The Role of Chimeric Antigen Receptor T-Cell Therapy in Immune-Mediated Neurological Diseases

Gavin Brittain, MD [1,2†] Elisa Roldan, MD,[3,4†] Tobias Alexander, MD,[5,6] Riccardo Saccardi, MD,[7] John A. Snowden, MD,[3,4] Basil Sharrack, MD, PhD,[1,2‡] and Raffaella Greco, MD [8‡]

Despite the use of 'high efficacy' disease-modifying therapies, disease activity and clinical progression of different immune-mediated neurological diseases continue for some patients, resulting in accumulating disability, deteriorating social and mental health, and high economic cost to patients and society. Although autologous hematopoietic stem cell transplant is an effective treatment modality, it is an intensive chemotherapy-based therapy with a range of short- and long-term side-effects. Chimeric antigen receptor T-cell therapy (CAR-T) has revolutionized the treatment of B-cell and other hematological malignancies, conferring long-term remission for otherwise refractory diseases. However, the toxicity of this treatment, particularly cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome, and the complexity of production necessitate the need for a high level of specialization at treating centers. Early-phase trials of CAR-T therapies in immune-mediated B cell driven conditions, such as systemic lupus erythematosus, neuromyelitis optica spectrum disorder and myasthenia gravis, have shown dramatic clinical response with few adverse events. Based on the common physiopathology, CAR-T therapy in other immune-mediated neurological disease, including multiple sclerosis, chronic inflammatory polyradiculopathy, autoimmune encephalitis, and stiff person syndrome, might be an effective option for patients, avoiding the need for long-term immunosuppressant medications. It may prove to be a more selective immunoablative approach than autologous hematopoietic stem cell transplant, with potentially increased efficacy and lower adverse events. In this review, we present the state of the art and future directions of the use of CAR-T in such conditions.

ANN NEUROL 2024;00:1–12

Multiple sclerosis (MS), myasthenia gravis (MG), neuromyelitis optica spectrum disorder (NMOSD), chronic inflammatory polyradiculopathy, autoimmune encephalitis, and stiff person syndrome are debilitating neurological disorders with heterogeneous clinical and pathological manifestations, which share an underlying, albeit different, immune-mediated mechanism, with a central role of B cells.[1] In MS, B cells drive disease through

View this article online at wileyonlinelibrary.com. DOI: 10.1002/ana.27029

Received Jan 11, 2024, and in revised form May 20, 2024. Accepted for publication Jun 23, 2024.

Address correspondence to Dr Gavin Brittain, Division of Neurosciences, School of. Medicine and Population Health, University of Sheffield and Sheffield Teaching Hospitals NHS Trust, Sheffield, S10 2RX, UK. E-mail: gavin.brittain@sheffield.ac.uk
Dr Raffaella Greco, Hematology and Bone Marrow Transplantation Unit, San Raffaele Scientific Hospital, Vita-Salute San Raffaele University, via Olgettina 60, 20132, Milano, Italy. E-mail: greco.raffaella@hsr.it

[†]Co-first authors.

[‡]Co-last authors.

From the [1]Neuroscience Institute, University of Sheffield, Sheffield, UK; [2]Department of Neurology and Sheffield NIHR Neuroscience BRC, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK; [3]Department of Haematology, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK; [4]Division of Clinical Medicine, School of Medicine and Population Health, University of Sheffield, Sheffield, UK; [5]Department of Rheumatology and Clinical Immunology—Charité–Universitätsmedizin Berlin, Corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and the Berlin Institute of Health (BIH), Berlin, Germany; [6]Deutsches Rheuma-Forschungszentrum (DRFZ Berlin)—a Leibniz Institute, Autoimmunology Group, Berlin, Germany; [7]Cell Therapy and Transfusion Medicine Unit, Careggi University Hospital, Florence, Italy; and [8]Unit of Hematology and Bone Marrow Transplantation, IRCCS San Raffaele Scientific Hospital, Vita-Salute San Raffaele University, Milan, Italy

several mechanisms, including antigen presentation to T cells, production of proinflammatory cytokines peripherally, and are resident in the central nervous system across the disease spectrum.[2] However, pathogenic antibodies have not been identified for most neurological immune-mediated disorders, including MS. Two typical conditions that have such antibodies are MG (acetylcholine receptors or muscle-specific tyrosine kinase [MuSK] antibodies) and NMOSD (aquaporin-4 [AQP4]–immunoglobulin G [IgG]). Although vast improvements in treatment have been made over the past 20–30 years, with a spectrum of relatively safe and tolerable therapies, there is no cure for such disorders, regardless of the knowledge of the pathogenic antibody(ies). Most patients require ongoing treatment, potentially causing cumulative immunosuppressive and off-target adverse events, often without completely suppressing disease activity. To mitigate this, and the progressive accumulation of disability, the goal of future treatments might focus on 'resetting' the immune system to reintroduce a long lasting immunotolerant state with no future immunosuppression required.

Discussion

Standard Disease-Modifying Treatments

There has been considerable progress in the use of disease-modifying therapies (DMTs) in different immune-mediated conditions that modulate or deplete the immune system with varying efficacy and risk profiles. The use of monoclonal antibodies has revolutionized the management of many of these conditions. Treatment options for highly active or refractory presentations include alemtuzumab (anti-CD52),[3] ocrelizumab (anti-CD20),[4] ofatumumab (anti-CD20),[5] or natalizumab (anti- α4-integrin)[6] in relapsing remitting MS (RRMS), or rituximab (anti-CD20)[7] satralizumab (anti-interleukin-6)[8] and inebilizumab (anti-CD19)[9] eculizumab (C5 inhibitor)[10] in NMO, and the latter in MG, are, particularly for anti-CD20 antibodies in RRMS, increasingly used as first-line therapies.[11] The dramatic success of anti-CD20 at reducing relapses in RRMS, or the closely related anti-CD19 therapy for NMOSD, compared with animal models,[12] in these conditions has prompted a rethink about the underlying disease mechanisms with the current target of recently approved highly active therapies being B cells. Such treatments, however, are not a cure, breakthrough disease is unpredictable and there is no proven stopping strategy, making the use of these treatments usually long term, conferring a potential cumulative longitudinal risk of adverse effects and healthcare costs, and an ongoing risk of further disease activity. Therefore, targeted one-off immunosuppression that provides freedom from long-term immunosuppression and treatment activity, in the case of MS, this would be both relapses and progression independent of relapses, has been a longstanding aspiration as a potential cure.

Hematopoietic Stem Cell Transplantation

The use of autologous haematopoietic stem cell transplantation (aHSCT) in immune-mediated neurological disease has increased in the past 2 decades, with MS being the fastest growing indication for this treatment in Europe.[13,14] aHSCT is a procedure that involves the ablation and reconstitution of the myeloid and lymphoid systems, aiming to eradicate malignant cells (in its use in cancer) or to develop a new and tolerant immune repertoire (in its use in immune conditions).[15] The main indications in neurological diseases include highly active RRMS failing DMTs and other refractory types of MS, chronic inflammatory polyradiculopathy, NMO, MG, and stiff person syndrome.

