of redirecting CAR-T cells against autoreactive T cell populations. Notably, CAR-T cells engineered to target pan-T cell antigens such as CD7 or CD70 have shown encouraging results in the context of T cell malignancies, including relapsed or refractory T cell acute lymphoblastic leukemia, where both autologous and allogeneic CD7-CAR-T products achieved promising efficacy with manageable safety profiles.^{50–53} These approaches are particularly attractive in the allogeneic setting, as CD7- or CD70-directed CAR-T cells not only eliminate malignant or autoreactive T cells but they may also reduce host T cell-mediated alloreactivity, thereby

Table 1. Preclinical studies of CAR-T cell therapy in the treatment of MS

CAR target	Mouse model	Result	Conclusion	Limitations	Year and reference
MOG	EAE	CAR/FoxP3-engineered regulatory T cells alleviate disease symptoms, reduce IL-12 and IFN- γ mRNA expression in brain tissue, and prevent EAE disease	CNS-directed Tregs administer intranasally efficiently home to the CNS, where they attenuate inflammation and alleviate disease manifestations	limited numbers of therapeutic cells reaching the CNS; intranasal delivery not yet validated in humans; may risk systemic immunosuppression or off-target cell distribution; fate of transferred cells remains uncertain; model different from established clinical disease	2012 ⁶⁷
MBP or MOG	EAE	CAR-Treg cells maintain regulatory signatures and prevent EAE disease	adoptive transfer of MOG and MBP scFv CAR-Tregs ameliorate MOG-induced EAE	short persistence of xenogeneic human Tregs in mice; CNS migration of scFv CAR-Tregs not yet demonstrated; efficacy of individual MBP- or MOG-specific CAR-Tregs unknown; suppressive function of patient-derived CAR-Tregs and their mechanisms remain to be established; model different from established clinical disease	2020 ⁶⁹
CD19	EAE	CAR-T cells eliminate meningeal B cell aggregates but exacerbate EAE disease	meningeal B cell aggregates may play an immunomodulatory role, and CAR-T cells carry side effects such as neurotoxicity	meningeal pathology confined to spinal cord white matter, not cortical gray matter; regulatory versus pathogenic roles of meningeal B cell aggregates remain unresolved mechanistically; antibody-secreting functions and intrathecal antibodies were not directly assessed; translational relevance of B cell depletion of human meningeal aggregates remains uncertain; model different from established clinical disease	2021 ⁷⁰
MOG ₃₅₋₅₅ -recognized TCR	EAE	pMHCII CAR-T cells delete antigen-specific CD4 T cells and prevent EAE disease	high-affinity autoreactive T cells are essential to initiate neuroinflammatory injury, whereas lower-affinity counterparts are sufficient to sustain disease progression.	CARs did not fully reverse established disease; durability and optimal treatment window remain unclear; constructs need further optimization of homing, signaling domain, and multi-epitope targeting; model different from established clinical disease	2022 ⁷¹
CD19	EAE	CAR-T cells deplete B cell in peripheral lymphoid tissue and in the CNS and ameliorate EAE disease	CAR-T cells exhibit potent therapeutic efficacy in treating MS without detectable systemic toxicity and provide superior, long-lasting benefits compared with monoclonal antibodies	B cell depletion did not clearly account for the clinical improvement; characterization of adaptive immune system including Bregs and cytokine profile changes were not demonstrated; model different from established clinical disease	2023 ⁷²
XCR1	EAE	CAR-T or CAR-Treg cells deplete DC1 and suppress Th1-driven EAE	EAE suppression results from DC1 depletion, with CAR-T cells enabling precise and sustained targeting of DC1, and DC1-specific CAR-Tregs offering complementary immunoregulatory effects	high cost of manufacturing; risk of off-target toxicity, CRS, and CAR-Treg cell instability; failure of XCR1 CAR-T cells to engraft in immunocompetent mice; modest efficacy in passive Th1-driven EAE; model different from established clinical disease	2023 ⁷³

(Continued on next page)

Table 1. Continued

CAR target	Mouse model	Result	Conclusion	Limitations	Year and reference
MBP-reactive B cells	None	MBP-targeting CAAR-engineered T cells demonstrated potent cytotoxic activity against autoreactive B cells, along with robust proliferation and inflammatory cytokine release	CAAR-T cells represent a promising strategy for treating or modulating autoimmunity and offer an approach for clone-specific B cell depletion	variations exist in the autoantigens, so therapies based on a single antigen may be challenging; overcoming epitope spreading requires multi-antigen targeting; ineffectiveness against plasma cells downregulating surface immunoglobulin G	2023 ⁷⁴

