



B cell-targeting chimeric antigen receptor T cells as an emerging therapy in neuroimmunological diseases

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Summary

Background Neuroimmunology research and development has been marked by substantial advances, particularly in the treatment of neuroimmunological diseases, such as multiple sclerosis, myasthenia gravis, neuromyelitis optica spectrum disorders, and myelin oligodendrocyte glycoprotein antibody disease. With more than 20 drugs approved for multiple sclerosis alone, treatment has become more personalised. The approval of disease-modifying therapies, particularly those targeting B cells, has highlighted the role of immunotherapeutic interventions in the management of these diseases. Despite these successes, challenges remain, particularly for patients who do not respond to conventional therapies, underscoring the need for innovative approaches.

Recent developments The approval of monoclonal antibodies, such as ocrelizumab and ofatumumab, which target CD20, and inebilizumab, which targets CD19, for the treatment of various neuroimmunological diseases reflects progress in the understanding and management of B-cell activity. However, the limitations of these therapies in halting disease progression or activity in patients with multiple sclerosis or neuromyelitis optica spectrum disorders have prompted the exploration of cell-based therapies, particularly chimeric antigen receptor (CAR) T cells. Initially successful in the treatment of B cell-derived malignancies, CAR T cells offer a novel therapeutic mechanism by directly targeting and eliminating B cells, potentially overcoming the shortcomings of antibody-mediated B cell depletion.

Where next? The use of CAR T cells in autoimmune diseases and B cell-driven neuroimmunological diseases shows promise as a targeted and durable option. CAR T cells act autonomously, penetrating deep tissue and effectively depleting B cells, especially in the CNS. Although the therapeutic potential of CAR T cells is substantial, their application faces hurdles such as complex logistics and management of therapy-associated toxic effects. Ongoing and upcoming clinical trials will be crucial in determining the safety, efficacy, and applicability of CAR T cells. As research progresses, CAR T cell therapy has the potential to transform treatment for patients with neuroimmunological diseases. It could offer extended periods of remission and a new standard in the management of autoimmune and neuroimmunological disorders.

Introduction

Neuroimmunology has witnessed major advances in immunotherapeutic approaches, with various drugs targeting a range of cellular and subcellular immunological processes. In multiple sclerosis alone, more than 20 approved drugs are available, allowing some personalisation of treatment on the basis of disease activity, patient preference, and tolerability. In less common neuroimmunological disorders, such as myasthenia gravis, neuromyelitis optica spectrum disorders, and myelin oligodendrocyte glycoprotein antibody disease, disease-modifying therapies, including B-cell-targeting drugs, have also been approved or are in late-stage trials.

Monoclonal antibodies that target B cells have an increasingly important role. Rituximab has been in off-label use for various neuroimmunological disorders for around two decades. Ocrelizumab, approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for relapsing and primary progressive multiple sclerosis, and ofatumumab, approved by the US FDA and the EMA for relapsing multiple sclerosis, are directed against CD20 and have been effective in reducing disease activity while displaying an acceptable safety profile.¹ Additionally, the recent approval of inebilizumab,² an anti-CD19 antibody,

for treatment of neuromyelitis optica spectrum disorders reflects the ongoing efforts to address B-cell activity in neuroimmunological disorders. However, some individuals with neuroimmunological disorders, such as myasthenia gravis or neuromyelitis optica spectrum disorders, do not have reduced disease activity with antibody-mediated B-cell depletion, and there is growing evidence that, despite suppressing relapses in multiple sclerosis, disease progression continues.³

In this Rapid Review, we provide an overview of cell-based therapies, particularly B cell-targeting chimeric antigen receptor (CAR) T cells, and explore their potential to transform the treatment of neuroimmunological disorders. We take into account the swiftly moving translational research that allows the interdisciplinary use of CAR T cell therapies in neurology and neuroimmunology, and take stock of past experience from the field of haemato-oncology. We also discuss the latest developments and planned CAR T trials in neuroimmunological disorders.

CAR T cells targeting B cell-derived malignancies Therapeutic principle and lessons learned from treating cancer patients

CAR T cells have revolutionised the treatment of B cell-derived neoplasms, such as B-cell lymphoma and

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For more on approved drugs for multiple sclerosis see <https://www.nationalmssociety.org/Treating-MS/Medications>

