

Department of Neurology Faculty Papers

Department of Neurology

1-2-2023

Repurposing MS Immunotherapies for CIDP and Other Autoimmune Neuropathies: Unfulfilled Promise or Efficient Strategy?

Felix Kohle University of Cologne and University Hospital Cologne

Marinos Dalakas Thomas Jefferson University

Helmar C Lehmann University of Cologne and University Hospital Cologne

Follow this and additional works at: https://jdc.jefferson.edu/neurologyfp

Part of the Neurology Commons
<u>Let us know how access to this document benefits you</u>

Recommended Citation

Kohle, Felix; Dalakas, Marinos; and Lehmann, Helmar C, "Repurposing MS Immunotherapies for CIDP and Other Autoimmune Neuropathies: Unfulfilled Promise or Efficient Strategy?" (2023). *Department of Neurology Faculty Papers*. Paper 309. https://jdc.jefferson.edu/neurologyfp/309

This Article is brought to you for free and open access by the Jefferson Digital Commons. The Jefferson Digital Commons is a service of Thomas Jefferson University's Center for Teaching and Learning (CTL). The Commons is a showcase for Jefferson books and journals, peer-reviewed scholarly publications, unique historical collections from the University archives, and teaching tools. The Jefferson Digital Commons allows researchers and interested readers anywhere in the world to learn about and keep up to date with Jefferson scholarship. This article has been accepted for inclusion in Department of Neurology Faculty Papers by an authorized administrator of the Jefferson Digital Commons. For more information, please contact: JeffersonDigitalCommons@jefferson.edu.

Ther Adv Neurol Disord

2023, Vol. 16: 1-23

17562864221137129

© The Author(s), 2023. Article reuse guidelines: sagepub.com/journalspermissions

Felix Kohle^(D), Marinos C. Dalakas^(D) and Helmar C. Lehmann^(D)

Repurposing MS immunotherapies for

CIDP and other autoimmune neuropathies:

unfulfilled promise or efficient strategy?

Abstract: Despite advances in the treatment of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) and other common autoimmune neuropathies (AN), stillmany patients with these diseases do not respond satisfactorily to the available treatments. Repurposing of disease-modifying therapies (DMTs) from other autoimmune conditions, particularly multiple sclerosis (MS) and neuromyelitis optica spectrum disorders (NMOSD), is a promising strategy that may accelerate the establishment of novel treatment choices for AN. This approach appears attractive due to homologies in the pathogenesis of these diseases and the extensive post-marketing experience that has been gathered from treating MS and NMOSD patients. The idea is also strengthened by a number of studies that explored the efficacy of DMTs in animal models of AN but also in some CIDP patients. We here review the available preclinical and clinical data of approved MS therapeutics in terms of their applicability to AN, especially CIDP. Promising therapeutic approaches appear to be B cell-directed and complement-targeting strategies, such as anti-CD20/anti-CD19 agents, Bruton's tyrosine kinase inhibitors and anti-C5 agents, as they exert their effects in the periphery. This is a major advantage because, in contrast to MS, their action in the periphery is sufficient to exert significant immunomodulation.

Keywords: autoimmune neuropathies, CIDP, demyelinating diseases, drug repurposing, MS, anti complement, NMOSD

Received: 9 July 2022; revised manuscript accepted: 19 October 2022.

Introduction

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is a treatable chronic autoimmune disease of the peripheral nervous system (PNS) and the most common one of the chronic autoimmune neuropathies (AN). The pathogenesis of CIDP involves autoreactive T cells, autoantibodies, complement, activated macrophages mediating demyelination and secondary axonal degeneration (Figure 1). A clinical meaningful response to first-line treatments (immunoglobulin, corticosteroids, plasma exchange) is only seen in 75–80% of CIDP patients.^{1,2} There is consensus that more effective immunotherapies are needed, particularly for non-responders to first-line treatments or with an aggressive disease course that requires chronic immunosuppression with an improved side-effect profile.

CIDP is rare and drugs specifically designed for CIDP are not available, which also applies to a greater extent to other AN such as multifocal motor neuropathy (MMN) and anti-myelin-associated glycoprotein (MAG) neuropathy. Thus, the prevailing strategy for drug development in AN has been to examine drugs already approved for other autoimmune conditions. A particular 'mine' for this repurposing strategy are disease modifying treatments (DMTs), developed and licensed for multiple sclerosis (MS),³ or neuromyelitis optica spectrum disorders (NMOSD). The rationale is that most AN, especially CIDP, share some immunopathological features with MS, such as macrophage-mediated demyelination, and with NMOSD, such as complement activation and autoantibodies, while the availability of animal models shares methodological similarities with both of them (Table 1).4

Correspondence to: Helmar C. Lehmann Department of Neurology, Faculty of Medicine, University of Cologne and University Hospital Cologne, Kerpener Strasse, 62, 50937 Cologne, Germany. helmar.lehmann@ googlemail.com; helmar.lehmann@ukkoeln.de

Felix Kohle

Department of Neurology, Faculty of Medicine, University of Cologne and University Hospital Cologne, Cologne, Germany

Marinos C. Dalakas

Department of Neurology, Thomas Jefferson University, Philadelphia, PA, USA

Neuroimmunology Unit, National and Kapodistrian University of Athens Medical School, Athens, Greece

journals.sagepub.com/home/tan





Figure 1. Pathogenesis of chronic inflammatory demyelinating polyneuropathy (CIDP) and potential targets of disease-modifying treatments (DMTs).