CAAR, chimeric autoantibody receptor; CAR, chimeric antigen receptor; CNS, central nervous system; CRS, cytokine release syndrome; DC1, conventional type 1 dendritic cells; EAE, experimental autoimmune encephalomyelitis; IFN, interferon; IL, interleukin; MBP, myelin basic protein; MOG, myelin oligodendrocyte glycoprotein; MS, multiple sclerosis; pMHCII, peptide-major histocompatibility complex class II; scFv, single-chain variable fragment; TCR, T cell receptor; Th1, T helper 1 cell; Treg, regulatory T cell; XCR1, X-C motif chemokine receptor 1.

enhancing the persistence and function of transferred CAR-T cells.^{54–56} Translating such strategies into MS could allow for the dual targeting of autoreactive B cells and T cells, addressing two major pathological arms of disease. The development of combination or multi-specific CAR designs that simultaneously suppress B cell- and T cell-driven autoimmunity may thus represent a powerful next-generation therapeutic avenue for MS. From a clinical perspective, several design features of CAR constructs will directly influence how these therapies behave in patients. The choice of co-stimulatory domain, most commonly CD28 or 4-1BB, shapes the balance between rapid early expansion and long-term persistence, while the underlying metabolic program of CAR-T cells, ranging from glycolysis-dominated effector states to oxidative phosphorylation (OXPHOS)-dependent memory states, helps determine the durability of response.^{57–59} In parallel, evolving *in vivo* gene-delivery strategies, including viral vectors and lipid nanoparticle-based platforms, are beginning to offer more streamlined and scalable ways to generate CAR-T cells.^{60–64} These translational considerations are discussed in greater detail in subsequent sections.

PRECLINICAL EVIDENCE FOR CAR-T CELL THERAPY IN MS

Experimental autoimmune encephalomyelitis (EAE) is the most widely used preclinical model for MS and has been instrumental in elucidating the contribution of autoreactive immune cells to neuroinflammation and demyelination.^{65–68} EAE can be induced in rodents through active immunization with myelin antigens (e.g., myelin oligodendrocyte glycoprotein [MOG], myelin basic protein [MBP], proteolipid protein [PLP]) in combination with adjuvants or by adoptive transfer of myelin-reactive T cells. These models recapitulate many pathological hallmarks of MS, including infiltration of autoreactive CD4⁺ T cells and B cells into the CNS, activation of microglia and astrocytes, demyelination, and progressive neurological deficits. Because of their immunological similarity to human disease, EAE models provide a valuable platform to test the efficacy of novel therapeutic strategies, including CAR-T cells (Table 1). In particular, EAE allows assessment of how B cell- or T cell-directed CAR-T cell therapies impact disease onset, relapse

frequency, CNS infiltration, and tissue pathology, thereby generating mechanistic insights and proof-of-concept evidence for translation into clinical studies.

Mitsdoerffer et al. engineered CD19-targeting CAR-T cells and evaluated their efficacy in an EAE model in which both T and B cells recognize the CNS autoantigen MOG.⁷⁰ The study compared CAR-T cell therapy with systemic anti-CD20 mAb treatment. While anti-CD20-mediated systemic B cell depletion in opticospinal encephalomyelitis (OSE) mice after disease onset failed to effectively reduce meningeal B cell aggregates and had a minimal impact on disease progression, administration of CD19 CAR-T cells successfully eliminated these aggregates.⁷⁰ Unexpectedly, this intervention exacerbated clinical disease in OSE mice.⁷⁰ The apparent paradox may be explained by the observation that approximately 20% of B cells within meningeal aggregates produce regulatory cytokines, such as IL-10 or IL-35, suggesting that these aggregates could exert immunomodulatory effects on adjacent spinal cord white matter.⁷⁰ These findings highlight the dual role of meningeal B cell aggregates in MS pathophysiology and underscore the need to carefully consider their potential regulatory functions when designing therapies targeting these structures. Moreover, the pronounced inflammatory response observed within the CNS following CAR-T cell treatment raises concerns about therapy-associated toxicities, including cytokine release syndrome (CRS) and neurotoxicity, which have been well documented in oncology and other CAR-T applications.^{75–78} Collectively, these results indicate that while CAR-T cells can effectively deplete pathogenic B cells, strategies to mitigate the associated proinflammatory effects will be critical for their safe translation in MS.