Evidence for the use of aHSCT in MS is incomplete. A phase 3 trial by Burt et al., which compared aHSCT using a nonmyeloablative regimen (cyclophosphamide/antithymocyte immunoglobulin) versus approved DMTs, reported no deaths or serious toxicity in the aHSCT group.[16] The results of this study provided evidence that aHSCT is safe and has superior efficacy compared with several DMTs, with no evidence of disease activity rates of 66 to 83% although, for historical reasons, the standard treatment arm of the trial did not include several currently approved high-efficacy DMTs. Several European phase 3 trials are currently ongoing (Star-MS [ISRCTN88667898], NET-MS [EudraCT: 2022-002654-95], RAM-MS [NCT03477500]) to establish the use of aHSCT in the treatment paradigm of RRMS. Although aHSCT is a relatively safe and cost-effective procedure for select MS patients, there remain concerns about the treatment-related mortality risk (within 100 days of treatment). Treatment-related mortality remains higher than that of DMTs, although, with improvements in patient selection and treatment regiments, it has reduced considerably from 1.3% (between 2001 and 2007) to 0.2 to 0.3%, based on large registry data.[13–15,17–20] Additional considerations include the loss of previous immunity, resulting in a risk of infections and a requirement for re-vaccination, infertility or subfertility, early menopause, secondary autoimmune disease, and a theoretical risk of secondary malignancies. Regardless of the outcome of ongoing trials, refinement of our ability to reset the immune system to improve outcomes for these conditions over the long term with less toxicity is still needed.

CAR-T Therapy. A chimeric antigen receptor (CAR) is a synthetic transmembrane protein expressed at the surface of immune effector cells (IECs) that are reprogrammed either in vitro or in vivo.[21] CARs are engineered synthetic

receptors that function to redirect lymphocytes, most commonly T cells, to recognize and eliminate cells expressing a specific target antigen. Conventional T cells expressing CARs revealed impressive clinical results in hematological malignancies driven by B cells, plasma cells, or other malignancies, and result in durable remission.[22]

The therapeutic strategy is based on the genetic modification of the patient's T cells, such that they express the immunoglobulin receptor that specifically recognizes a target cell antigen regardless of the human leukocyte antigen. The structure of CAR-T receptors consists of an extracellular antigen-recognition part (single-chain variable fragment), a transmembrane region, an intracytoplasmic costimulatory domain (usually 4-1BB or CD28), and a CD3 intracellular signaling domain (Fig 1).[23] Based on the composition of the intracellular region, different generations of CARs can be constructed: (1) the first generation comprising only CD3-zeta (CD3z); (2) the second generation with two different domains, most commonly CD28-CD3z and 4-1BB-CD3z; and (3) a third generation with 3 domains, generally obtained by adding OX-40 to a second-generation CAR.[24] Production of CAR-T cells requires the collection of the patient's T cells by leukapheresis, enrichment and activation of the T cells, transduction with a viral vector, and expansion and isolation of CAR-T-expressing T cells (Fig 2).

Products targeting B-cell surface antigens, such as CD19 or B-cell maturation antigen (BCMA), are available through academic or commercial laboratories (Table 1).[25–27]

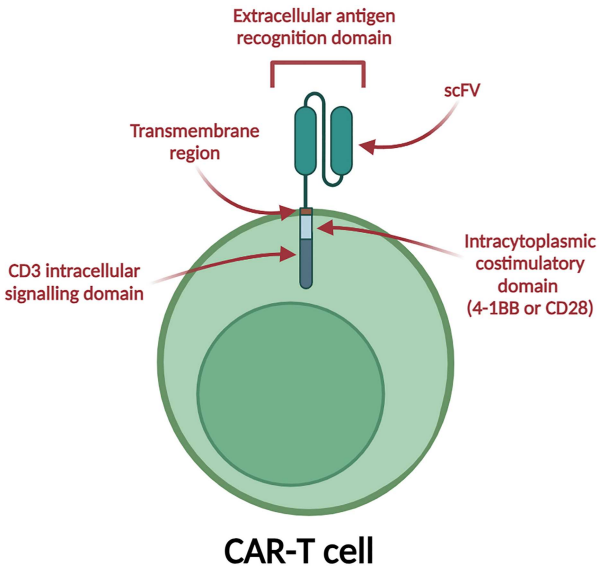

FIGURE 1: Illustration of chimeric antigen receptor T-cell (CAR-T) structure. The structure of CAR-T receptors consists of an extracellular antigen-recognition part, composed of a single-chain variable fragment (scFv), a transmembrane region, an intracytoplasmic costimulatory domain (usually 4-1BB or CD28 in 2nd-generation constructs), and a CD3 intracellular signaling domain.

Once the lymphocytes have been modified, the patient receives lymphodepletion chemotherapy and then receives the infusion of CAR-T cells. In malignant conditions, chemotherapy both reduces tumour mass and is also an essential part of the CAR-T-cell cycle by maximising the expansion of the CAR-T, and, therefore, increasing the efficacy and long-term survival of the circulating CAR-T cells. By eliminating endogenous lymphocytes and modulating cytokine production, an appropriate microenvironment for the CAR-T cells to expand and persist is created.[28]

Different lymphodepleting conditioning regimens have been used, with varied combinations of agents, dosing, and timing pre-CAR-T. Typical regimens are based on fludarabine/cyclophosphamide with a range of doses (fludarabine/cyclophosphamide 25/250 mg/m^2 up to 30/750 mg/m^2), duration of treatment (between 3 and 5 days of fludarabine and 1–3 days of cyclophosphamide), and time until transfusion (1 day up to 14 days prior to transfusion) of CAR-T are common.[28] Other agents, such as bendamustine, etoposide, or cyclophosphamide alone, have been used in various different lymphodepleting regimens.

Most CAR-T products are produced with autologous T cells that, due to the need for leukapheresis, are therefore associated with manufacturing and transit delays, increased cost, and depend on the functional fitness of patient T cells, which are often reduced by the disease or previous immunological therapies.[29] The use of allogeneic CAR-T cells from donors has many potential advantages over autologous approaches, including the immediate availability of cryopreserved batches for patient treatment, possible standardisation of the CAR-T-cell product, time for multiple cell modifications, redosing or combination of CAR-T cells directed against different targets, and decreased cost using an industrialized process.[30] However, allogeneic CAR-T cells have to overcome two significant challenges: the risk of causing graft-versus-host disease, and a rapid recognition and elimination of the CAR-T by the host immune system, which impede their activity. To avoid host recognition, new generation of T-cell receptor-deficient T cells (or other key immunogenic molecules) using genome editing tools have been developed and used in clinical trial settings.[31,32]

Other experimental CAR-T constructs include CAR engineered natural killer cells, CAR-T regulatory cells, dual-targeting CAR-T, RNA CAR-T (rCAR-T), chimeric autoantibody receptor cells, and synthetic Notch T cells are all in development.[33–38] Some of these novel constructs have not used different lymphodepleting regimens for their delivery.