leukaemia.⁴ CAR T cells are created by genetically engineering T cells to target other cells by identifying specific cell surface antigens. CARs are artificial receptors and consist of an antibody fragment that functions as the antigen-binding domain, a hinge region, a transmembrane domain, and one or more intracellular signalling domains (figure 1A).⁵ The antigen-binding domain, which in most cases is a single-chain variable fragment, enables binding to the target antigen without the need for it to be presented by MHC. The hinge region connects the antigen-binding domain with the rest of the receptor, and the transmembrane domain anchors the CAR into the T cell's membrane. The intracellular part of the CAR contains the parts of the T-cell receptor (TCR) that initiate T-cell activation upon antigen recognition. From the second generation of constructs onwards, CARs also incorporate one or more co-stimulatory domains (eg, CD28) to enhance T-cell activation, proliferation, and survival. After binding their antigen, CAR T cells proliferate and release cytotoxic molecules that kill their target cell (figure 1B, C). Each individual CAR T cell can destroy multiple cells. Clinically approved CAR T cells are indicated exclusively for B-cell neoplasms, including lymphomas, leukaemias, and multiple myeloma. The most widely used constructs are directed against CD19, which can be found on B cells (from the differentiation state of pro-B cells to plasmablasts; figure 1C),⁶ and a number of B cell-derived malignancies.⁷ Approved products are acquired through apheresis of autologous lymphocytes (figure 1B). Some cell separation strategies already exist, where CD4 and CD8 CAR T cells are reinfused in a fixed ratio after CD4 and CD8 T cells are separated and processed to limit toxicity.⁸ However, persistent CAR T cells found in long-term survivors also display a CD4 phenotype.⁹ The use of autologous preparations might negatively affect

production of CAR T cells, because the fitness of T cells can be compromised by cytotoxic (or immunosuppressive) therapies or the underlying disease.¹⁰ Strategies to overcome this issue include, among others, the use of allogeneic CAR T cells.¹¹ Upon collection, cells are stimulated *in vitro* to facilitate genetic modification leading to CAR expression, which is done by gene transfer with a viral vector. Manufacturing of CAR T cells can last for up to 4 weeks. At present, rapid protocols, such those using T cells with stem cell characteristics, are being investigated.¹² After their expansion, CAR T cells are reinfused following a process known as lymphodepletion. In most cases, the chemotherapeutics cyclophosphamide and fludarabine are administered for lymphodepletion, which promotes proliferation and potential activation of the infused CAR T cells.¹³

Despite the success of CAR T-cell therapy, clinically significant therapy-associated toxic effects have been observed, some of which can be life-threatening. These toxic effects include cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS).¹⁴ During CRS, activated CAR T cells communicate with myeloid cells, which release large amounts of inflammatory mediators, leading to sepsis-like symptoms, such as fever or hypotension. Standard therapy for CRS is IL-6 blockade, because myeloid cell-derived IL-6 has a crucial role in triggering symptoms. ICANS occurs in 20–70% of patients treated with anti-CD19 CAR T cells and varies both in terms of severity and quantity of symptoms, but typically results in a toxic encephalopathy.¹⁵ Early symptoms of ICANS include dysgraphia, word-finding difficulties, tremor, cognitive impairment, and fatigue, which require consistent monitoring. In more severe cases, epileptic seizures, increased intracranial pressure, and even coma can occur. Although the mechanisms of ICANS remain unclear, disruption of the

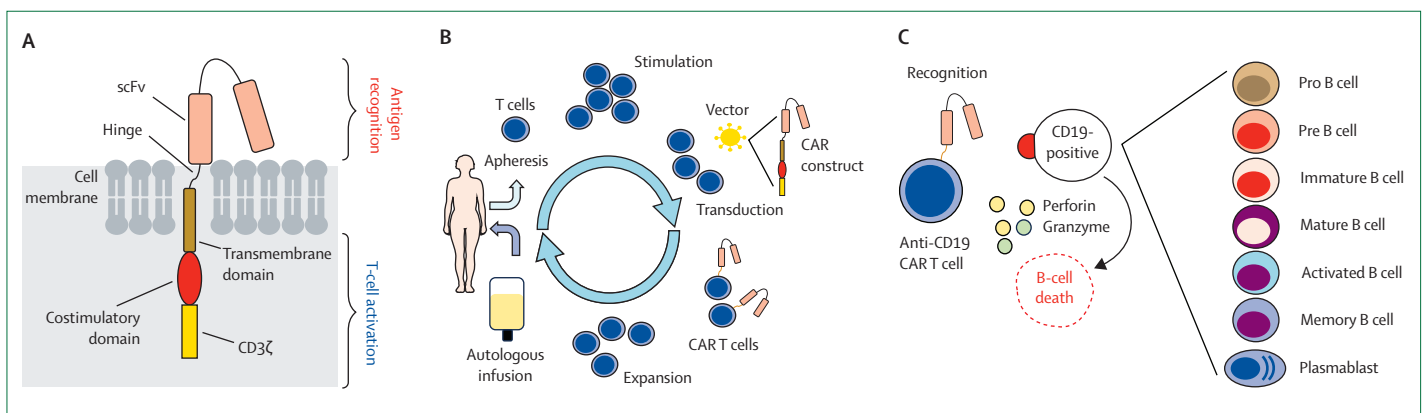


Figure 1: Design, production, and mode of action of CAR T cells

(A) A prototypical second-generation CAR with an antibody-derived antigen-binding single-chain variable fragment (scFv), hinge region, transmembrane domain, costimulatory domain (eg, CD28 or 4-1BB), and CD3 ζ -chain of the T cell receptor. (B) To produce CAR T cells, patients undergo lymphapheresis. Upon collection, autologous T cells are stimulated *in vitro* (eg, by triggering the T cell receptor or co-stimulatory molecules, such as CD28) and genetically modified by, for example, transduction with viral vectors to express a CAR. The CAR T cells produced in this way will be further expanded and subsequently reinfused into the patient after lymphodepletion (done with a combination of fludarabine and cyclophosphamide). The depicted process typically requires up to 4 weeks. (C) CAR T cells, directed, for example, against CD19, recognise CD19 expressed at various stages of the B-cell lineage, become activated, and destroy the target cell by releasing effector molecules, such as granzyme and perforin. CAR=chimeric antigen receptor.