Antigen presentation leads to activation of macrophages, T cells and B cells [inhibited by dimethyl fumarate (DMF)]. Migration of T cells over the blood-nerve barrier (BNB) and further production of chemokines prompt macrophages to the myelin sheath. Demyelination is triggered by T-cell and macrophage-mediated cytotoxicity. Antibodies produced by B cell-derived plasma cells [impaired by anti-CD20 agents, inebilizumab, cladribine and Bruton's tyrosine kinase (BTK) inhibitors] recognize myelin antigens and lead to complement (inhibited by eculizumab) and macrophage activation. Created with BioRender.com.

DMTs for MS and NMOSD as related to AN

Over the past two decades, various DMTs have been approved and licensed for MS and NMOSD. They differ in terms of efficacy (i.e. reduction of relapse rate), mechanism of action, route of administration and potential side effects (Table 2).

Some of these have already been explored in AN, while others have been tested in preclinical models or applied to individual patients or smaller patient cohorts.

Methods: For this narrative review, we reviewed data from trials, reviews and other articles of DMTs approved for MS or NMOSD in terms of clinical mechanism of action, side effects (with a focus on PNS neurotoxicity), and available data derived from neuritis models or from use in patients with chronic autoimmune neuritis from the database PubMed. We further assessed the database for clinical trials of the U.S. National Library of Medicine between July 2021 and September 2022 for any ongoing trials for MS/ NMOSD and AN. Phase I trials were excluded in the review. We excluded classical chemotherapeutics like cyclophosphamide or mitoxantrone due to their declining relevance for MS treatment algorithms and other immunomodulatory therapies like bone-marrow transplantation.

DMTs approved for moderate-active MS

Interferon-beta (*IFN-\beta*). IFN- β is a cytokine secreted by various cells and its immunomodulatory effects are mediated through genetic activation and the Janus Kinases and signal transducer and activator of transcription proteins (JAK-STAT) signalling pathway, which is also involved in CIDP

Animal model	Induction	Clinical course	Histopathology	Disease model
EAN ⁴	Myelin proteins, mostly P0 or P2 Injection of auto- aggressive T-cell lines (AT-EAN)	Monophasic	T-cell activation Antibody production Disruption of the BNB Activation and invasion of macrophages in the nerve Secretion of inflammatory mediators like cytokines Complement activation Demyelination Axonal damage	GBS
SAP ⁴	Breeding of NOD-mice with a knockout of the costimulatory molecule B7-2	Spontaneous Chronic and relapsing	T-cell activation Disruption of the BNB Activation and invasion of macrophages in the nerves Secretion of inflammatory mediators like cytokines Complement activation Demyelination Axonal damage	CIDP
EAE ⁵	CNS myelin antigens, mainly MBP, MOG, PLP AT-EAE	Monophasic to relapsing remitting	T-cell activation Antibody production Disruption of the BBB Activation and invasion of microglia Secretion of inflammatory mediators like cytokines Complement activation Demyelination Axonal damage	RRMS
AQP4-IgG-related models ⁶	EAE + AQP4-IgG AT-EAE	Monophasic to relapsing	Great variations in the models: AQP4 and GFAP loss Complement activation T-cell activation Activation of microglia Sparse to significant demyelination Sparse to extensive axonal damage	AQP4-positive NMOSD

Table 1. Overview of preclinical animal models of MS and NMOSD with their induction and histopathological hallmarks and of their 'counterparts' in the PNS, Guillain–Barré syndrome (GBS) and CIDP.

Abbreviations: AQP4, aquaporin-4; AT, adoptive transfer; BBB, blood-brain barrier; BNB, blood-nerve barrier; CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; CNS, central nervous system; EAE, experimental autoimmune encephalomyelitis; EAN, experimental autoimmune neuritis; GBS, Guillain-Barré syndrome; GFAP, glial fibrillary acidic protein; IgG, immunoglobulin G; MBP, myelin basic protein; MOG, myelin oligodendrocyte glycoprotein; MS, multiple sclerosis; NMOSD, neuromyelitis optica spectrum disorders; NOD, non-obese diabetic; PLP, myelin proteolipid protein; RRMS, relapsing-remitting multiple sclerosis; SAP, spontaneous autoimmune neuritis.

disease activity.^{7–10} This pathway reduces myeloid dendritic cells in the peripheral blood and prevents antigen presentation by antigen-presenting cells (APCs).¹¹ IFN- β further induces regulatory T (T_{reg}) cells and prevents the differentiation of T helper (T_h)17 cells.¹² Direct effects on cluster of differentiation (CD) 80 and CD86 receptor expression on B cells are also observed, which leads to a modulation of their antigen-presenting function to T cells and inducing T_h^2 instead of T_h^{13}

Data in experimental neuritis: One study explored treatment with IFN- α/β protein *before* immunization in experimental autoimmune neuritis (EAN) and found attenuation of disease severity.¹⁴ A second study used IFN- β at start of the immunization and with first clinical signs and described less inflammation in affected nerves.¹⁵

Clinical data: In two randomized clinical trials (RCTs), IFN- β showed no beneficial effects in

THERAPEUTIC ADVANCES in Neurological Disorders

Table 2. Indications, application routes and the principal mode of action of disease-modifying drugs currently used or evaluated in MS or NMOSD.