CAR-T Toxicity. CAR-T-cell treatment can result in specific adverse effects, including cytokine release syndrome

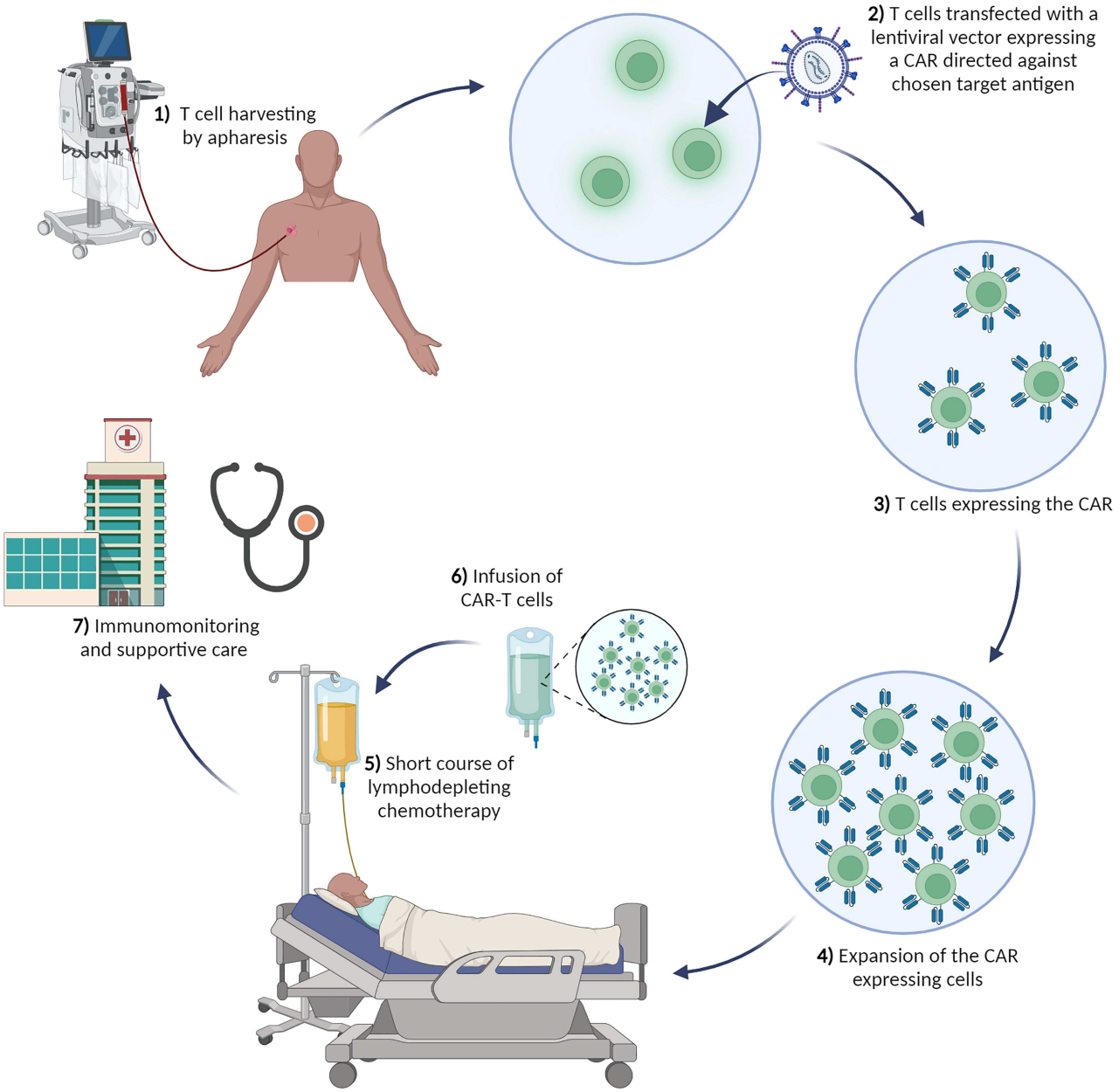

FIGURE 2: Illustration of chimeric antigen receptor T-cell (CAR-T) treatment. Production of CAR-T cells requires the collection of the patient's T cells by leukapheresis (1). T cells are separated and removed, then genetically modified to include a chimeric antigen receptor (CAR) and finally expanded to obtain millions of CAR T-cells (2–4). A short course of lymphodepleting chemotherapy is given (5), then the CAR-T cells are infused (6). Careful clinical and immunological monitoring is needed after infusion (7).

(CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS; Table 2).[39,40]

CRS is an acute systemic inflammatory syndrome characterized by fever and multiple organ dysfunction. It usually presents as fever with or without hypotension or hypoxia, with multiorgan failure occurring in severe cases. Treatment is highly successful with tocilizumab (anti-interleukin-6), and steroids. Currently, the management of CRS is well established, and prompt treatment usually successfully prevents grade 3–4 CRS symptoms (the most severe forms).[41] The frequency and severity of CRS after CAR-T-cell therapy varies between products (any grade: 37–93%, G3/4: 1–23%).[42–44] Some factors, such as high tumor burden and CAR-T-cell dose, seem to be associated with a higher risk of CRS.

Neurotoxicity, most commonly in the form of ICANS, can occur in the days to weeks following administration of a CAR-T (usually 4–10 days post-infusion), dependent on the CAR-T product received. It has been postulated that the disruption of the blood–brain barrier leads to migration of CAR-T cells into the brain parenchyma, and to elevated

TABLE 1. Chimeric Antigen Receptor T-Cell Therapy Products and Indications Approved by the Medicines and Healthcare Products Regulatory Agency European Medicines Agency and the United States Food and Drug Administration

Generic name	Brand name	Antigen target	Target disease(s)
Tisagenlecleucel	Kymriah	CD19	B-cell ALL
			B-cell NHL
Axicabatagene ciloleucel	Yescarta	CD19	NHL
			Follicular lymphoma
Brexucabtagene autoleucel	Tecratus	CD19	Mantle cell lymphoma
			ALL
Lisocabtagene maraleucel	Breyanzi	CD19	NHL
Idecantagene vicleucel	Abecma	BCMA	MM
Ciltacabtagene autoleucel	Carvykti	BCMA	MM

Abbreviations: ALL = acute lymphoblastic leukemia, BCMA = B-cell maturation antigen, NHL = non-Hodgkin's lymphoma, MM = multiple myeloma.

levels of cytokines and protein in the cerebrospinal fluid leading to inflammation of the central nervous system. Greater and faster CAR-T expansion in vivo correlates with higher ICANS risk.[40] ICANS presents with varying nonspecific symptoms ranging from confusion to seizure and cerebral oedema. Treatment is with dexamethasone or, for grade 4 ICANS, high-dose methylprednisolone, with response seen in the vast majority of patients.[45] Adjuvant tocilizumab should be given if ICANS occurs concurrently with CRS.[46] Prompt treatment reduces the incidence of severe ICANS. Other agents, such as Anakinra (anti-interleukin-1), have shown responses in up to 70% of refractory cases.[47] Reassuringly, evidence suggests that steroids do not impact CAR-T efficacy, although longer courses can be associated with shorter progression-free survival in hematological malignancies.[48] Levetiracetam is usually part of routine preventive measures, and with close working with neurology and intensive treatment unit, seizures are managed urgently with appropriate agents. The incidence of ICANS varies with the type of CAR-T infused, approximately 15 to 30% of treatments, but usually <20% of cases have severe (grade 3–4) ICANS.[49] Additional risk factors for ICANS, for patients with hematological malignancies, include high disease burden and older age. Tumor inflammation-associated neurotoxicity is an on-tumor, on-target neurotoxicity syndrome, distinct from ICANS, observed in central nervous system tumors treated with CAR-T-cell therapies.[50] Its symptom spectrum varies from headache or fever to hydrocephalus. Although ICANS results in global neurological dysfunction leading to seizures, decreased level of consciousness, or speaking/movement disorders, tumor inflammation-associated neurotoxicity manifests with focal symptoms, linked to the site of the tumor and to local inflammation, without signs of widespread neuronal damage.[51]

Other neurological complications have been described specifically in anti-BCMA CAR-T products, specifically parkinsonism, cranial nerve palsies, and peripheral neuropathy, which are increasingly recognized, but may be irreversible.[52,53] Although neurotoxicity related to CAR-T is traditionally considered to be off-target, due to neural expression of BCMA, which appears to have a role in neural development, on-target physiopathology has been proposed.[54] The safety of using CAR-T anti-BCMA to treat immune-mediated neurological conditions should be carefully considered, although they have been used with early signs of efficacy and safety (discussed below).[55]