In another study, Gupta et al. developed CD19-targeting CAR-T cells and evaluated their efficacy using a similar EAE model, directly comparing outcomes with anti-CD20 mAb treatment.⁷² CAR-T cells induced robust B cell depletion in both peripheral lymphoid tissues and the CNS, achieving a markedly prolonged duration of B cell suppression compared with anti-CD20 therapy. Specifically, CAR-T cells maintained B cell depletion in the blood for up to 24 weeks, whereas anti-CD20 mAbs achieved only transient depletion lasting

Table 2. Clinical reports of CAR-T cell therapy in the treatment of MS

Disease indication	CAR target	Preconditioning strategy	Dosing regimen and strategy	Outcome (safety)	Outcome (efficacy)	ClinicalTrials.gov ID and reference
Two patients: one with RRMS that progressed to SPMS, and one with PPMS	CD19	lymphodepletion with fludarabine (30 mg/m ² on days -5, -4, and -3) and cyclophosphamide (300 mg/m ² on days -5, -4, and -3)	a single dose of 1 × 10 ⁸ autologous second-generation CD19 CAR-T cells	grade 1 CRS occurred in the SPMS case; no ICANS signs in either case; transient increase in transaminases occurred (SPMS: CTCAE grade 2; PPMS: CTCAE grade 3)	CAR-T cell enrichment in the CSF; SPMS case: OCB number decreases; PPMS case: no new neurological symptoms occurred, and EDSS remained stable throughout observation	NCT06451159 ⁹
Four patients: one with SPMS, one with PPMS, and two with RRMS	CD19	lymphodepletion with fludarabine (30 mg/m ² on day -5, -4, -3) and cyclophosphamide (300 mg/m ² on day -5, -4, -3)	a single dose of 1 × 10 ⁸ second-generation anti-CD19-directed CAR-T cells	grade 1 CRS occurred in three of the four patients; one suspicious grade 1 ICANS; transient transaminitis in all patients (CTCAE grades 1-3); hematotoxicity occurred (neutropenia, CTCAE grades 2-4)	selective CAR-T cell enrichment within the CNS; temporary target effects; MRI imaging revealed new spinal cord lesions in three patients: one experienced increased EDSS; one patient showed no OCB and reduction remained stable	NCT06451159 ¹⁰

CSF, cerebrospinal fluid; CTCAE, Common Terminology Criteria for Adverse Events; EDSS, Expanded Disability Status Scale; ICANS, immune effector cell-associated neurotoxicity syndrome; OCB, oligoclonal band; PPMS, primary progressive multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis.

approximately 8 weeks, with gradual B cell recovery thereafter.⁷² The extent and duration of B cell depletion closely correlated with disease control, demonstrating that CAR-T cells offer superior and sustained therapeutic benefits relative to mAb treatment.

Beyond conventional CAR targets such as CD19, novel CAR-T cell strategies have been developed to directly target autoreactive T cells. Given that MS is widely thought to be driven by myelin-specific autoreactive CD4⁺ T cells, investigators have engineered peptide-major histocompatibility complex (MHC) class II CARs (pMHCII-CARs) using intact MHC class II molecules.⁷¹ In this design, the myelin peptide is fused to I-A^bβ via a flexible linker, and the intracellular signaling domains (CD28/CD3ζ) are attached to the C terminus of I-A^bβ. These pMHCII-CAR-T cells selectively deplete peptide-reactive CD4⁺ T cells in mice.⁷¹ Moreover, by co-expressing a dominant-negative Fas receptor, pMHCII-CAR-T cells extend their activity to lower-affinity autoreactive CD4⁺ T cells and are capable of reversing established clinical EAE.⁷¹ This work not only demonstrates the feasibility of CD4-targeting CAR-T cells but it also provides mechanistic insight, confirming that high-affinity autoreactive T cells are required to initiate neuroinflammatory injury, whereas lower-affinity T cells are sufficient to perpetuate ongoing disease.

In addition, other strategies include the development of X-C motif chemokine receptor 1 (XCR1)-targeting CAR-T and CAR-engineered regulatory T (CAR-Treg) cells to deplete conventional type 1 DCs (DC1) and suppress Th1-driven EAE⁷³; chimeric autoantibody receptor (CAAR)-engineered T cells, which incorporate autoantigen epitopes in their extracellular domains to trap autoreactive

B cells, demonstrating enhanced cytotoxicity against autoreactive B cells *in vitro*⁷⁴; and MBP- or MOG-specific CAR-Tregs, which ameliorate EAE, underscoring their therapeutic potential for MS.^{67,69} Collectively, these approaches highlight the versatility of CAR-based platforms in modulating diverse immune cell subsets and provide a strong rationale for their further exploration as innovative therapies for MS.

Overall, these preclinical studies highlight multiple CAR-T cell-based strategies that target autoreactive B cells, T cells, and other immune cell populations, with the EAE model serving as the most widely used system to study MS (Table 1). While EAE provides valuable insights into disease mechanisms and therapeutic efficacy, it remains a murine model that relies on mouse immune cells, limiting its translational relevance for evaluating human CAR-T cell therapies. At present, human B cell line xenograft models, such as Raji or Nalm6 in NSG mice, are commonly used to assess CD19-targeting CAR-T cell activity; however, these models primarily capture tumor cell depletion and do not recapitulate the complex autoimmune pathology of MS. Thus, the field would benefit from the development of improved humanized mouse models that more accurately reflect human immune responses and MS pathogenesis, enabling rigorous preclinical evaluation of CAR-T cell-based therapies for autoimmune disease.