Drug	Indication	Route of administration	Principal mode of action
β-interferon	RRMS, SPMS	s.c., i.m.	Induction of anti-inflammatory T _h 2 subsets Induction of JAK-STAT pathway Prevention of antigen presentation by APCs
Glatiramer acetate	RRMS	S.C.	Antagonist of MBP in APCs for MHC binding Induction of anti-inflammatory T _h 2 subsets Induction of T _{reg} cells
Dimethyl fumarate/diroximel fumarate	RRMS, SPMS	p.o.	Induction of anti-inflammatory T _h 2 subsets Increased expression of Nrf2 and alteration of oxidative stress response Induction of T _{reg} cells
Teriflunomide/leflunomide	RRMS, SPMS	p.o.	Lymphopenia
Cladribine	RRMS, SPMS	p.o.	Inhibition of pyrimidine biosynthesis, lymphopenia
Functional sphingosine 1-phosphate receptors (S1PR) antagonists (fingolimod, ozanimod, siponimod, ponesimod, amiselimod, ceralifimod)	RRMS, SPMS	p.o.	Impaired lymphocyte trafficking
CD20 antibodies (ofatumumab, rituximab, ublituximab and ocrelizumab)	RRMS, SPMS, PPMS, NMOSD	i.v., s.c.	Depletion of CD20 ⁺ (B) cells
CD19 antibody (inebilizumab)	NMOSD	i.v.	Depletion of CD19 ⁺ (B) cells
Natalizumab	RRMS, SPMS	i.v.	Inhibition of lymphocyte migration into the CNS
Tyrosine kinase inhibitors (tolebrutinib, evobrutinib, remibrutinib, zanubrutinib, orelabrutinib)	RRMS, PPMS, SPMS, NMOSD	p.o.	Inhibition of B-cell maturation
Laquinimod	/	p.o.	Activation of the aryl hydrocarbon-receptor pathway
IL-6-receptor antagonists (satralizumab and tocilizumab)	NMOSD	i.v., s.c.	Inhibition of binding of IL-6 to its receptor
Complement-5 inhibitors (eculizumab and ravulizumab)	NMOSD	i.v.	Prevention of cleavage of C5a and C5b, inhibition of MAC formation

Abbreviations: APC, antigen-presenting cell; CD, cluster of differentiation; CNS, central nervous system; GA, Glatiramer acetate; i.v., intravenously; IL, interleukin; JAK, Janus kinases; MAC, membrane attack complex; MBP, major basic protein; MHC, major histocompatibility complex; NMOSD, neuromyelitis optica spectrum disorders; Nrf2, nuclear factor erythroid 2-related factor 2; p.o., per os; PPMS, primary-progressive multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis; s.c., subcutaneously; S1 P-R, functional sphingosine 1-phosphate receptors; SPMS, secondary-progressive multiple sclerosis; STAT, signal transducer and activator of transcription proteins; T_h2, T helper cell type 2; T_{req}, regulatory T cell.

CIDP.^{16,17} One case report even indicated an exacerbation of CIDP after treatment of a MS patient with IFN- β .¹⁸ There are also a few case reports of IFN- β -induced peripheral neuropathy in patients with MS that resolved with treatment cessation.^{19,20} The long-term safety data indicate, however, no neurotoxic potential. In MMN, IFN- β was used in non-randomized trials and showed moderate beneficial effects in three of nine patients in one study²¹ and in four patients who failed other therapies.²²

Conclusion on AN relevance: Although not neurotoxic, there is no convincing evidence that IFN- β can be of potential benefit to CIDP or other AN.

Glatiramer acetate (GA). GA is a random polymer of four amino acids that structurally resembles myelin basic protein (MBP) which is present in the central nervous system (CNS) and PNS.²³ GA competes with MBP in APCs for binding to the major histocompatibility complex (MHC) and thereby induces T_h2 cells via secretion of interleukin-10 (IL-10).^{24–28} GA was also shown to elevate T_{reg} and to decrease $T_h 17$ levels.²⁹ A more specific mode of action is the binding of GA and MHC to the T-cell receptor. It reacts as an antagonist of the immunogenic peptide MBP^{82-100.30} MBP is essential for formation of CNS myelin. While it is also present in the PNS with identical amino acid sequences, it is non-essential for peripheral myelin formation since other proteins like P2 or P0 compensate lacking MBP.31,32 The above-mentioned mechanisms of GA mainly affect the peripheral immune compartments,^{33,34} even though there is some evidence that GA might be taken up by dendritic CNS cells.35

Data in experimental neuritis: Two studies described beneficial effects of GA in EAN. Zhang *et al.*³⁶ injected GA daily subcutaneously (s.c.), before and during the induction phase of EAN. Aronovich *et al.*³⁷ administered GA intraperitoneally (i.p.), after onset of EAN. Clinical score improved but without significant effects on nerve conduction studies and histological assessment.

Clinical data: In CIDP patients with atypical manifestations, elevated MBP⁸²⁻¹⁰⁰ specific T-cell responses were found in low frequency.³⁸ Another study evaluated the activation of mononuclear cells specific for MBP in CIDP samples but found no specific activation pattern.³⁹ Case series or studies that evaluated the use of GA in patients with AN were not found.

Conclusion on AN relevance: Immunomodulatory effects of GA are mainly mediated through the resemblance to MBP. As MBP is non-essential for myelin formation in the PNS, GA is not an ideal candidate as a treatment option for patients with AN.