Other toxicities related to CAR-T treatment are immune effector cell-associated hemophagocytic lymphohistiocytosis (HLH)-like syndrome (IEC-HS)[56] and immune effector cell-associated hematotoxicity.[57] IEC-HS incidence is variable across CAR-T-cell constructs and patient population, but an incidence of up to 40% has been described.[58] IEC-HS is characterized by high fever, hyperferritinaemia, prolonged cytopenia, and eventually multiorgan failure.[57] Although these lymphohistiocytosis-like manifestations are frequently seen in patients with severe CRS, IEC-HS often has a delayed onset and manifests as CRS is resolved/resolving. Interestingly, lymphohistiocytosis-like toxicities are often not as directly associated with CRS

TABLE 2. Chimeric Antigen Receptor T-Cell Therapy Cell Toxicity

CAR-T toxicity type	Clinical presentation	Treatment
CRS	Fever	Supportive care with broad-spectrum antibiotics
	Hypotension	Tocilizumab 8 mg/kg IV (max 800 mg)
	Hypoxia	Dexamethasone 10 mg
	Multiorgan failure	Anakinra 12 mg/kg/day
ICANS	Confusion	Supportive care
	Aphasia	Dexamethasone 10 mg IV/6 h or methylprednisolone 1 g/day for 3 days
	Deterioration of handwriting and tremor	Levetiracetam
	Seizures	
	Cerebral oedema	
IEC-HS	Fever	As per severe CRS
	Hepatomegaly	
	Cytopenia >2 lineages	
	Hypertriglyceridemia	
	Hemophagocytosis	
	Hypofibrinogenaemia	
	Hepatitis	
ICAHT	Early ICAHT (day 0–30)	Antimicrobial prophylaxis
	ANC <500/μL	Transfusion support
	Late ICAHT (after day +30)	G-CSF
	ANC <1,500/μL	Eltrombopag
		CD34 stem cell boost
Hypogammaglobulinemia and B-cell aplasia	Immunoglobulin G <400 mg/dL Recurrent infections	IVIg 0.4 g/kg bodyweight every 3–6 weeks

Abbreviations: ANC = absolute neutrophil count, CRS=cytokine release syndrome, G-CSF = granulocyte colony-stimulating factor, ICANS = immune effector cell-associated neurotoxicity syndrome, IEC-HS = immune effector cell-associated hemophagocytic lymphohistiocytosis-like syndrome, ICAHT = immune effector cell-associated hematotoxicity, IV = intravenous, IVIg = intravenous immunoglobulin.

and/or its severity as initially described.[56] Immune effector cell-associated hematotoxicity results in prolonged cytopenia, and its treatment is based on supportive treatment with granulocyte colony-stimulating factor, eltrombopag (thrombopoietin receptor agonist), and transfusion support, although CD34 stem cell boost (from previously stored autologous stem cells) or allogeneic stem cell transplant has been required in exceptional cases.[57] Hypogammaglobulinemia is commonly seen after CAR-T, and prophylaxis with intravenous immunoglobulin is advised to reduce the risk of recurrent infections.

A recent, but concerning, toxicity risk is the possibility of secondary malignancies after CAR-T-cell therapy. A total of 20 reports of T-cell malignancies have been reported for >34,400 patients that have been treated with these therapies.[59–62] The US Food and Drug Administration has determined that the risk of T-cell lymphoma is applicable to all currently approved BCMA-directed and CD19-directed genetically modified autologous CAR-T-cell immunotherapies. Genetic sequencing was performed for 4 cases with the CAR transgene identified in the malignant clone. However, the current recommendation of the US

and European transplant societies, and other experts' opinion is that the benefits of CAR-T therapies continue to outweigh the potential risk of having a secondary CAR-positive lymphoma.

CAR-T Therapy in Non-Neurological Immune-Mediated Disease

The ability of CAR-T cells to selectively target antigens and to simultaneously boost cell activation is an attractive therapeutic potential within a broad spectrum of autoimmune diseases.[37] In 2022, remission (absence of disease activity and freedom from immunosuppressive medication), was reported in 5 refractory systemic lupus erythematosus patients 3 months after treatment with autologous CD19 CAR-conventional T cells, delivered with fludarabine and cyclophosphamide conditioning, despite the reconstitution of B cells and the disappearance of the CAR-T cells.[63] Clinical (lower Systemic Lupus Erythematosus Disease Activity Index [SLEDAI], 2000 scores and reduction in proteinuria) and serological (disappearance of dsDNA antibodies) improvements were also seen. Treatment was safe, with mild cytokine-release syndrome, in the form of fever, the only adverse event over a median follow-up of 8 months. Antibody titers against viral and bacterial pathogens commonly vaccinated against were sustained despite CAR-T therapy,[64] indicating the sparing of immunoglobulin-producing cells, an advantage over nonselective ablative approaches, such as aHSCT. Immunophenotyping of reconstituted cells showed memory B cells were naïve, B-cell receptors were nonclass switched, $CD38^{+}CD20^{-}$ plasmablasts were suppressed, and there was an absence of pathogenic $CD11c^{+}CD21^{lo}$ activated memory B cells. Mackensen et al. theorized that this 'deep depletion' of B cells, which has previously been demonstrated among patients treated for B-cell malignancies, including the suppression of plasmablasts, is crucial to the response seen in systemic lupus erythematosus patients who had previously failed anti-CD20 therapy. Since then, an additional 15 patients with systemic lupus erythematosus have been reported as receiving CD19 CAR-T therapy,[65] and several early-phase studies are ongoing.

A single patient with refractory antisynthetase syndrome with widespread clinical manifestations and a high level of disability has been reported to have responded dramatically to CD19 CAR-T therapy, with improvements continuing beyond the reconstitution of B cells.[66] A transient increase in myositis occurred post-treatment, but after 6 months of follow-up, serological parameters (creatinine kinase previously >6,000 U/L and anti-Jo-1 antibodies previously >300 U/mL) became undetectable, longstanding myositis on magnetic resonance imaging recovered, and oxygen-dependent interstitial lung disease fully regressed. Grade 1 CRS and a worsening of pre-existing hypogammaglobulinemia, to a level requiring intravenous immunoglobulin replacement, were the only adverse effects.

Successful treatment of a single patient with severe, treatment refractory systemic sclerosis with CD19 CAR-T cells has been reported.[67] Previously treated with methotrexate and mycophenolate (cyclophosphamide not used due to cardiac involvement), the CAR-T-cell therapy was well tolerated. The patient had CRS grade 1, no signs of ICANS, and no anti-interleukin-6 receptor treatment was needed. Serological (ANA reactivity and RP11 autoantibodies normalized) and clinical (right ventricular function, carpal arthritis, skin fibrosis, and Raynaud's phenomenon) improvements occurred while other parameters, including left ventricular function and pulmonary fibrosis, as seen on computed tomography imaging of the thorax, remained stable.