CLINICAL ADVANCES OF CAR-T CELL THERAPY IN MS

The first published clinical experience of CAR-T cells in MS involved two PMS patients, one SPMS and one PPMS, treated with a single infusion of fully human anti-CD19 product (KYV-101) following standard lymphodepletion with fludarabine 30 mg/m² and

cyclophosphamide 300 mg/m² on days –5 to –3 (Table 2).⁹ Short-term safety was acceptable: no immune effector cell-associated neurotoxicity syndrome (ICANS) occurred, CRS was limited to grade 1 and managed with tocilizumab and corticosteroids, and transient transaminitis resolved with supportive care. Notably, CAR-T cells expanded and were enriched in CSF relative to blood by day 14 without neurological toxicity. In the SPMS case, CSF OCBs fell from 13 to 6 by day 14 and remained reduced at day 64, with circulating B cells depleted and serum immunoglobulin G reduced. CAR-T cells persisted in blood to day 100 in that patient, and magnetic resonance imaging (MRI) revealed a single new non-enhancing T2 spinal cord lesion during follow-up.⁹

Subsequently, a four-patient compassionate-use series, including one SPMS patient, one PPMS patient, and two RRMS patients, reported consistent pharmacodynamics: peripheral expansion with relative CSF enrichment in all patients, reappearance of peripheral B cells at a mean of 88 days, and predominantly grade 1 CRS, which were managed with tocilizumab, dexamethasone, or anakinra.¹⁰ One patient had opioid refractory headaches that were considered possible grade 1 ICANS. Transient transaminitis with Common Terminology Criteria for Adverse Events (CTCAE) grades 1–3 and neutropenia of grades 2–4 occurred and were manageable. Three patients showed a rapid initial OCB decline, in which one became transiently OCB-negative at day 14, followed by partial re-increase; new spinal cord lesions were observed in these patients with initial OCB reductions, and disability remained largely stable, except for one patient who showed Expanded Disability Status Scale worsening at 6 months. Overall, early signals suggest on-target activity within the CNS with a tolerable acute safety profile, but heterogeneity in durability and MRI/OCB dynamics underscores the need for controlled trials and longer follow-up.¹⁰

Across these initial cases, CD19-targeting CAR-T cells show tolerable short-term safety, CNS access with consistent CSF enrichment, and biologic activity within the intrathecal compartment without explicit early neurotoxicity despite heterogeneous MRI and clinical trajectories and relatively short durability of peripheral B cell depletion in the series. These data provide proof-of-concept for CNS-compartment targeting in MS and motivate controlled trials to define dose, persistence, and strategies to consolidate intrathecal responses while minimizing adverse effects. Multiple early-phase trials such as NCT06451159, NCT06384976, and NCT06138132 targeting PMS or non-relapsing PMS are now active, reflecting rapid translation from individual-patient use to structured evaluation. In parallel, a phase 1, dose-escalation study (NCT06680037) is now enrolling up to 32 adults with progressive forms of MS to evaluate azercabtagene zapreleucel (azer-cel), an allogeneic, CD19-directed CAR-T cell product. The primary objective is to determine the recommended phase 2 dose and to characterize the safety and clinical activity of this off-the-shelf approach in B cell-mediated autoimmune disease, including PMS. While not yet reporting outcomes, their designs explicitly leverage the CSF-enrichment signal observed in the initial reports.

KEY CHALLENGES AND FUTURE PERSPECTIVES FOR CAR-T CELL THERAPY IN MS

Antigen selection and avoiding off-target effects

A central challenge in developing CAR-T cell therapy for MS is the selection of appropriate target antigens (Figure 2A). Unlike B cell malignancies, where lineage-specific markers such as CD19 and BCMA serve as well-defined and disease-restricted targets, MS is characterized by a complex and heterogeneous autoimmune response against multiple myelin-derived proteins, including MBP, MOG, and PLP.⁷⁹ The polyclonal nature of autoreactive T and B cell responses complicates the identification of a single antigen that can be safely and effectively targeted.

Equally critical is the risk of off-target toxicity. Many candidate antigens implicated in MS are expressed, at least partially, by healthy neural or glial cells. Direct targeting of these proteins could therefore result in unintended damage to CNS tissue and exacerbate neuroinflammation. Similarly, systemic depletion of broad immune cell populations (e.g., CD4⁺ or CD19⁺ cells) may compromise protective immunity and increase susceptibility to infections or secondary malignancies.