Dimethyl fumarate (DMF). Fumaric acid esters were for a long time used in psoriasis and reports of coincidental amelioration of comorbid MS led

to the conduction of first clinical trials in remitting-relapsing MS (RRMS).40 To improve gastrointestinal tolerability, the drug was modified to DMF.⁴¹ DMF is rapidly metabolized to the active metabolite monomethyl fumarate (MMF) that shifts the immune response to an anti-inflammatory T_h2 subset with production of IL-4 and IL-5 in a dose-dependent manner.42,43 Increased overall T_{reg} cell counts with a corresponding decrease in inflammatory T_h17 cells were observed.⁴⁴ Activation of APCs is inhibited ex vivo and in vitro by reduced expression of costimulatory molecules and MHC II on B cells.43,45,46 Lymphopenia in DMF treatment preferentially affects CD8⁺ memory rather than CD4⁺ T cells.^{47–49} B memory cells are also reduced.⁵⁰ MMF upregulates expression of the nuclear factor erythroid 2-related factor 2 (Nrf2), which enables transcription of anti-oxidative genes in experimental autoimmune encephalomyelitis (EAE).51,52 MMF also shifts the balance of pro-inflammatory M1 and antiinflammatory M2 macrophages to the latter.53

Data in experimental neuritis: Three studies examined the effects of DMF in EAN. In a study by Pitarokoili et al.,54 rats were treated twice daily with 45 mg/kg body weight DMF orally. The authors demonstrated that DMF exerted immunomodulatory effects through the gut-associated lymphoid tissue by increasing T_{reg} cell number and activation of Nrf2. Transfer of Peyer's patches derived immune cells from DMF treated to treatment-naive rats during the induction phase of EAN significantly attenuated clinical, electrophysiological and histopathological signs of the neuritis.⁵⁴ Another study from the same group explored preventive effects of DMF in EAN. As a possible mode of action, induction of Nrf2 in axons was detected.55 Han et al.53 also detected anti-inflammatory effects of DMF in EAN in a preventive and a therapeutic paradigm. DMF treatment induced an anti-inflammatory shift from M1 to M2 macrophages. They also showed an increase in Nrf2 production in the nerves.

Clinical data: There are no RCTs or case reports with DMF or its variants in patients with CIDP or AN. There is no evidence of potential PNS neurotoxicity.

Conclusion on AN relevance: DMF mediates its immunomodulatory effects in the periphery, indicating a potential role for DMF as a treatment option. However, the overall immunosuppressant effects of DMF are not considerate strong. The common adverse effects such as flush, diarrhoea and nausea often cause a treatment switch in MS patients.⁵⁶ A promising and recently approved alternative is diroximel fumarate, a second-generation fumarate with bioequivalent active levels of MMF, which showed a reduced severity and frequency of gastrointestinal events.⁵⁷

Teriflunomide/leflunomide. Leflunomide is a prodrug which is metabolized to the active compound teriflunomide and its two isoforms.58 Teriflunomide inhibits pyrimidine biosynthesis via the inhibition of the enzyme dihydroorotate dehydrogenase. The inhibition of the pyrimidine synthesis affects only rapidly proliferating cells, like antigen-stimulated lymphocytes.59,60 It induces a mild lymphopenia with absolute reduction of T_h1 cells but not T_h2 and T_h17 cells. Therefore, a proportional increase in anti-inflammatory subsets can be expected.^{61,62} In EAE, teriflunomide showed a decreased infiltration of the CNS by macrophages, T cells and neutrophils.^{63,64} This is further supported by observed reduction of APCs in Peyer's patches with an increase in T_{reg} cells. Adoptive transfer of T_{reg} cells from teriflunomide-treated mice, isolated from gut-associated lymphoid tissue, attenuated EAE severity.65

Data in experimental neuritis: In one study, leflunomide was administered orally in dosages of 1.5, 10, 12.5 and 20 mg/kg daily during the induction phase of EAN, which are fourfold to 50-fold higher as used for rheumatoid arthritis treatment.⁶⁶ EAN was attenuated in all treatment groups. In a therapeutic setting, leflunomide 20 mg/kg daily p.o. halted disease progression. Histopathological studies showed a corresponding decrease in demyelination and cellular infiltration.⁶⁶ Similar results were seen in adoptive transfer EAN.⁶⁶

Clinical data: Teriflunomide was not explored in patients with immune-mediated neuropathy. However, a low incidence of mild-to-moderate peripheral neuropathy has been reported in patients with rheumatoid arthritis or MS, treated with teriflunomide.^{67–69} An *in vitro* screening on mouse embryonic stem cell–derived neurons found that high concentrations of teriflunomide lead to neurotoxicity, while neurodevelopment may be affected in undifferentiated cell lines in lower concentrations, which might be related to the teratogenic effects of teriflunomide in observed *in vivo* experiments.^{70,71}

Conclusion on AN relevance: Teriflunomide and leflunomide as a prodrug are not appropriate due to the reported neurotoxicity.

Oral DMTs approved for highly active MS

Cladribine. Cladribine is a chlorated adenosine analogion. After cell uptake, it gets phosphorylated and is integrated in the cellular DNA and RNA.⁷² Cladribine preferentially targets lymphocytes, which are more susceptible for integration of cladribine in their DNA and RNA due to higher levels of deoxycytidine kinase. It catalyses the rate-limiting step in the nucleotide salvage pathway, and opposing cytosol enzymes 5'-nucleotidases.⁷³⁻⁷⁵

Immunomodulatory effects: Cladribine induces a long-lasting depletion of autoreactive lymphocytes (approximately 45-33% compared with baseline after the end of the second cycle).⁷⁶ The effects are observed throughout all subpopulations.⁷³ The suppression of B cells is more pronounced compared with T-cell suppression.76 Single-strand breaks lead to cell apoptosis via activation of p53 and through mitochondrial release of cytochrome c and apoptosis-inducing factor.77,78 The DNA incorporation of chlorated adenosine impairs cell repair mechanisms, proexpression.77 transcription and gene tein Cladribine enhanced production of anti-inflammatory cytokines IL-4, IL-5 and IL-10.79,80

Data in experimental neuritis: We could not identify any studies investigating the use of cladribine in models of AN.