CAR-T Therapy in Neurological Immune-Mediated Disease. The consideration for use of CAR-T therapy in the treatment of neurological immune-mediated conditions, specifically MS, is not new.[68] Compared with the use of monoclonal antibodies, CAR-T treatment has the theoretical advantage of a broader depletion of autoreactive B cells, especially those maintained within inflamed tissues, such as the central nervous system, and access to lymphoid organs, such as deep lymph nodes and the spleen.[37] This approach may result in the removal of 'difficult to target' pathogenic B cells and plasmablasts. This is highly relevant for patients with MS, given what is known about the underlying disease mechanism and the role of Epstein–Barr virus infection and persisting autoreactive B cells, a target for which refractory Epstein–Barr virus-related lymphomas are successfully treated with CAR-T cells.[69–72]

Preclinical trials in neurological disorders, in the experimental autoimmune encephalomyelitis (EAE) animal model of MS, and mice models of MuSK MG and anti-N-methyl-D-aspartate receptor encephalitis, have targeted specific antibodies rather than entire populations of cells expressing CD19 or BCMA with sustained treatment effects seen.[73–76] CAR-T therapy targeting myelin basic protein and myelin oligodendrocyte glycoprotein (in EAE) and MuSK IgG (in MuSK MG) led to sustained treatment effect. Fransson et al. demonstrated the creation of an immunotolerant environment post-treatment when symptom-free mice were rechallenged with EAE induction.[74] Targeting MuSK had a similar efficacy to CD19 CAR-T therapy, but resulted in specific MuSK B-cell depletion without reducing total B cells or IgG levels, and with a freedom from off-target effects.[75] Gupta et al. used anti-CD19 CAR-T cells in mice models, showing improvement in clinical scores and lymphocyte infiltration in the tissue, contrasting with previous data that showed exacerbation of EAE after anti-CD19 CAR-T cells.[77]

Several international trials of CAR-T therapy in immune-mediated neurological disorders in humans are ongoing (Table 3).

Interim results from 12 refractory NMOSD patients treated with autologous BCMA CAR-T therapy (NCT04561557) showed an improvement in the clinical examination score of all patients, whereas 11 of 12 remained in remission (absence of relapses free and freedom from immunosuppression), at a median follow-up of 5.5 months.[55] AQP4-IgG antibody reversal was seen in 70% of the patients. A patient whose AQP4-IgG level increased after an initial decrease was the only patient to relapse, at 14 months. Improvements were seen in clinical examination, visual function, bowel and bladder function, quality of life, and ambulation. A dose escalation approach was used, 3 patients receiving half dose, with cyclophosphamide and fludarabine lymphodepletion. CAR-T-cell expansion occurred maximally by 10 days, and persistence reduced over follow-up with detection at 6 months seen in 1 of 6 patients, whereas BCMA levels were significantly reduced at 1 month, but returned to baseline by month 6. The single patient who relapsed received the lower dose of CAR-T cells, and at the time of relapse, was found to have low CAR-T cells and an increased AQP4-IgG level. All patients experienced expected hematological toxicity (anemia and leukopenia) and grade 1 or 2 CRS, whereas 7 of 12 patients developed an infection, and a minority developed transient gastrointestinal disturbance.

Granit et al. presented the first study using rCAR-T therapy in individuals with MG using RNA to improve

TABLE 3. Trials in Immune-Mediated Neurological Disorders According to clinicaltrials.gov, as of February 26, 2024

National Clinical Trial number (and location)	Construct	Disease(s)	Phase	Recruitment target	Status
NCT03605238 (Beijing, China)	CD19 and CD20 tandem	Refractory AQA4+ NMOSD	1	-	Withdrawn due to recruitment difficulties (2019)
NCT04146051[34] (Multi site, US)	BCMA (RNA)	Refractory MG (including seronegative)	2	30	Recruiting since 12/2019
NCT04561557[55] (Wuhan, China)	BCMA	Refractory AQA4+ NMOSD, MG, CIDP, IMNM	1	18	Recruiting since 09/2020
NCT05451212 (Philadelphia, US)	MuSK CAR-T	MuSK MG	1	24	Recruiting since 11/2022
NCT05828225 (Zhejiang, China)	CD19	Refractory AChR MG	1	9	Recruiting since 04/2023
NCT05828212 (Zhejiang, China)	CD19	Refractory AQA4+ NMOSD	1	9	Recruiting since 04/2023
NCT06220201 (Multi site, US)	CD19	MS (relapsing or progressive)	1	98	Recruiting since 02/2024
NCT06138132 (Multi site, US)	CD19	Non relapsing, progressive MS (secondary or primary progressive MS)	1	12	Not yet open
NCT06249438 (Shanghai, China)	CD20 and BCMA tandem	Relapsing remitting MS, NMOSD, IMNM	1	30	Not yet open
NCT06193889 (Not listed)	CD19	MuSK or AChR refractory MG	2	20	Not yet open

Abbreviations: AChR = acetylcholine receptor antibodies, AQA4+ = aquaporin-4-positive, CIDP = chronic inflammatory demyelinating polyradiculopathy, IMNM = immune-mediated necrotizing myopathy, MG = myasthenia gravis, MS = multiple sclerosis, MuSK = muscle-specific tyrosine kinase.

the safety profile of the CAR-T.[34] They theorized that the temporary, nonreplicable influence of mRNA would confer predictable pharmacokinetics and, consequently, a more favorable safety profile, with no requirement for lymphodepleting conditioning, versus the standard DNA approach. The trial (NCT04146051) is a prospective, multicenter, open-label, phase 1b/2a study of Descartes-08, an autologous anti-BCMA rCAR-T therapy. A dose escalation protocol followed (3 patients received 3 doses, 11 were planned to receive 6 doses). Interim results include 16 adult patients with generalized treatment refractory MG and a Myasthenia Gravis Activities of Daily Living score of ≥6. Almost all the patients (13/14) were seropositive (11/14 acetylcholine receptor antibody-positive, 2/14 anti-MuSK antibody-positive). Treatment was completed as planned in 12 patients, and was safe and well tolerated, showing clinically meaningful decreases on Myasthenia Gravis Severity Scales after up to 9 months of follow-up. Although antibody reversal was not demonstrated, there were reductions in acetylcholine receptor antibody, but not MuSK titers. rCAR-T was shown in peripheral blood for 1–2 hours post-infusion, but not at later timepoints. There was no dose-limiting toxicity, CRS, or neurotoxicity, with withdrawals cited as due to 1 patient experiencing urticaria requiring intravenous steroids (in the dose escalation group), which was felt to be related to rCAR-T therapy, and 1 withdrawal due to personal reasons.

Haghika et al. highlighted the utility of testing different CAR-T-cell constructs in the same condition by treating a single patient with refractory MG with a CD19 approach.[78] Self-resolving transaminitis was the only adverse event during the short follow-up time (62 days) reported, and clinical improvements in the Besinger disease activity and the Quantitative Myasthenia Gravis scores have been seen. Immunosuppression, in the form of prednisolone 10 mg, had been continued at the point of reporting, with an intent to withdraw this at follow up.

Two patients with secondary and primary progressive MS have been treated with a single dose of an autologous CD19 CAR-T.[79] Both patients had experienced progression while taking ocrelizumab, and had Expanded Disability Status Scale scores (EDSS) of 4.5 and 6.5, respectively, indicating moderate or severe disability and, following a 4-month washout, were treated with fludarabine and cyclophosphamide conditioning followed by the CAR-T infusion. Expansion of CAR-T cells was seen in the blood and cerebrospinal fluid post treatment. The first patient, who had secondary progressive MS with a disease duration of 23 years, experienced CRS grade 1, requiring multiple doses of tocilizumab and steroids, and a transient increase in transaminases. At the time of CRS, a temporary worsening of disability (EDSS increased to 6), which was felt to be due to a rise in body temperature and resultant Uhthoff's phenomenon, was reported. Although the EDSS score returned to baseline, 2 months after treatment a new spinal cord lesion was identified on magnetic resonance imaging. Intrathecal production of immunoglobulins (oligoclonal bands) was reduced at follow-up.