To address these challenges, several strategies are under investigation. pMHC-based CARs aim to selectively target autoreactive T cells, whereas CAARs are designed to eliminate pathogenic B cell clones while sparing non-pathogenic populations. Additionally, CAR-Tregs may provide a means to fine-tune immune responses without widespread immune depletion (Table 1). Ultimately, precise antigen selection combined with careful CAR engineering will be essential to achieve safe and effective CAR-T cell therapy for MS.

Although CAR-T cells targeting MBP, MOG, and other myelin-derived antigens have shown promise in preclinical models, their clinical efficacy and safety remain untested, making immediate translation to human studies impractical. In contrast, CD19- and BCMA-targeting CAR-T cells currently represent the most clinically viable options, as both have received US Food and Drug Administration approval and have been extensively evaluated in clinical trials for B cell-mediated diseases. The optimal strategy—whether single-targeting (CD19 or BCMA), dual-targeting, or co-infusion of CD19- and BCMA-targeting CAR-T cells—remains to be determined. Notably, recent clinical studies in SLE have demonstrated that co-infusion of CD19- and BCMA-targeting CAR-T cells can achieve favorable efficacy and safety profiles, suggesting that similar approaches could be explored for the treatment of MS.⁸⁰

Managing CAR-T cell-associated toxicity

A major concern in CAR-T cell therapy for autoimmune diseases, including MS, is the risk of treatment-related toxicity (Figure 2B). CRS and neurotoxicity, commonly reported in CAR-T cell therapy for hematologic malignancies, are particularly relevant in MS due