Clinical data: One case report describes the occurrence of GBS with positive anti-GD1b antibodies after exposure to cladribine.⁸¹ Cladribine is therapeutically used in Waldenström macroglobulinemia that often goes along with a demyelinating peripheral neuropathy.⁸² Fludarabine, another purine-analogion, showed some beneficial effects in patients with MAG neuropathy in a small study.^{83,84}

A common concern of using nucleoside analogues is peripheral neuropathy. Regarding cladribine, in a study of 44 children with Langerhans cell histiocytosis treated with cladribine, none of the patient developed neuropathy.⁸⁵ With higher dosages, neurotoxicity was observed in 6 of 36 patients with refractory acute myeloid leukaemia.^{86,87} In the large phase III trials in MS, peripheral neuropathy was not increasingly observed.⁸⁸

Conclusion on AN relevance: The mainly observed immunomodulatory effects of cladribine are targeting peripheral lymphocytes and are exploited in the treatment of MS, indicative to be a good candidate for treating AN patients. This is encouraged by the data deriving from anti-MAG neuropathy patients. Neurotoxic effects were no concern in MS trials.

Functional sphingosine 1-phosphate receptor (S1PR) antagonists. Functional S1PR-antagonists exert immunosuppressive effects on CD4+T cells.^{89,90} Fingolimod was the first one to be evaluated in MS.⁹¹⁻⁹⁴ It reduces peripheral lymphocytes by impaired lymphocyte trafficking.95 T cells seem to be the main cells affected by fingolimod, with intermediate effects on B cells and cells of the innate immune system.96-98 Fingolimod binds to different S1P-receptors. Effects on lymphocytes have been attributed to the S1PR1, while S1PR3 has been linked to the occurrence of atrioventricular block.99,100 Recently, more selective S1P-inhibitors that target S1PR1 and S1PR5 have been developed. Of those is siponimod the first oral medication approved for active secondary-progressive MS (SPMS), with a reduced risk of bradycardia.101 Ozanimod and ponesimod have a similar mode of action as siponimod. Ozanimod was approved for RRMS, and ponesimod for active forms of MS, including active forms of SPMS.^{102,103} Other S1PR modulators currently invested are amiselimod and ceralifimod with a more selective modulation of the S1PR1.99

Data in experimental neuritis: Zhang et al.¹⁰⁴ showed that fingolimod treatment nearly suppressed development of EAN, if administrated from the day of immunization, and reduced severity, when given with onset of symptoms. Fingolimod treatment led to a reduction in B and T cells as well as reduced macrophage infiltration of the sciatic nerve. Decreased T_h17 cell proportion in peripheral blood, but an increased fraction in the lymph node, was also observed in EAN rats treated with fingolimod.105 Ambrosius et al. reported EAN attenuation with oral fingolimod treatment (0.1 mg/kg body weight) in a preventive setting. Beneficial effects were also observed with fingolimod 1 mg/kg body weight i.p. in spontaneous autoimmune (poly-) neuritis (SAP) mice^{106,107} and oral treatment of 0.3 to 1 mg/kg body weight¹⁰⁸ in terms of reduction in

journals.sagepub.com/home/tan

disease severity, relapse rate and inhibition of demyelination, inflammation and axonal degeneration, while another study did not observe any effects in non-obese diabetic (NOD)-mice treated with 1 mg/kg daily i.p.¹⁰⁹ Schwann cells (SCs) promoting axonal regeneration under fingolimod stimulation were described for low concentrations,¹¹⁰ while higher concentrations of fingolimod applied in cell culture models of dorsal root ganglia and SCs induce SC apoptosis and impede remyelination.¹¹¹

Clinical data: The FORCIDP trial investigated fingolimod in CIDP. Patients were randomized to either fingolimod 0.5 mg once daily or placebo in addition to standard treatment.¹¹² Overall, 106 participants were randomly assigned. The trial was ended after an interim analysis with worsening events in both groups, showing no superiority of fingolimod compared with placebo. Notably, S1PRs are expressed on the surface of peripheral and central neurons, as well as SCs;¹¹¹ however, there is no clinical evidence for potential neurotoxicity of S1PR antagonists.

Conclusion on AN relevance: Due to the negative results from the FORCIDP trial, S1PR antagonists will likely be of no relevance for AN treatment.

DMTs approved for highly active MS

Anti-CD20 antibodies. Up to date, three different anti-CD20 antibodies are established in the treatment of MS: rituximab, ocrelizumab and ofatumumab. Ofatumumab is the most recently approved anti-CD20 monoclonal antibody for RRMS and the only one given s.c., while the other two are given intravenously (i.v.).¹¹³ In addition, while rituximab is a chimeric antibody and ocrelizumab a humanized anti-CD20 murine antibody, of a tumumab is the first immunoglobulin G (IgG)1 monoclonal anti-CD20 antibody that is fully human.113 Ublituximab as another novel chimeric anti-CD20 antibody was recently evaluated in a phase II trial of 45 patients with RRMS showing promising results with 74% of the patients achieving no evidence of disease activity.¹¹⁴ The epitopes differ between ofatumumab, rituximab, ublituximab and ocrelizumab. All four antibodies cause antibody-dependent cell lysis and complementdependent cytotoxicity to CD20 expressing B cells.115 The B-cell lineage expresses CD20 throughout all states of maturity and differentiation with the exception of plasma blasts, plasma

cells and stem cells. Ocrelizumab, ofatumumab, rituximab and ublituximab induce cross-linking of CD20, which leads to an efficient activation of antibody-dependent cellular and complementdependent cytotoxicity via the fragment crystallisable (Fc) domain.^{116,117} Ofatumumab strongly induces complement, while ocrelizumab has more antibody-dependent cellular cytotoxicity (ADCC) activity than rituximab.¹¹⁵ The highest ADCC is shown by ublituximab. Its Fc domain has reduced fucose content, which results in an increased binding to the FcγIIIa receptor.¹¹⁸ In addition, inebilizumab, a CD19-antibody targeting also early plasma cells, received approval for NMOSD.^{119,120}