The second patient, who had primary progressive MS with a disease duration of 4 years, experienced a transient increase in transaminases only during the 28 days of follow-up. Their EDSS remained stable, and no reduction in intrathecal production of immunoglobulins was observed. Fischbach et al. theorized that the ability of CAR-T cells to enter the central nervous system may eliminate the cells responsible for progression independent of relapse activity in MS. A number of phase 1/2 CAR-T trials in relapsing and progressive MS, targeting CD19 cells, are in an early phase (included within Table 3).[80]

To clarify the role of CAR-T-cell treatment in immune-mediated neurological disease, more clinical trials with longer follow-up are needed to identify which patient populations can be treated effectively and safely. Recently, a broad set of guidelines has been published by the EBMT to guide patient selection moving forward in the field of innovative cellular therapies and CAR-T.[81] Even so, these initial experiences in neurological and other immune-mediated conditions open an interesting and promising field for ongoing investigation, with an evolving range of CAR-T-cell constructs and products.

Conclusion

A cure for immune-mediated neurological diseases has long been a goal. The use of aHSCT in these disorders has already been demonstrated to be highly successful, particularly for RRMS patients. The efficacious use of CD20 B-cell depleting therapies demonstrates that autoreactive B cells are a successful target for such conditions. The use of CAR-T therapy, particularly a B-cell directed construct, such as CD19, which is shared on almost all B cells, represents a promising approach that has the potential to selectively target and modify a defective immune system; confer long-term, potentially permanent, remission; and eliminate the need for ongoing immunosuppression. Such a response may ultimately have not only favorable long-term clinical impacts, but also health economic and societal benefits. Long-term follow-up from clinical trials and registry data are needed to establish the value of this new strategy in neurological immune-mediated diseases.

Author Contributions

All authors contributed to the conception and design of the article. G.B. and E.R. jointly performed the initial

literature search. and created the first draft and figures, which all authors refined. B.S. and R.G. provided joint senior authorship.

Acknowledgments

We are grateful for the support by EBMT and ADWP, without which this work would not have been possible. The authors thank Manuela Badoglio and Myriam Labopin in the EBMT Paris Office, EBMT centers for their contributions to the EBMT registry, and those active in the ADWP. This work is dedicated to the memory, life, and work of Riccardo Saccardi MD.

Figures created in Biorender.

Potential Conflicts of Interest

Nothing to report.

References

1. Bhagavati S. Autoimmune disorders of the nervous system: pathophysiology, clinical features, and therapy. Front Neurol 2021;12. https://doi.org/10.3389/fneur.2021.664664.
2. Sabatino JJ, Pröbstel A-K, Zamvil SS. B cells in autoimmune and neurodegenerative central nervous system diseases. Nat Rev Neurosci 2019;20:728–745. https://doi.org/10.1038/s41583-019-0233-2.
3. Cohen JA, Coles AJ, Arnold DL, et al. Alemtuzumab versus interferon beta 1a as first-line treatment for patients with relapsing-remitting multiple sclerosis: a randomised controlled phase 3 trial. Lancet 2012;380:1819–1828. https://doi.org/10.1016/s0140-6736(12)61769-3.
4. Hauser SL, Bar-Or A, Comi G, et al. Ocrelizumab versus interferon Beta-1a in relapsing multiple sclerosis. N Engl J Med 2017;376:221–234. https://doi.org/10.1056/NEJMoa1601277.
5. Hauser SL, Bar-Or A, Cohen JA, et al. Ofatumumab versus Teriflunomide in Multiple Sclerosis. N Engl J Med 2020;383:546–557. https://doi.org/10.1056/NEJMoa1917246.
6. Polman CH, O'Connor PW, Havrdova E, et al. Placebo-controlled trial of Natalizumab for relapsing multiple sclerosis. N Engl J Med 2006;354:899–910. https://doi.org/10.1056/NEJMoa044397.
7. Tahara M, Oeda T, Okada K, et al. Safety and efficacy of rituximab in neuromyelitis optica spectrum disorders (RIN-1 study): a multicentre, randomised, double-blind, placebo-controlled trial. Lancet Neurol 2020;19:298–306. https://doi.org/10.1016/S1474-4422(20)30066-1.
8. Yamamura T, Kleiter I, Fujihara K, et al. Trial of Satralizumab in Neuromyelitis Optica Spectrum disorder. N Engl J Med 2019;381:2114–2124. https://doi.org/10.1056/NEJMoa1901747.
9. Cree BAC, Bennett JL, Kim HJ, et al. Inebilizumab for the treatment of neuromyelitis optica spectrum disorder (N-MOmentum): a double-blind, randomised placebo-controlled phase 2/3 trial. Lancet 2019;394:1352–1363. https://doi.org/10.1016/S0140-6736(19)31817-3.
10. Pittock SJ, Berthele A, Fujihara K, et al. Eculizumab in Aquaporin-4–positive Neuromyelitis Optica Spectrum disorder. N Engl J Med 2019;381:614–625. https://doi.org/10.1056/NEJMoa1900866.
11. Montalban PX. *Update of the ECTRIMS/EAN guidelines on the treatment of multiple sclerosis*. ECTRIMS, 2021.
12. Sefia E, Pryce G, Meier U-C, et al. Depletion of CD20 B cells fails to inhibit relapsing mouse experimental autoimmune encephalomyelitis. Mult Scler Relat Disord 2017;14:46–50. https://doi.org/10.1016/j.msard.2017.03.013.
13. Alexander T, Greco R. Hematopoietic stem cell transplantation and cellular therapies for autoimmune diseases: overview and future considerations from the autoimmune diseases working party (ADWP) of the European Society for Blood and Marrow Transplantation (EBMT). Bone Marrow Transplant 2022;57:1055–1062. https://doi.org/10.1038/s41409-022-01702-w.
14. Sharrack B et al. Autologous haematopoietic stem cell transplantation and other cellular therapy in multiple sclerosis and immune-mediated neurological diseases: updated guidelines and recommendations from the EBMT autoimmune diseases working party (ADWP) and the joint accreditation committee of EBMT and ISCT (JACIE). Bone Marrow Transplant 2020;55:283–306. https://doi.org/10.1038/s41409-019-0684-0.
15. Brittain G et al. Autologous haematopoietic stem cell transplantation for immune-mediated neurological diseases: what, how, who and why? Pract Neurol 2022;23:139–145. https://doi.org/10.1136/pn-2022-003531.
16. Burt RK, Balabanov R, Burman J, et al. Effect of Nonmyeloablative hematopoietic stem cell transplantation vs continued disease-modifying therapy on disease progression in patients with relapsing-remitting multiple sclerosis: a Randomized clinical trial. JAMA 2019;321:165–174. https://doi.org/10.1001/jama.2018.18743.
17. Burt RK, Han X, Quigley K, et al. Real-world application of autologous hematopoietic stem cell transplantation in 507 patients with multiple sclerosis. J Neurol 2022;269:2513–2526. https://doi.org/10.1007/s00415-021-10820-2.
18. Silfverberg T, Zjukovskaja C, Ljungman P, et al. Haematopoietic stem cell transplantation for treatment of relapsing-remitting multiple sclerosis in Sweden: an observational cohort study. J Neurol Neurosurg Psychiatry 2024;95:125–133. https://doi.org/10.1136/jnnp-2023-331864.
19. Muraro PA, Martin R, Mancardi GL, et al. Autologous haematopoietic stem cell transplantation for treatment of multiple sclerosis. Nat Rev Neurol 2017;13:391–405. https://doi.org/10.1038/nrneurol.2017.81.
20. Snowden JA, Badoglio M, Labopin M, et al. Evolution, trends, outcomes, and economics of hematopoietic stem cell transplantation in severe autoimmune diseases. Blood Adv 2017;1:2742–2755. https://doi.org/10.1182/bloodadvances.2017010041.
21. June CH, Sadelain M. Chimeric antigen receptor therapy. N Engl J Med 2018;379:64–73. https://doi.org/10.1056/NEJMra1706169.
22. Milone MC, Xu J, Chen SJ, et al. Engineering-enhanced CAR T cells for improved cancer therapy. Nat Cancer 2021;2:780–793. https://doi.org/10.1038/s43018-021-00241-5.
23. Kalos M et al. T cells with chimeric antigen receptors have potent antitumor effects and can establish memory in patients with advanced leukemia. Sci Transl Med 2011;3:95ra73. https://doi.org/10.1126/scitranslmed.3002842.
24. Sadelain M, Riviere I, Riddell S. Therapeutic T cell engineering. Nature 2017;545:423–431. https://doi.org/10.1038/nature22395.
25. European Medicines Agency. Medicines, https://www.ema.europa.eu/en/medicines 2023.
26. U.S. Food & Drug Administration. Approved cellular and gene therapy products, https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/approved-cellular-and-gene-therapy-products 2022.
27. Medicines and Healthcare products Regulatory Agency. Orphan registered medicinal products, https://www.gov.uk/government/publications/orphan-registered-medicinal-products 2023.
28. Lickefett B, Chu L, Ortiz-Maldonado V, et al. Lymphodepletion - an essential but undervalued part of the chimeric antigen receptor T-cell therapy cycle. Front Immunol 2023;14:1303935. https://doi.org/10.3389/fimmu.2023.1303935.
29. Martínez Bedoya D, Dutoit V, Migliorini D, Allogeneic CART. Cells: an alternative to overcome challenges of CAR T cell therapy in glioblastoma. Front Immunol 2021;12:640082. https://doi.org/10.3389/fimmu.2021.640082.