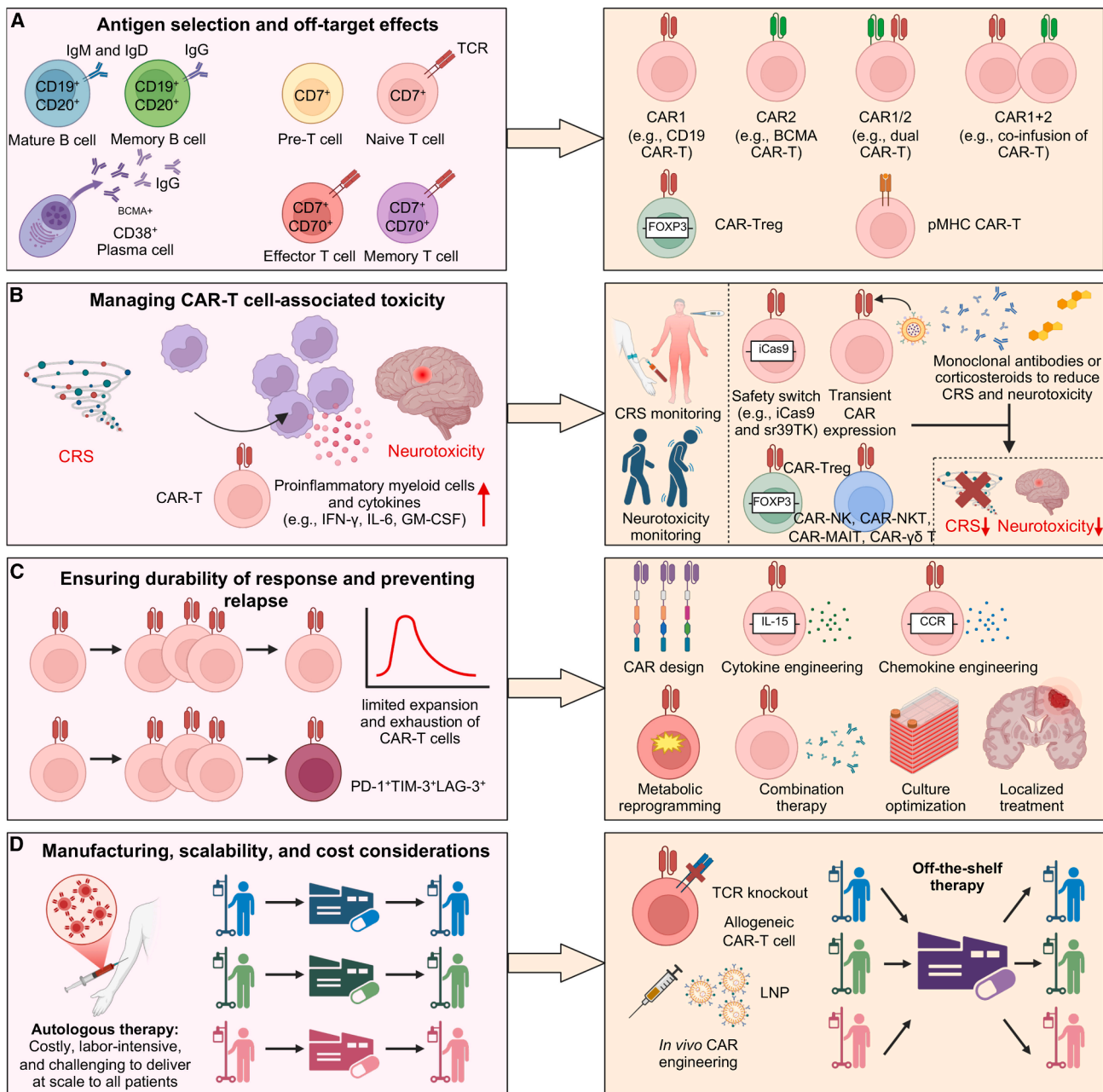


Figure 2. Current limitations of CAR-T cell therapy in treating MS and potential future directions

(A) Antigen selection and off-target effects. Multiple CAR constructs have been designed against autoreactive lymphocytes. For B cells, targets include CD19, CD20, and BCMA, whereas for T cells, CD7 and CD70 have been explored. However, antigen expression varies across developmental stages—for example, BCMA is restricted to plasma cells and absent on mature or memory B cells. Proper antigen selection is critical to maximize depletion of pathogenic cells while minimizing off-target effects. Approaches such as dual CARs or co-infusion of complementary CAR-T cell products may improve specificity and coverage. (B) Managing CAR-T cell-associated toxicities. Adverse events such as CRS and neurotoxicity represent major risks. These challenges may be amplified in MS since pathogenic cells reside in the CNS, a microenvironment rich in microglia and prone to inflammatory amplification. Safety strategies include incorporation of suicide switches, transient CAR expression systems, and the use of alternative cell types such as CAR-engineered regulatory T cells, NK cells, NKT cells, mucosal-associated invariant T (MAIT) cells, or $\gamma\delta$ T cells. (C) Ensuring durability of response and preventing relapse. Although CAR-T cells can persist as living drugs, functional decline due to exhaustion or reduced persistence can compromise efficacy. Strategies to enhance durability include engineering CAR-T cells with immunosuppressive genes, improving metabolic fitness, and augmenting homing to the CNS. (D) Manufacturing, scalability, and cost considerations. Current autologous CAR-T approaches are expensive, labor-intensive, and challenging to scale for widespread patient access. Development of off-the-shelf products, such as allogeneic CAR-T cells or *in vivo* CAR gene delivery platforms, may overcome these barriers and broaden clinical applicability.

to the involvement of the CNS.^{81–83} Preclinical studies using CD19-targeting CAR-T cells in the EAE model have shown that while CAR-T cells can eliminate meningeal B cell aggregates at disease sites, they may exacerbate disease at later stages.⁷⁰ This observation suggests that CAR-T cell-associated toxicity, particularly neurotoxicity, is a critical consideration when targeting CNS autoimmune pathology. Although meningeal tertiary lymphoid structures are strongly associated with cortical demyelination and worse clinical outcomes in PMS, they also contain a substantial fraction of regulatory B cells (Bregs) constituting 20% of B cells in organized aggregates, which can exert local immunoregulatory effects on adjacent CNS tissue through IL-10 and IL-35 production.^{70,84} Experimental and human data indicate that B cell-derived IL-10 and IL-35 are important for limiting CNS autoimmunity and restraining proinflammatory myeloid cell and microglial activation, while broad B cell depletion can enhance monocyte and microglial activity and aggravate disease.^{85–87} In the context of MS, ablation of meningeal aggregates mediated by CD19-targeting CAR-T cells may simultaneously remove pathogenic effector B cells and Bregs, disrupting the local balance and unleashing encephalitogenic T cells and myeloid-driven inflammation, thereby worsening neuroinflammation despite efficient B cell clearance.^{70,72}

These observations have direct implications for CAR-T cell design and clinical translation in MS. One approach is to shift from broad pan-B cell targeting to more selective strategies that preferentially eliminate autoreactive clones while sparing regulatory subsets—for example, CAAR T cells that present myelin epitopes and selectively trap autoantibody-producing B cells or antigen-tuned CARs with lower affinity or restricted epitope specificity.^{26,74} Complementary strategies include integrating regulatory modules such as CAR-Tregs, which can provide active immunosuppression and help restore tolerance after effector B cell depletion, and combining B cell-directed CAR-T therapy with immunomodulatory agents, such as IL-6/IL-1 blockade, low-dose steroids, or Treg-supporting interventions, to dampen myeloid and microglial activation during peak CAR-T activity.^{88–90} Along with the administration of CAR-T cells, CNS-focused pharmacovigilance, and biomarker monitoring of Breg frequencies and IL-10/IL-35 levels may be essential to balance pathogenic B cells elimination and immunoregulation.