Data in experimental neuritis: There are several studies with conflicting results of B-cell depletion in models of autoimmune neuritis. Most of these are based on knockdown experiments or depletion of B cells via CD19 antibodies, which also target early plasma cells. Knock-down of CD4⁺ and CD8⁺ T cells ameliorated EAN, while B-cell knockout did not influence EAN course induced by P0¹⁸⁰⁻¹⁹⁹ peptide.¹²¹ In SAP mice, P0-specific B cells and plasma cells were found to be increased and disease severity was attenuated by treatment with anti-CD19 antibodies.¹²² However, another study reported that B-cell deficiency did not prevent SAP development.¹²³

Clinical data: Case reports and smaller series reported the beneficial use of anti-CD20 agents in therapy-refractory CIDP patients.124 Some patients with CIDP harbour antibodies against nodal and paranodal proteins, and these patients tend to respond to rituximab but not to intravenous immunoglobulin (IVIg).125 There is no evidence for PNS neurotoxicity of anti-CD20 or anti-CD19 agents. A phase II study showed promising results in untreated and relapsed Waldenström macroglobulinemia patients treated with ofatumumab monotherapy.¹²⁶ Two small, controlled studies investigated effects of rituximab in anti-MAG neuropathy patients; however, both studies failed to meet the primary endpoints using sensory scales.^{127,128} Secondary endpoints in the second study based on disability and timeto-walk scales, however, were met, and 40% improved under treatment.¹²⁸ Three case series or case reports also report the successful use of rituximab-monotherapy in non-IVIg-responsive MMN.¹²⁹⁻¹³¹ As shown in anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis, rituximab might be a promising alternative for severe non-systematic vasculitic neuropathy (NSVN).¹³²

Conclusion on AN relevance: There is strong evidence for high relevance of anti-CD19/20 agents in the therapeutic armamentarium for AN. They are already used as off-label therapy in non-responders.

Natalizumab. Natalizumab is a humanized monoclonal antibody directed against an $\alpha 4$ integrin. It prevents interaction between very late antigen 4 (VLA4) and its ligand vascular cell adhesion molecule 1 (VCAM1) and inhibits thereby the migration of lymphocytes into the CNS.133,134 It is one of the most potent DMTs for MS. A well-characterized severe adverse effect is the - compared with other disease-modifying drugs - high incidence of progressive multifocal leukoencephalopathy (PML) under patients treated with natalizumab.135 Therefore, before treatment initiation, anti-John Cunningham virus (JCV) seropositivity should always be checked and anti-ICV-positive patients should not be treated longer than 2 years or the JCV-copy status should be monitored.¹³⁶ Another emerging treatment strategy is to extend the dosage intervals of natalizumab to approximately 6 weeks. A randomized, open-label phase III trial confirmed effectiveness of natalizumab in patients when switched from standard dosage interval of 4 weeks to extended dosage intervals after more than 1 year of natalizumab treatment.137

Data in experimental neuritis: Two studies examined the effects of antibodies against VLA4 in EAN. Preventive¹³⁸ and therapeutic¹³⁹ administration of natalizumab attenuated EAN course and histopathological inflammation.

Clinical data: One CIDP patient with treatmentresistant CIDP worsened after natalizumab treatment, even though T cells expressing $\alpha 4$ integrin were found in the inflamed nerve biopsy.¹⁴⁰ In a case series, three other treatment-resistant CIDP patients were successfully treated with an improvement in two and a stabilization in one patient.¹⁴¹ There is no evidence of any neurotoxic potential of natalizumab.

Conclusion on AN relevance: Further studies would be needed to investigate the role of natalizumab as a treatment option. The high incidence of PML, which increases significantly after 2 years, limits its potential.¹⁴²

Currently investigated DMTs

Tyrosine kinase inhibitors (TKIs). TKIs were initially designed for tumour therapy, for example, imatinib, which inhibits ABL-tyrosine kinase in chronic myeloid leukaemia. Many different TKIs are currently under clinical evaluation or already integral part of tumour treatment. Bruton's tyrosine kinase (BTK) is involved in B-cell receptor signalling. BTK inhibitors (BTKIs) prevent B-cell maturation without wiping out resident B cells. BTK is essential for B-cell maturation, and the lack of the enzyme is responsible for the development of x-linked agammaglobulinemia.143,144 It controls the progression of pre-B cells and the entry of B cells into follicular structures.145,146 Furthermore, activation of mature B cells and their termination into memory or plasma cells is impaired.147 Two brain-penetrant BTKIs have been tested in MS. Tolebrutinib showed in a phase II trial promising results on safety and on radiological disease activity.¹⁴⁸ Evobrutinib was also tested in a phase II trial for dosage and safety profile against placebo and DMF.149 Tolebrutininb and evobrutinib are irreversible inhibitors of BTK.¹⁵⁰ In EAE, a dose-dependent effect of evobrutinib was seen, with reduced expression of antigen-presentation molecules on B cells and a reduced development of encephalitogenic T cells.¹⁵¹ This led the pathway for the evaluation of other BTKIs in MS. Fenebrutinib, currently evaluated in a phase II trial (NCT05119569),¹⁵² and remibrutinib are reversible BTKIs,153,154 while orelabrutinib is another irreversible BTKI evaluated in a phase II trial (NCT04711148).153,155 Overall, there are nine phase III trials ongoing, six for RRMS against teriflunomide and three in primary-progressive MS (PPMS)^{156,157} and SPMS.¹⁵⁸ The results should further enlighten the role of BTKs for all forms of MS. Zanubrutinib is another irreversible BTKI tested in a phase II trial in NMOSD (NCT05356858).¹⁵⁹ In addition, tolebrutinib is tested in patients with generalized myasthenia gravis.160

Data in experimental neuritis: To our knowledge, no studies investigated the role of TKIs or BTKIs in models of AN.