blood–brain barrier as a result of activated endothelial cells has a role in its pathophysiology.¹⁶ Due to the permeable blood–brain barrier, inflammatory mediators can enter the CNS causing neuronal dysfunction. Unlike CRS, IL-6 blockade is ineffective in other neurotoxicities, and steroids are mainly used.¹⁷ Risk factors for CRS or neurotoxicity comprise high tumour burden, systemic inflammation (eg, elevated CRP or ferritin), and pre-existing neurological conditions predisposing to neurotoxic effects.¹⁸ Cytopenia is another adverse effect that, depending on timing and duration (ie, <3 vs >3 months), is linked to haematotoxic lymphodepletion or immunological processes.¹⁹ Extended cytopenia can require a stem cell boost, leaving patients susceptible to infectious complications. As anticipated, anti-CD19 CAR T cells also eradicate non-malignant B cells (on-target, off-tumour effect), resulting in prolonged B-cell depletion, sometimes necessitating a year-long therapy for immunoglobulin replacement.¹⁴

CART cells in patients with autoimmunopathies

The prolonged and deep depletion of B cells in cancer patients receiving CAR T-cell therapy was used as the rationale for their first use in rheumatoid autoimmune diseases.²⁰ Unlike B cell-targeting antibodies, such as rituximab, CAR T cells are autonomous and do not require natural killer (NK) cells, macrophages, or the complement system²¹ to perform their function, even deep within tissues. This autonomous mechanism might be the reason why the deployment of therapeutic antibodies often does not result in the same degree of B-cell depletion as seen in patients treated with CAR T cells, especially in compartments of interest, such as the CNS (table 1).²² In autoimmune diseases, B cells not only act as producers of autoantibodies, but they can also present self-peptides through MHC, thereby activating autoreactive T cells.²³ Several reports, including those related to systemic lupus erythematosus,²⁴ antisynthetase syndrome,²⁵ and scleroderma,²⁶ indicate that anti-CD19 CAR T cells could generate long-lasting remissions in therapy-resistant cases. In a German case series, patients with treatment-refractory severe forms of systemic lupus erythematosus, myositis, or scleroderma remained disease-free during a median follow-up of 15 months (range 4–29) and despite reappearance of B cells in 14 of 15 patients a mean of 112 days (SD 50) after infusion.²⁷ These findings could affect the treatment of autoimmune diseases, and several early phase clinical trials evaluating B cell-directed CAR T cells have been initiated or are planned (>10 studies in systemic lupus erythematosus).²⁸ Although the patient population is small, available case series present compelling discoveries—ie, despite infusion of CAR T cells into a pro-inflammatory or autoimmune context, no augmented toxicity signals have been observed.²⁰ Additionally, the quantity of targeted CD19-positive cells (ie, B-cells) is substantially lower than in B cell-derived

	Monoclonal antibodies	CART cells
Availability	Prompt, off the shelf	Around 4 weeks, individual production*
Persistence	Limited	In-vivo expansion
Biodistribution	Slow, passive	Fast, passive and migration
Mode of action	Complement-dependent cytotoxicity, cell-mediated cytotoxicity, cell-mediated phagocytosis	Release of cytotoxic molecules

CAR=chimeric antigen receptor. *Allogeneic CAR T cells are in development.

Table 1: Therapeutic differences between monoclonal antibodies and CAR T cells targeting B cells

malignancies, resulting in less CAR T-cell mediated toxicity.¹⁸ Despite the substantial reduction or even complete absence of autoantibody production following infusion of CAR T cells, most patients with rheumatic conditions maintain sufficient immunoglobulin concentrations, and their protective vaccination titres are maintained.²⁰

An explanation of this paradox might be that CD19 is still present on plasmablasts but is no longer on long-lived plasma cells.²⁹ This explanation would lead to the following hypotheses: (1) CD19-positive, CD20-negative plasmablasts are central to autoimmunity; and (2) protective antibodies are still produced in sufficient amounts by CD19-negative, CD20-negative, long-lived plasma cells (in the bone marrow). The compelling efficacy of CAR T cells in the treatment of rheumatoid autoimmune diseases, together with the favourable safety data, provide the impetus to pursue such strategies in B cell-driven neuroimmunological disorders.