On-target, off-tissue effects represent an additional risk. CAR recognition of antigens expressed on healthy neural or glial cells could result in irreversible tissue damage. Broad depletion of B or T cell populations may further compromise immune homeostasis, increasing susceptibility to infections and secondary complications. Moreover, proinflammatory myeloid cells contribute to CRS and neurotoxicity, and interactions between CAR-T cells and these cells—mediated, at least in part, via CD40/CD40L signaling—can amplify inflammatory side effects.^{91–93}

Several strategies are under investigation to mitigate these risks. Incorporation of suicide or safety switches allows rapid elimination

of CAR-T cells in the event of severe toxicity.^{94–96} Transient CAR expression, achieved through mRNA or non-viral platforms, can limit prolonged immune activation while maintaining therapeutic activity. CAR design optimization, including modulation of co-stimulatory domains, antigen-binding affinity, and target specificity, can reduce the likelihood of off-target effects. Fractionated or stepwise dosing strategies may further minimize acute toxicity.^{97–99}

CAR-Tregs offer a complementary approach, providing targeted immunomodulation without inducing broad immune depletion. By selectively suppressing autoreactive immune responses, CAR-Tregs can achieve disease control while minimizing systemic toxicity.^{69,100–102} In addition, CAR-engineered unconventional T cells, such as CAR-engineered invariant natural killer T (CAR-NKT) cells, may provide dual benefits by targeting both disease-driving antigen-expressing cells and proinflammatory myeloid populations through CD1d/ T cell receptor (TCR) interactions. This dual-targeting strategy has the potential to reduce disease progression while enhancing both efficacy and safety.^{78,103–105} Collectively, these approaches underscore the importance of balancing therapeutic efficacy with toxicity management in the clinical development of CAR-engineered cell therapies for MS.

Ensuring durability of response and preventing relapse

Achieving long-term disease control and preventing relapse represent major challenges in CAR-T cell therapy for MS (Figure 2C). The heterogeneous and polyclonal nature of autoreactive T and B cell populations in MS increases the risk of disease recurrence even after initial CAR-T cell-mediated depletion. Limited CAR-T cell persistence and functional exhaustion can further compromise sustained therapeutic efficacy.

Several strategies are under investigation to enhance the durability of CAR-T cell responses. Optimization of CAR construct design, including the choice of co-stimulatory domains such as 4-1BB or CD28 and fine-tuning of signaling strength, can significantly influence CAR-T cell persistence, proliferation, and resistance to exhaustion. For instance, 4-1BB domains have been associated with enhanced long-term persistence and memory formation, whereas CD28 domains may promote rapid initial expansion but shorter persistence.^{98,106,107} Conceptually, CD28-based CARs tend to behave like “fast-acting” effector products, achieving brisk early debulking but with a greater tendency to differentiate and exhaust, whereas 4-1BB-based CARs more often generate central memory-like populations that expand more slowly but persist longer.^{58,59,74} This dichotomy is closely linked to metabolism; highly effector CAR-T cells rely predominantly on glycolysis, while long-lived memory cells favor OXPHOS and fatty acid oxidation, an energy-efficient program that supports durability in chronic diseases such as MS.^{108–110} Incorporating memory-like or stem-like T cell subsets during manufacturing can further improve engraftment and longevity *in vivo*. Strategies to achieve this include selective enrichment of central memory or stem cell memory subsets, engineering of cytokine

support (e.g., constitutive or inducible IL-15 or IL-18 expression) to promote survival and self-renewal, and modulation of transcription factors such as TCF1 or BCL-2 that regulate T cell stemness and resistance to apoptosis.^{94,111–114} Additionally, metabolic reprogramming approaches, such as promoting OXPHOS over glycolysis, have been shown to enhance the persistence and functionality of CAR-T cells in preclinical models.¹¹⁵ In practical terms, strategies that push CAR-T cells toward an OXPHOS-dominant, memory-like state may be more desirable for MS, where sustained immune re-education is needed rather than only transient cytotoxic bursts. These strategies aim to generate CAR-T cells with enhanced durability, functional longevity, and sustained therapeutic potential, which are critical for preventing relapse in chronic autoimmune diseases such as MS.

Targeting multiple disease-driving antigens, either through dual-targeting CARs or combinatorial approaches, may reduce the likelihood of immune escape and relapse. Additionally, repeated or sequential CAR-T cell administrations could help maintain disease suppression, particularly in patients with high disease burden or ongoing autoreactive immune activity. Finally, integrating CAR-Tregs may provide ongoing immune modulation to prevent the reactivation of pathogenic autoreactive cells, thereby maintaining immune homeostasis without compromising systemic immunity. These approaches highlight the need to combine durable CAR-T cell persistence, multi-antigen targeting, and immunoregulation to achieve long-lasting disease control in MS.