30. Depil S, Duchateau P, Grupp SA, et al. 'Off-the-shelf' allogeneic CAR T cells: development and challenges. Nat Rev Drug Discovery 2020;19:185–199. https://doi.org/10.1038/s41573-019-0051-2.

31. Wang D, Quan Y, Yan Q, et al. Targeted disruption of the β2-microglobulin gene minimizes the immunogenicity of human embryonic stem cells. Stem Cells Transl Med 2015;4:1234–1245. https://doi.org/10.5966/sctm.2015-0049.

32. Ren J, Liu X, Fang C, et al. Multiplex genome editing to generate universal CAR T cells resistant to PD1 inhibition. Clin Cancer Res 2017;23: 2255–2266. https://doi.org/10.1158/1078-0432.Ccr-16-1300.

33. Zhang L, Meng Y, Feng X, Han Z. CAR-NK cells for cancer immunotherapy: from bench to bedside. Biomarker Res 2022;10:12. https://doi.org/10.1186/s40364-022-00364-6.

34. Granit V, Benatar M, Kurtoglu M, et al. Safety and clinical activity of autologous RNA chimeric antigen receptor T-cell therapy in myasthenia gravis (MG-001): a prospective, multicentre, open-label, non-randomised phase 1b/2a study. Lancet Neurol 2023;22:578–590. https://doi.org/10.1016/S1474-4422(23)00194-1.

35. Xie B, Li Z, Zhou J, Wang W. Current status and perspectives of dual-targeting chimeric antigen receptor T-cell therapy for the treatment of hematological malignancies. Cancers 2022;14:3230. https://doi.org/10.3390/cancers14133230.

36. Ruffo E, Butchy AA, Tivon Y, et al. Post-translational covalent assembly of CAR and synNotch receptors for programmable antigen targeting. Nat Commun 2023;14:2463. https://doi.org/10.1038/s41467-023-37863-5.

37. Doglio M, Alexander T, Del Papa N, et al. New insights in systemic lupus erythematosus: from regulatory T cells to CAR-T-cell strategies. J Allergy Clin Immunol 2022;150:1289–1301. https://doi.org/10.1016/j.jaci.2022.08.003.

38. Doglio M, Ugolini A, Bercher-Brayer C, et al. Regulatory T cells expressing CD19-targeted chimeric antigen receptor restore homeostasis in systemic lupus erythematosus. Nat Commun 2024;15:2542. https://doi.org/10.1038/s41467-024-46448-9.

39. Shimabukuro-Vornhagen A, Gödel P, Subklewe M, et al. Cytokine release syndrome. J Immunother Cancer 2018;6:56. https://doi.org/10.1186/s40425-018-0343-9.

40. Garcia Borrega J, Gödel P, Rüger MA, et al. In the eye of the storm: immune-mediated toxicities associated with CAR-T cell therapy. Hema 2019;3:e191. https://doi.org/10.1097/hs9.0000000000000191.

41. Neelapu SS, Tummala S, Kebriaei P, et al. Chimeric antigen receptor T-cell therapy — assessment and management of toxicities. Nat Rev Clin Oncol 2018;15:47–62. https://doi.org/10.1038/nrclinonc.2017.148.

42. Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene Ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. N Engl J Med 2017; 377:2531–2544. https://doi.org/10.1056/NEJMoa1707447.

43. Schuster SJ, Bishop MR, Tam CS, et al. Tisagenlecleucel in adult relapsed or refractory diffuse large B-cell lymphoma. N Engl J Med 2019;380:45–56. https://doi.org/10.1056/NEJMoa1804980.

44. Abramson JS, Palomba ML, Gordon LI, et al. Lisocabtagene maraleucel for patients with relapsed or refractory large B-cell lymphomas (TRANSCEND NHL 001): a multicentre seamless design study. Lancet 2020;396:839–852. https://doi.org/10.1016/s0140-6736(20)31366-0.

45. Hayden PJ, Roddie C, Bader P, et al. Management of adults and children receiving CAR T-cell therapy: 2021 best practice recommendations of the European Society for Blood and Marrow Transplantation (EBMT) and the joint accreditation committee of ISCT and EBMT (JACIE) and the European Haematology association (EHA). Ann Oncol 2022;33:259–275. https://doi.org/10.1016/j.annonc.2021.12.003.

46. Yáñez L, Alarcón A, Sánchez-Escamilla M, Perales MA. How I treat adverse effects of CAR-T cell therapy. ESMO Open 2020;4:e000746. https://doi.org/10.1136/esmoopen-2020-000746.

47. Gazeau N, Liang EC, Wu Q"V", et al. Anakinra for refractory cytokine release syndrome or immune effector cell-associated neurotoxicity syndrome after chimeric antigen receptor T cell therapy. Transplant Cell Ther 2023;29:430–437. https://doi.org/10.1016/j.jtct.2023.04.001.

48. Lakomy T, Akhoundova D, Nilius H, et al. Early use of corticosteroids following CAR T-cell therapy correlates with reduced risk of high-grade CRS without negative impact on neurotoxicity or treatment outcome. Biomolecules 2023;13:382.

49. Tallantyre EC, Evans NA, Parry-Jones J, et al. Neurological updates: neurological complications of CAR-T therapy. J Neurol 2021;268: 1544–1554. https://doi.org/10.1007/s00415-020-10237-3.

50. Mahdi J, Dietrich J, Straathof K, et al. Tumor inflammation-associated neurotoxicity. Nat Med 2023;29:803–810. https://doi.org/10.1038/s41591-023-02276-w.

51. Gatto L et al. CAR-T cells neurotoxicity from consolidated practice in hematological malignancies to fledgling experience in CNS tumors: fill the gap. Front Oncol 2023;13. https://doi.org/10.3389/fonc.2023.1206983.