Role of B-cells in neuroimmunological disorders

Antibody-mediated depletion of B cells (ie, by anti-CD19 or anti-CD20 therapeutic antibodies) does not necessarily lead to clinical stabilisation of neuroimmunological disorders.^{3,30,31} One possible explanation could be the prevalence of TBX21-high (or T-bet-high) memory B-cells, which drive chronic inflammation. They do not circulate but reside in the tissue close to the site of inflammation and can adopt a double-negative (CD19-negative, CD20-negative) phenotype.³² Additionally, in the context of autoimmunity, B cells have shown to be producers of pro-inflammatory cytokines, such as IFN γ , IL-6, and GM-CSF, as well as autoantibodies.^{33,34} This feature allows cytokine-producing B cells to drive and to maintain the formation of tertiary lymphoid structures, which could cause disease progression in multiple sclerosis despite anti-inflammatory interventions and disease-modifying therapy. As shown extensively in multiple sclerosis, for which a specific autoantibody has not been identified, inhibition of B-cell functions, such as cytokine production, antigen presentation, and chronic tissue inflammation, might be the main treatment effect of B-cell depletion.³⁵ Therefore, the ability of CAR T cells to penetrate into the tissue and sufficiently deplete these otherwise inaccessible B cells that drive chronic, tissue-resident inflammation

could explain the rapid and long-lasting therapeutic effect of CAR T cells.

Myasthenia gravis

Myasthenia gravis is an antibody-mediated neuro-immunological disorders and the most common neuromuscular disease. About 90% of the seropositive cases have antibodies against the acetylcholine receptor (AChR), and the remaining myasthenia gravis types (eg, muscle-specific tyrosine kinase [MuSK] antibody-positive cases or other autoimmune neuromuscular disorders) are much rarer and can be associated with malignancies.³⁶ Although the main pathological mechanism is auto-antibody-mediated blockade of AChR, complement activation leads to destruction of the receptor and renders the muscle unresponsive to nerve signals. Several studies (case series and open-label trials) have investigated the therapeutic efficacy of rituximab. Although patients with anti-MuSK antibody-positive myasthenia gravis responded favourably to B-cell depletion, rituximab did not result in stabilisation for all patients with anti-AChR-positive myasthenia gravis.³⁷ This observation has led to the introduction of complement-targeting antibodies, such as eculizumab³⁸ and ravulizumab,³⁹ or the overall reduction of immunoglobulins by efgartigimod.⁴⁰ These therapeutic approaches have proven effective in highly active myasthenia gravis. However, their use is associated with increased infections, high frequency of administration, or (sometimes prolonged) hypogammaglobulinaemia.

B cell-targeting CAR T cells might lead to a sustained suppression of disease activity. A US phase 1b/2a study⁴¹ investigated the safety of RNA-engineered CAR T cells targeting B-cell maturation antigen (BCMA) in 14 adults with myasthenia gravis and suggested that the therapy is safe to use. In a 12-month update of the study,⁴² five of the seven patients treated continued to show clinical improvement in MG-ADL, QMG, and MGC scores. In a 33-year-old woman with highly active myasthenia gravis (despite previous treatment with rituximab, bortezomib, and mycophenolate), anti-CD19 CAR T cells led to long-term disease stabilisation with a good safety profile.⁴³ Overall, IgG concentrations remained stable, and no increased susceptibility to infections was observed. In summary, available data are encouraging, with the forthcoming clinical trials (table 2) expected to yield further insight into the potential of anti-CD19 CAR T cell therapy as a durable treatment option for myasthenia gravis.

Antibody-mediated neuroimmunological disorders

Progress in diagnostics, including MRI and serum and CSF biomarkers, has allowed for a clearer differentiation of antibody-mediated neuroimmunological disorders from multiple sclerosis.^{48,49} The pace of therapy development in multiple sclerosis has been matched by implementation of clinical trials in less common antibody-mediated neuroimmunological disorders, resulting in the approval

of multiple drugs for neuromyelitis optica spectrum disorders and myelin oligodendrocyte glycoprotein antibody disease. Although rituximab has been used off-label to target B cells in cases where immunomodulatory therapies, such as azathioprine and mycophenolate, did not elicit a response, its efficacy is only supported by retrospective data.⁵⁰ Similarly, the diverse and expanding set of antibody-mediated autoimmune encephalitides have been subject to empirical treatment. The range of immunotherapies used in this category varies from IVIG, steroids, and plasma exchange in the acute stage to rituximab and, the plasma cell-targeting drug, bortezomib in refractory cases.⁵¹ Antibodies targeting cytokines (eg, tocilizumab) or complement (eg, eculizumab) have also been used to treat autoimmune encephalitides.⁵² The first drug approvals for the treatment of antibody-mediated neuroimmunological disorders have been granted for the anti-aquaporin-4-positive neuromyelitis optica spectrum disorders following randomised clinical trials that investigated the anti-CD19, B cell-depleting antibody inebilizumab,² the complement-binding and complement-neutralising antibodies eculizumab⁴⁶ and ravulizumab,⁵³ and the anti-IL6 receptor antibody satralizumab.⁵⁴ These advancements offer a potent therapeutic arsenal, with safety data requiring long-term evaluation. Similar challenges to those in myasthenia gravis are anticipated. In the context of neuromyelitis optica spectrum disorders, characterised by severe inflammatory attacks, achieving long-term remission is the primary objective. An initial phase 1 trial⁵⁵ in 12 adults with neuromyelitis optica spectrum disorders using anti-BCMA CAR T cells, although not primarily assessing clinical efficacy, showed that 11 patients remained drug-free and relapse-free after a median of 5.5 months follow-up. Another trial using a tandem CAR T cell against CD19 and CD20 has been announced in China, but the results have not yet been reported (table 2). In conclusion, CAR T-cell therapy might become a valid option for severe, refractory cases of antibody-mediated neuroimmunological disorders.