Manufacturing, scalability, and cost considerations

The clinical translation of CAR-T cell therapy for MS is closely linked to challenges in manufacturing, scalability, and cost (Figure 2D). Traditional autologous CAR-T approaches require individualized cell collection, *ex vivo* expansion, and genetic engineering for each patient. This process is labor-intensive, time-consuming, and associated with high production costs, limiting broad accessibility, especially for chronic autoimmune diseases such as MS. Additionally, variability in patient-derived T cell quality can lead to inconsistent product potency and persistence.

Allogeneic off-the-shelf CAR-T products offer a potential solution to these limitations. By using healthy donor-derived T cells, engineered to eliminate alloreactivity (e.g., via TCR or human leukocyte antigen knockout) and resist host immune rejection, allogeneic CAR-T cells can be manufactured in large batches and cryopreserved for immediate use.^{54,116–119} This approach not only reduces production timelines and cost per patient but it also enables standardized product quality and more consistent therapeutic outcomes. Early clinical studies of allogeneic CAR-T therapies in hematologic malignancies have demonstrated safety, feasibility, and promising persistence, providing a blueprint for autoimmune disease applications.¹²⁰

Emerging *in vivo* CAR engineering approaches provide an additional strategy to overcome manufacturing bottlenecks. These methods utilize gene delivery systems, such as lipid nanoparticles, polymers, or viral vectors, to directly reprogram T cells within the patient's

body, eliminating the need for extensive *ex vivo* manipulation.¹²¹ Most current *in vivo* approaches rely either on viral vectors or non-viral lipid nanoparticle systems. Viral vectors provide efficient and durable gene transfer but raise concerns about integration, immunogenicity, and manufacturing complexity, whereas LNPs can deliver DNA or mRNA cargoes transiently with flexible chemistry that may be easier to scale and adapt across indications.^{77,122} *In vivo* CAR-T cell generation could dramatically reduce costs and logistical complexity, allowing scalable treatment of large patient populations while enabling rapid iterative optimization of CAR constructs. Preclinical and early clinical studies have demonstrated the feasibility of this approach, with engineered T cells persisting, expanding, and exerting disease-modifying activity *in vivo*.^{123,124}

Despite these advances, key challenges remain, including controlling CAR expression levels, ensuring selective targeting, avoiding systemic toxicity, and achieving long-term persistence in the patient. Addressing these issues will be critical to realize the full potential of scalable, cost-effective CAR-T cell therapies for MS. Integration of allogeneic and *in vivo* engineering approaches represents a promising path toward broader accessibility and sustainable clinical implementation.

CONCLUSION

CAR-T cell therapy represents a paradigm shift in the treatment of autoimmune diseases, including MS, offering the unprecedented potential to selectively eliminate autoreactive immune cells, restore immune tolerance, and modulate disease progression. Preclinical studies have demonstrated the feasibility of targeting myelin-specific antigens, B cell populations, or autoreactive T cells (Table 1), while early clinical experiences with CD19-targeting CAR-T cells in the treatment of MS also provide encouraging evidence for both efficacy and safety (Table 2).

Despite this promise, several critical challenges remain. Precise antigen selection is essential to avoid off-target toxicity, particularly in the CNS, while optimizing CAR design and engineering strategies is key to enhancing persistence, reducing exhaustion, and minimizing systemic side effects. Durable responses may require dual-targeting approaches, incorporation of memory-like T cell subsets, CAR-Tregs, or CAR-engineered unconventional T cells to maintain immune homeostasis and prevent relapse.^{125,126}

Advances in allogeneic, off-the-shelf CAR-T products offer opportunities to overcome manufacturing bottlenecks, reduce costs, and increase accessibility, while *in vivo* CAR engineering holds the potential to bypass *ex vivo* manufacturing entirely, enabling rapid and scalable therapeutic interventions. Integration of these strategies, combined with precise dosing, safety switches, and modulation of proinflammatory microenvironments, will be crucial to maximize therapeutic efficacy while minimizing risks.

Collectively, these developments underscore the transformative potential of CAR-T cell therapy in MS. Continued translational

research, innovative engineering, and carefully designed clinical trials will be necessary to fully realize CAR-T cell therapy as a safe, effective, and potentially curative approach for patients with MS.

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AUTHOR CONTRIBUTIONS

This paper was written by Y.-R.L., Y.C., and L.Y. All authors contributed to the article and approved the submitted version.

DECLARATION OF INTERESTS

L.Y. is a scientific advisor to AlzChem and Amberstone Biosciences and is a cofounder, stockholder, and advisory board member of Appia Bio. None of the declared companies contributed to this study.

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