52. Berdeja JG, Madduri D, Usmani SZ, et al. Ciltacabtagene autoleucel, a B-cell maturation antigen-directed chimeric antigen receptor T-cell therapy in patients with relapsed or refractory multiple myeloma (CARTITUDE-1): a phase 1b/2 open-label study. Lancet 2021;398: 314–324. https://doi.org/10.1016/S0140-6736(21)00933-8.

53. Mohyuddin GR, Banerjee R, Alam Z, et al. Rethinking mechanisms of neurotoxicity with BCMA directed therapy. Crit Rev Oncol Hematol 2021;166:103453. https://doi.org/10.1016/j.critrevonc.2021.103453.

54. Osório C, Chacón PJ, White M, et al. Selective regulation of axonal growth from developing hippocampal neurons by tumor necrosis factor superfamily member APRIL. Mol Cell Neurosci 2014;59:24–36. https://doi.org/10.1016/j.mcn.2014.01.002.

55. Qin C, Tian DS, Zhou LQ, et al. Anti-BCMA CAR T-cell therapy CT103A in relapsed or refractory AQP4-IgG seropositive neuromyelitis optica spectrum disorders: phase 1 trial interim results. Signal Transduct Target Ther 2023;8:5. https://doi.org/10.1038/s41392-022-01278-3.

56. Hines MR et al. Immune effector cell-associated Hemophagocytic Lymphohistiocytosis-like syndrome. Transpl Cell Ther 2023;29:e431–e438. https://doi.org/10.1016/j.jtct.2023.03.006.

57. Rejeski K et al. Immune effector cell-associated Hematotoxicity (ICAHT): EHA/EBMT consensus grading and best practice recommendations. Blood J 2023;142:865–877. https://doi.org/10.1182/blood.2023020578.

58. Lichtenstein DA, Schischlik F, Shao L, et al. Characterization of HLH-like manifestations as a CRS variant in patients receiving CD22 CAR T cells. Blood 2021;138:2469–2484. https://doi.org/10.1182/blood.2021011898.

59. Levine BL, Pasquini MC, Connolly JE, et al. Unanswered questions following reports of secondary malignancies after CAR-T cell therapy. Nat Med 2024;30:338–341. https://doi.org/10.1038/s41591-023-02767-w.

60. Elsallab M, Ellithi M, Lunning MA, et al. Second primary malignancies after commercial CAR T cell therapy: analysis of FDA adverse events reporting system (FAERS). Blood 2024;143:2099–2105. https://doi.org/10.1182/blood.2024024166.

61. Verdun N, Marks P. Secondary cancers after chimeric antigen receptor T-cell therapy. N Engl J Med 2024;390:584–586. https://doi.org/10.1056/NEJMp2400209.

62. Harrison SJ, Nguyen T, Rahman M, et al. CAR+ T-cell lymphoma post Ciltacabtagene Autoleucel therapy for relapsed refractory multiple myeloma. Blood 2023;142:6939. https://doi.org/10.1182/blood-2023-178806.

63. Mackensen A, Müller F, Mougiakakos D, et al. Anti-CD19 CAR T cell therapy for refractory systemic lupus erythematosus. Nat Med 2022; 28:2124–2132. https://doi.org/10.1038/s41591-022-02017-5.

64. Nunez D et al. Cytokine and reactivity profiles in SLE patients following anti-CD19 CART therapy. Mol Ther-Methods Clin Dev 2023;31. https://doi.org/10.1016/j.omtm.2023.08.023.

65. Müller F, Taubmann J, Bucci L, et al. CD19 CAR T-cell therapy in autoimmune disease—a case series with follow-up. N Engl J Med 2024;390:687–700. https://doi.org/10.1056/NEJMoa2308917.

66. Müller F, Boeltz S, Knitza J, et al. CD19-targeted CAR T cells in refractory antisynthetase syndrome. Lancet 2023;401:815–818. https://doi.org/10.1016/S0140-6736(23)00023-5.

67. Bergmann C, Müller F, Distler JHW, et al. Treatment of a patient with severe systemic sclerosis (SSc) using CD19-targeted CAR T cells. Ann Rheum Dis 2023;82:1117–1120. https://doi.org/10.1136/ard-2023-223952.

68. Baker D, Jacobs BM, Gnanapavan S, et al. Plasma cell and B cell-targeted treatments for use in advanced multiple sclerosis. Mult Scler Relat Disord 2019;35:19–25. https://doi.org/10.1016/j.msard.2019.06.030.

69. Giovannoni G, Hawkes CH, Lechner-Scott J, et al. Are we ready for CD19-targeted CAR T-cell therapies in MS? Mult Scler Relat Disord 2023;70:104590. https://doi.org/10.1016/j.msard.2023.104590.

70. Giovannoni G, Hawkes CH, Lechner-Scott J, et al. Is EBV the cause of multiple sclerosis? Mult Scler Relat Disord 2022;58:103636. https://doi.org/10.1016/j.msard.2022.103636.

71. Nair R, Ayers A, Nastoupil LJ, et al. CD19 CAR-T outcomes in patients with EBV-positive DLBCL. Blood 2022;140:3800–3802. https://doi.org/10.1182/blood-2022-171120.

72. Smith C, Khanna R. Adoptive T-cell therapy targeting Epstein-Barr virus as a treatment for multiple sclerosis. Clin Transl Immunol 2023;12:e1444. https://doi.org/10.1002/cti2.1444.

73. De Paula Pohl A, Schmidt A, Zhang A-H, et al. Engineered regulatory T cells expressing myelin-specific chimeric antigen receptors suppress EAE progression. Cell Immunol 2020;358:104222. https://doi.org/10.1016/j.cellimm.2020.104222.

74. Fransson M, Piras E, Burman J, et al. CAR/FoxP3-engineered T regulatory cells target the CNS and suppress EAE upon intranasal delivery. J Neuroinflammation 2012;9:112. https://doi.org/10.1186/1742-2094-9-112.

75. Oh S, Mao X, Manfredo-Vieira S, et al. Precision targeting of autoantigen-specific B cells in muscle-specific tyrosine kinase myasthenia gravis with chimeric autoantibody receptor T cells. Nat Biotechnol 2023;41:1229–1238. https://doi.org/10.1038/s41587-022-01637-z.

76. Reincke SM et al. Chimeric autoantibody receptor T cells deplete NMDA receptor-specific B cells. Cell 2023;186:5084–5097. https://doi.org/10.1016/j.cell.2023.10.001.

77. Gupta S et al. CAR-T cell–mediated B-cell depletion in central nervous system autoimmunity. Neurology 2023;10:e200080. https://doi.org/10.1212/NXI.0000000000200080.

78. Haghikia A et al. Anti-CD19 CAR T cells for refractory myasthenia gravis. Lancet Neurol 2023;22:1104–1105. https://doi.org/10.1016/S1474-4422(23)00375-7.

79. Fischbach F, Richter J, Pfeffer LK, et al. CD19-targeted chimeric antigen receptor T cell therapy in two patients with multiple sclerosis. Med 2024;5:550–558.e2. https://doi.org/10.1016/j.medj.2024.03.002.

80. Mullard A. CAR-T therapy for multiple sclerosis enters US trials for first time. Nature 2024. https://doi.org/10.1038/d41586-024-00470-5.

81. Greco R, Alexander T, del Papa N, et al. Innovative cellular therapies for autoimmune diseases: expert-based position statement and clinical practice recommendations from the EBMT practice harmonization and guidelines committee. EClinicalMedicine 2024;69:102476. https://doi.org/10.1016/j.eclinm.2024.102476.