Clinical data: There are no clinical data of the use of BTKIs or other TKIs in CIDP. However, TKIs are used for treatment of patients with chronic lymphatic leukaemia and Waldenström macroglobulinemia. A case series reported the successful treatment of patients with anti-MAG

neuropathy with ibrutinib.¹⁶¹ Some TKIs, for example, vascular endothelial growth factor receptor TKI, may induce sensory neuropathy;^{162,163} however, neurotoxicity was not reported in phase II MS trials with TKIs.^{148,149} A phase II trial is currently evaluating the safety of a combination therapy of an anti-CD20 agent with acalabrutinib, a BTKI, in patients with Waldenström macroglobulinemia, IgM monoclonal gammopathy of undetermined significance (MGUS) and anti-MAG neuropathy (NCT05065554).¹⁶⁴

Conclusion on AN relevance: There is some evidence that BTKIs may be useful in AN. The potential reversible effects of BTKI inhibition after treatment discontinuation are a major advantage during B-cell depletion. The existence of long-term data of different BTKIs with many patients from leukaemia treatment could accelerate the clinical translation. Hence, no penetration of the blood-brain barrier (BBB) is needed; more BTKIs could be applicable for AN treatment.

Laquinimod. Laquinimod is an orally available quinoline-3-carboxamide.¹⁶⁵ Laquinimod slowed progression of disability and reduced rate of relapse in RRMS.¹⁶⁶ However, it received a negative review by the European Medicines Agency due to concerns regarding long-term exposure with higher occurrence of cancers and its teratogenic potential in animal studies.167 The exact mode of action of laquinimod is currently unknown. Several studies point to an activation of the aryl hydrocarbon-receptor pathway and a dependency of laquinimod on this receptor to mediate anti-inflammatory effects.168-170 These effects are a decreased T_h1 and T_h17 response with an increased reactivity of T_{reg} cells. Neuroprotective effects are linked to other mechanisms, for example, upregulation of brain-derived neurotrophic factor receptors.171

Data in experimental models of neuritis: Two studies showed that laquinimod attenuated EAN. Zou *et al.*¹⁷² compared the effects of laquinimod in different concentrations (0.16, 1.6 and 16 mg/kg s.c.) to its predecessor linomide (16 mg/kg s.c.) and sham treatment. Dose-related reduction in EAN severity was shown with correlating reduced cellular infiltration and a shift towards antiinflammatory T_h2 cell response. Pitarokoili *et al.*¹⁷³ showed similar positive results with daily treatment of 12.5 or 25 mg/kg orally. *Clinical data*: To our knowledge, no clinical studies examining the effects of laquinimod on AN were performed or are currently conducted. There is also no evidence for PNS neurotoxicity.

Conclusion on AN relevance: Due to the limited data and the unknown exact mode of action, the role of laquinimod for AN treatment is unclear.

DMTs for NMOSD

IL-6-receptor antagonists. Satralizumab and tocilizumab are monoclonal antibodies against IL-6 receptors. Off-label uses of tocilizumab in NMOSD as mono- or add-on medication were shown to be effective to reduce disease activity and progression in myelin oligodendrocyte glycoprotein (MOG-) or aquaporin-4- (AQP4-) positive and negative patients.¹⁷⁴⁻¹⁷⁷ Satralizumab was engineered with an enhanced plasma resistance,¹⁷⁸ and it is given s.c. in contrast to tocilizumab, which is administered i.v.177 Satralizumab was tested in two phase III trials as add-on treatment or as monotherapy and reduced relapses in both trials. Primary endpoints were the time to and incidence of a relapse in both trials and satralizumab led to a risk reduction of 55%178 and 65%, respectively.¹⁷⁹ No significant difference in the secondary endpoints (change in Visual Analogue Scale pain score and the Functional Assessment of Chronic Illness Therapy fatigue score from baseline to week 24) was noted. It was generally well tolerated.^{178,179} The antibodies inhibit the binding of IL-6 to its receptor. There is clinical and experimental evidence that IL-6 plays a key role in the pathogenesis of NMOSD.¹⁸⁰⁻¹⁸³

Data in experimental neuritis: EAN is associated with increased IL-6 levels during disease onset.¹⁸⁴ Other studies hint to neuroprotective effects of IL-6 as its nasal application ameliorated disease severity in EAN.¹⁸⁵

Clinical data: IL-6 may be increased in the cerebrospinal fluid (CSF) of CIDP patients, while serum IL-6 levels are normal.¹⁸⁶ Another study could find no significant differences in IL-6 CSF expression.¹⁸⁷ Nerve biopsies of the sural nerve showed an upregulation of IL-6 in CIDP patients associated with upregulated neurotrophic growth factor receptors, indicating a role in nerve regeneration.¹⁸⁸ There is no evidence of any neurotoxic potential of satralizumab and tocilizumab. *Conclusion on AN relevance*: The role of IL-6 in AN pathogenesis appears to be minor, and therefore, IL-6-receptor antagonists are not relevant for repurposing in AN patients.