Multiple sclerosis

Multiple sclerosis research has driven innovation in the field of neuroimmunological disorders. Despite absence of a specific autoantigen, many immune-mechanistic discoveries have produced a multitude of therapies that inhibit, modulate, or deplete various immune targets. Most of the investigations that led to available therapies have provided a better understanding of the intricate autoimmune and neurodegenerative nature of multiple sclerosis. B cell targeting, in particular, and its strong effect on reducing disease relapses has challenged the notion that multiple sclerosis is a primarily T cell-mediated CNS disease.^{56,57} The most apparent involvement of B-cells in multiple sclerosis pathophysiology are oligoclonal bands in the CSF, which are detectable in the most patients with multiple sclerosis. Three B cell-depleting antibodies, all directed against CD20, have been approved for the

CART cell	Disease	Study design	Number of patients	Main inclusion criteria	Primary outcomes	Status	Main results
NCT03605238	Anti-CD19/CD20 CART cell	Open-label phase 1	N/A	12-75 years old, aquaporin-4-IgG seropositive, ≥2 relapses in the last year or ≥3 relapses in the last 2 years, therapy refractory (corticosteroid plus immunosuppressant)	Study-related adverse events (12 months), annual relapse rate, EDSS, visual acuity	Announced August, 2018; estimated completion August, 2020; results not published	Withdrawn owing to difficulties in recruiting patients
NCT04146051	Anti-BCMA CART T cell	Open non-randomised, multicentre, phase 2	30	≥18 years old, seropositive and seronegative (MGFA III-IV), MG-ADL >6	Safety, MG-ADL	Announced April, 2019; estimated completion December, 2023; published ⁴¹	7 completed the study (7 received MTD once weekly for 6 weeks [group 2]), MG-ADL mean score change to baseline -6 (95% CI -9 to -3) and QMG-7 (-11 to -3) after 24 weeks; group 1 (twice weekly for 3 weeks at MTD) and group 3 (once monthly for 6 months) discontinued; MTD was determined in phase 1 of the study (median 17.3 × 10 ⁶ cells [range 9.7-33.1] divided over a median of 6 infusions [3-6])
NCT04561557	Anti-BCMA CAR-T cell	Open-label, non-randomised, single-centre, phase 1	18	18-75 years old, seropositive, refractory to standard therapy	Dose-limiting toxic effects (3 months), treatment-emergent adverse events (2 years), serum antibody titres	Announced September, 2022; estimated completion May, 2024	..
Myasthenia gravis cohort	Myasthenia gravis	..	2	MG-ADL >6	QMG, MG-ADL	..	Patient 1: 33-year-old woman, positive for antibodies against AChR and Titin, received 6.16 × 10 ⁷ cells, grade 1 CRS, improved from QMG 12 at baseline to below 5 at month 18, was seronegative for antibodies against AChR at month 18; Patient 2: 60-year-old woman, positive for antibodies against MuSK, received 5.04 × 10 ⁷ cells, no CRS, improved from QMG 18 at baseline to below 2 at month 18, was seronegative for antibodies against AChR at month 18 ⁴⁴
Chronic inflammatory demyelinating polyradiculopathy cohort	Chronic inflammatory demyelinating polyradiculopathy	..	Unknown	INCAT score of 2-9	Inflammatory Neuropathy Cause and Treatment disability score, Medical Research Council sum score	..	Not known
Immune-mediated necrotising myopathy cohort	Immune-mediated necrotising myopathy	..	1	..	Manual Muscle Testing score	..	25-year-old man, positive antibodies against SRP, received 6.53 × 10 ⁷ cells, grade 1 CRS, improvement in MMT score (from 96 to 137) and negative for anti-SRP antibodies at month 18 ⁴⁵
Neuromyelitis optica spectrum disorder cohort	Neuromyelitis optica spectrum disorder	..	12	≥2 relapses in the last year or ≥3 relapses in the last 2 years, refractory to at least one immunosuppressant for >1 year	Time to first relapse, EDSS, visual acuity	Interim analysis published in 2023 ⁴⁶	12 patients completed the study; three groups were tested (dosed escalation group with two sub-groups of 3 each [0.5 × 10 ⁶ cells per kg or 1.0 × 10 ⁶ cells per kg] and dose expansion group of 6 [1 × 10 ⁶ cells per kg]); 11 patients remained drug and relapse free in interim analysis after a median of 5.5 months of follow-up, 1 patient had a relapse with optic neuritis of the left eye

(Table 2 continues on next page)

CART T cell	Disease	Study design	Number of patients	Main inclusion criteria	Primary outcomes	Status	Main results
<i>(Continued from previous page)</i>							
NCT05828225	Anti-CD19 CAR T cell Myasthenia gravis	Open-label phase 1	9	≥18 years old, seropositive (AChR; MGFA IIa-IVb), MG-ADL >5, QMG >11, refractory to standard therapy	Dose-limiting toxic effects (28 days), treatment-emergent adverse events (90 days)	Announced April, 2023; estimated completion April, 2026	Not known
NCT05451212	Anti-MuSK CAAR-T cell MuSK myasthenia gravis	Open-label phase 1	24	≥18 years old, seropositive for MuSK and AChR (MGFA I-IVa)	Dose-limiting toxic effects, treatment-emergent adverse events (9 months)	Announced December, 2023; estimated completion October, 2028	Not known
NCT06138132	Anti-CD19 CAR T cell Progressive multiple sclerosis	Open-label phase 1	12	≥18 years old, diagnosis according to 2017 McDonald criteria, progressive according to Lublin 2014 criteria	Dose-limiting toxic effects (12 months)	Announced December, 2023; estimated completion June, 2027	Not known
Individual case study ⁴⁷	CD19 CAR-T Myasthenia gravis	..	1	≥18 years old, seropositive (AChR; MGFA II-IV), refractory to standard therapy	Safety, QMG, Besinger score	Published in 2023	Treatment with 1 × 10 ⁸ total cells safe, QMG change from baseline -10

Current studies testing CART cells in neuroimmunological disorders ordered by date they were registered or published. AChR=acetylcholine receptor. BCMA=B-cell maturation antigen. CAR=chimeric antigen receptor. CAAR=chimeric autoantibody receptor. EDSS=Expanded Disability Status Scale. INCAT=Inflammatory Neuropathy Cause and Treatment Disability Score. MG-ADL=Myasthenia Gravis-Activity of Daily Living score. MGFA=Myasthenia Gravis Foundation of America (classification). MTD=maximum tolerated dose. MuSK=muscle-specific tyrosine kinase myasthenia gravis. N/A=not available. QMG=Quantitative Myasthenia Gravis score.

Table 2: Clinical studies of the use of CART cells in patients with neuroimmunological disorders

treatment of relapsing remitting multiple sclerosis (ie, ocrelizumab, ofatumumab, and ublituximab), and ocrelizumab is also approved for primary progressive multiple sclerosis. The anti-CD19 antibody inebilizumab showed safety in a phase 1 clinical trial and is being investigated in later stage clinical trials.⁵⁸

Although B cell targeting, like several other therapies, has proven effective in preventing inflammation originating from the periphery in multiple sclerosis (considered to be a correlate of new MRI lesions and relapses), an increasing body of evidence suggests that disease progression can occur without relapses.⁵⁹ Several scenarios have been suggested to explain disease progression without apparent cellular infiltration from outside the blood-brain barrier. For example, derived from the observation that B cells can form meningeal follicles, tertiary lymphoid structures⁶⁰ adjacent to the cortex, a plausible scenario entails continuous neuronal damage by locally secreted inflammatory cytokines, such as GM-CSF, IL-6, and lymphotoxin-α.³⁴ In addition to the clinical observation of ongoing disease progression without relapses, the notion that B cells are sustainably depleted in the periphery and the CSF, while oligoclonal bands persist in the CSF under therapy, supports the scenario that therapeutic antibodies are not able to sufficiently target tissue-resident B cells. Use of B cell-depleting anti-CD19 CAR T cells that have demonstrated their ability to penetrate into tissue might be advantageous. The phase 2 clinical trial KYSA-7 testing anti-CD19 CAR T cells in 12 patients with progressive multiple sclerosis (NCT06138132) will shed more light on this issue.

Challenges in treating neuroimmunological disorders with CART cells

CAR T cells can cause severe side-effects in patients with cancer, particularly CRS, neurotoxic effects, and haematotoxicity. Established risk factors in this patient population include systemic inflammation (ie, CRP or increased ferritin concentrations), pre-existing neurological damage, older age, and residual tumour burden before infusion of CAR T cells.^{18,19,61} Although patients with autoimmune disorders typically have increased inflammatory activity and, in the case of neuroimmunological disorders, neurological pre-damage (figure 2A), good safety outcomes have been observed in admittedly small cohorts, without occurrence of higher grade CRS or neurotoxic effects.²⁰ One reason for this safety profile could be the amount of target antigen, which in autoimmune disorders and neuroimmunological disorders is lower than in malignancies and might lead to reduced activation of CAR T cells and, thus, fewer side-effects. Additionally, the effects of long-term immunosuppression on the immune system and its responsiveness—for example, in the form of released IL-6—are still open questions that need to be addressed. As previously discussed, case numbers are small, and more trials are warranted to provide a more conclusive

picture; this is especially apparent in view of the heterogeneity in terms of underlying biology and clinical presentation of the autoimmune disorders and neuroimmunological disorders treated so far. To mitigate the potential toxic effects of CAR T cells, one strategy that is used is transient CAR expression through mRNA gene transfer, a method that has demonstrated promising outcomes in people with myasthenia gravis.⁴¹ Additionally, it will be necessary to reconsider risk factors and the according scores, such as the CAR-HEMATOTOX score¹⁹ for CAR-related haematotoxicity, that have been established in CAR T-cell therapy for malignancies. Monitoring strategies might also need to be adapted, particularly for neurotoxicity. Patients with conditions such as autoimmune encephalitis might be unable to provide responses necessary for assessing functional status using ICE or CARTOX scores.⁶² Therefore, new clinical monitoring tools need to be developed for such patients, including continuous EEG-monitoring or routine (structural) brain MRI (figure 2C).^{63,64}

A prerequisite for the efficacy of CAR T-cell therapy is their proximity to the target cells (figure 2C).⁶⁵ CAR T cells can be detected in the CSF of patients with cancer, regardless of neurotoxic effects.^{16,61} Initially, CNS involvement was an exclusion criterion for trials in lymphoma owing to concerns about neurotoxic effects.^{66,47} However, the efficacy of CAR T cells against CNS lymphomas is now well established.⁶⁷

Regarding the ideal target antigen, one size might not fit all. In fact, one potential explanation for the limited effectiveness of anti-CD20 antibody-mediated B-cell depletion is that autoantibody production might be attributed to CD20-negative plasmablasts or CD20-negative plasma cells (either short-lived or long-lived variants). Plasmablasts express CD19, but plasma cells do not. Antigens shared by plasma cells and plasmablasts include CD38 and BCMA. Previous experience in systemic lupus erythematosus, myositis, or myasthenia gravis has shown that eliminating CD19-positive plasmablasts, but not CD19-negative plasma cells, has proven sufficient to reach clinical response.^{24,25,43} Reduction in disease activity was achieved without large depletion of IgG and increasing susceptibility to infection in most patients. A more specific approach is the use of so-called chimeric autoantibody receptor (CAAR) T cells.⁶⁸ Unlike CARs, which identify and attach to their target through an extracellular antibody fragment, CAARs direct the cytotoxic effects of T cells only to B cells producing autoantibodies, which has the advantage of reducing the risk of general immunosuppression. Because CAAR T cells also bind circulating autoantibodies, CAARs could become saturated, so a higher number of infused CAAR T cells than CAR T cells might be required to be effective. An additional potential risk of CAAR T-cell therapy is the so-called tip of the iceberg phenomenon in autoimmunity, which implies that all autoantibodies

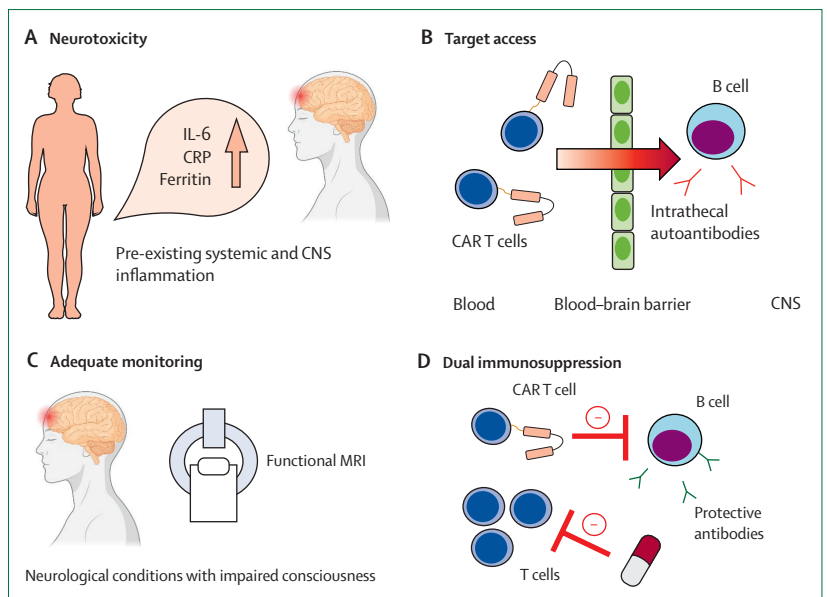


Figure 2: Potential challenges in the treatment of neuroimmunological disorders with CAR T cells

(A) Pre-existing inflammatory milieu and neurological disorders can be risk factors for therapy-associated toxic effects, such as cytokine release syndrome, neurotoxic effects, and haematotoxicity. (B) In some neuroimmunological disorders, autoantibodies are produced by B cells intrathecally. CAR T cells must overcome the blood-brain barrier to ensure effective treatment. (C) Because neuroimmunological disorders affect the nervous system, close neurological monitoring during and after CAR T-cell therapy is required to detect and manage potential neurological side-effects. New routines, such as functional MRI or continuous EEG monitoring, need to be developed, because reduced vigilance could render traditional clinical tests for assessing neurotoxicity obsolete. (D) Many neuroimmunological disorders require the use of immunosuppressants, affecting the T-cell compartment. Following B cell-targeting CAR T-cell therapy with consecutive depletion of B cells, such an approach should be carefully considered to avoid double immunosuppression with highly increased infection risk.

contributing to pathology are not always identified. To overcome this problem, at least partly, CAAR T cells with multiple specificities would be advantageous. However, it is possible that various neuroimmunological disorders will benefit differently from distinct approaches. Therefore, we must await the data from ongoing and future clinical trials (table 2).

The efficacy of CAR T cells naturally correlates with the fitness of the T cells (ie, their ability to expand, meet their metabolic demands, and kill their target cells). However, patients with neuroimmunological disorders are usually treated for long periods with immunosuppressive drugs, including those that target the T cell compartment, such as mycophenolate mofetil, which interferes with the function of the T cell, or natalizumab, which interferes with T cell-trafficking. This immunosuppression should be considered before lymphocyte apheresis and before implementing appropriate washout periods based on the drug's half-life and mechanism of action. Additionally, caution must be exercised with therapeutic T cell-targeted interventions following CAR T cell-mediated depletion of B cells. Simultaneous suppression of cellular and humoral immune responses could further increase the risk of infection (figure 2D). On the basis of the available data (which are limited),^{69,70} it would be preferable to resume such therapy after the functional reconstitution of B cells if

disease activity permits or requires it. Another issue with autologous T cells is the risk that autoreactive T cells might be transfected in CAR T cell production. T cells directed against self-antigens such as MBP⁷¹ seem to have a role in neuroimmunological disorders, and expanding CAR T cells carrying an autoreactive endogenous TCR could theoretically worsen the clinical picture after infusion. One strategy to avoid both heavily pretreated, unfit T cells or autoreactive CAR T cells could be the use of so-called allogeneic T cells from third-party donors.¹¹ To prevent graft-versus-host disease, the endogenous TCR is eliminated by genome editing or the immunogenicity is reduced by modifying MHC-I expression. It remains to be seen whether the initial success of allogeneic CAR T cells in malignant diseases can be replicated in autoimmune diseases.

Overall, therapies using genetically modified cell products are a multidisciplinary and complex effort involving at least neurologists and cell therapists (typically haematologists). Therefore, we refer readers to a position paper from the European Bone Marrow Transplantation's multidisciplinary working group on autoimmune diseases, which details the intended modus operandi of this collaboration between disciplines and the qualitative requirements.⁷²

Conclusions and future directions

The use of CAR T cells in the treatment of neuroimmunological disorders is expected to attract considerable attention in the coming years. Although data are scarce, the results so far are encouraging. This innovative approach could potentially result in extended periods of disease-free survival and treatment discontinuation. The pathophysiology of neuroimmunological disorders is complex and will require confirmation in pre-clinical models and controlled trials to determine if an immunological reset, similar to what has

Search strategy and selection criteria

We searched PubMed, medRxiv, bioRxiv, and Google Scholar for literature published between Jan 1, 2010, and March 1, 2024. Our search criteria included terms such as "CAR T cell" and "chimeric antigen receptor" and phrases targeting specific areas of interest, including "B-cell depletion", "B-cell targeting", "treatment and autoimmune disease", "treatment and autoimmune neurological disease", "treatment and neuroimmunological disease", and "treatment and neuroinflammation". We limited our search to papers published in English, and considered various types of publications, including clinical studies, mechanistic studies, case reports, case series, and review articles. In terms of cell therapy approaches, we have limited ourselves to CAR T cells and have not included studies of autologous or allogeneic stem cell transplantation or other types of adoptive cell therapies, such as regulatory T-cells or mesenchymal stromal cells.

been observed in autoimmune diseases, can be induced and under which specific conditions. When using CAR T cells in neuroimmunological disorders, safety should be carefully considered, particularly neurotoxicity. Patients' pre-existing neurological conditions, particularly those associated with CNS inflammation, might further increase the risk of CAR T cell-associated neurotoxicity and could also complicate monitoring for neurotoxicity. Several ongoing and planned studies are exploring the effects of CAR T cells in neuroimmunological disorders, offering an avenue for deeper insights into the potential of this innovative approach.

Contributors

AH and DM contributed equally to the writing, literature inclusion, and interpretation of the manuscript. GS helped writing the manuscript. AH had final responsibility to submit for publication.

Declaration of interests

AH has served on scientific advisory boards for Galapagos, Novartis, Merck Serono; has received speaker honoraria from Biogen Idec, Merck Serono, and Novartis; and has received research grants from Merck Serono. GS has received speaker honoraria from BMS, Cabaletta, Janssen, Kyverna, Miltenyi, and Novartis. DM has received speaker honoraria and consulting fees from Abbvie, BMS, Beigene, Celgene, Galapagos, Gilead, Janssen, Miltenyi, and Novartis.

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