Eculizumab and other anti-complement agents. Eculizumab is a humanized monoclonal antibody that is approved for NMOSD in AQP4-positive patients.¹²⁰ Ravulizumab is another terminal complement protein (C5) inhibitor, which is currently evaluated in NMOSD.¹⁸⁹ Due to drug modifications, it has – compared with eculizumab – a prolonged half-life, which extends the dosage intervals.¹⁹⁰ Eculizumab binds to C5 and prevents cleavage to C5a and C5b and thereby inhibiting membrane attack complex (MAC) formation. MAC is the final step of the complex cascade and is able to mediated cell lysis.¹⁹¹ Both soluble C5a and MAC can be detected in plasma and CSF of NMOSD patients.¹⁹²

Data in experimental neuritis: In EAN, complement depletion mitigates clinical course and nerve injury.¹⁹³⁻¹⁹⁵ The passive transfer of the disease with pathogenic IgG with complement C3 reactivity from CIDP patients into rats, results in nerve conduction impairment and demyelination¹⁹⁶ and suppression of disease following administration of soluble complement receptor one (sCR1), indicates potential association of complement in CIDP. Furthermore, deposition of complement components on nerves197 and of complement-fixing autoantibodies on the myelin sheath and high systemic complement levels that correlated with disease severity¹⁹⁸ further point to an essential role of complement in the pathogenesis of CIDP and GBS.199,200

Clinical data: There is no evidence of any neurotoxic potential of eculizumab. We found a phase II open-label study that is currently investigating potential effects on CIDP patients treated with a C1s inhibitor, which is part of the activation of the classical complement pathway (NCT04658472).²⁰¹ Eculizumab was used as an add-on therapy to IVIg in MMN patients to prove short-term safety in an open-label study. Reduction of IVIg dosage was not significant, but secondary outcome measures showed promising results like a small, but significant decrease in conduction block.202 A randomized phase II study recently started to further examine the role of complement in MMN by the use of a C2 inhibitor, which plays a role in both the classical and lectin pathway of complement activation (NCT05225675).²⁰³ Eculizumab was further evaluated in two phase II studies of GBS patients as add-on therapy to IVIg and showed inconclusive results. In one study, a benefit was observed in secondary outcomes,²⁰⁴ while the other study could randomize only eight patients with severe GBS.²⁰⁵ However, both showed the safety of eculizumab infusions. A phase III trial is currently ongoing (NCT04752566).²⁰⁶ ANX005 inhibits C1q and is another classical complement inhibitor currently evaluated in GBS in a phase II/ III trial (NCT04701164).²⁰⁷

Conclusion on AN relevance: There is strong evidence that anti-complement agents are highly relevant in CIDP treatment as indicated by the role of complement in CIDP pathogenesis and are also relevant for MMN and GBS.

DMTs for other autoimmune disorders

Even though out of the scope of this review, we would like to mention another drug class with highly promising potential to impact AN disease course, which are inhibitors of the neonatal Fc-receptor (FcRn). FcRn inhibitors are currently evaluated in myasthenia gravis and excellently reviewed elsewhere.208 In short, the neonatal Fc-receptor protects IgGs from lysosomal degradation and enables re-entering of IgGs into the circulation. In autoimmune disease with pathogenic antibodies, an inhibition of the receptors leads to a faster degradation of those autoantibodies. Several FcRn agents were evaluated in myasthenia gravis and showed promising results. Recently, efgartigimod (i.v.), a humanized IgG1 Fc fragment, was approved for acetylcholine receptor antibody-positive myasthenia gravis after a phase III trial with significant clinical improvement in the patients as measured by Myasthenia Gravis Activities of Daily Living (MG-ADL) after 8 weeks. Rozanolixizumab is an s.c. administered anti-FcRn IgG4 monoclonal antibody currently in a phase III trial in generalized myasthenia gravis (NCT04650854).²⁰⁹ Nipocalimab, given i.v., is another IgG1 anti-FcRn monoclonal antibody currently evaluated in a phase III trial (NCT04951622).²¹⁰ All three inhibitors led to a meaningful reduction of 70-90% of circulating IgG levels.²⁰⁸ A fourth FcRn inhibitor, batoclimab, is recently recruiting patients for a phase III trial (NCT05403541).²¹¹ In MOG-associated EAE, treatment with an FcRn-antibody ameliorated disease severity.²¹²

Data in experimental neuritis: We could not identify any specific studies evaluating FcRn inhibitors in autoimmune neuritis models.

Clinical data: There was no increased neurotoxic potential reported for the FcRn inhibitors. Currently one FcRn inhibitor – efgartigimod – is evaluated in a phase II trial in CIDP (NCT04281472).²¹³ Another phase II/III trial is planned for the evaluation of nipocalimab, a third FcRN inhibitor (NCT05327114).²¹⁴

Conclusion on AN relevance: FcRn is a promising therapeutic target in both CIDP and anti-MAG neuropathy. The reduction is not equally distributed throughout all subclass, with a less prominent effect on IgG4, which is of great relevance in IgG4-related nodopathies.²⁰⁸ Inhibition of FcRn is especially of interest for AN patients, as the IgG reduction is only transient without altering the function of plasma cells and memory B cells and, therefore, not increasing the risk of infections.²¹⁵

Discussion

The term 'drug repurposing' is not clearly defined²¹⁶ and includes a variety of different strategies ranging from hypothesis-driven approaches, that is, finding a new indication for a licensed drug, up to computational approaches by use of 'signature mapping', or pathway 'matching' ²¹⁷ to identify new indications out of the original scope of the drug. Repurposing licensed drugs is an attractive option particularly for rare diseases like CIDP where the pathogenesis is incompletely understood and studies are difficult to conduct, resulting in a high risk of failure. As a general limitation, it should be noted that DMTs for RRMS or NMOSD have been evaluated in a mainly welldefined and homogeneous clinical condition with well-established clinical outcome parameters (i.e. annual relapse rate) and specific laboratory parameters (i.e. non-invasive imaging biomarkers, like magnetic resonance imaging). This is, however, not the case for SPMS and PPMS with less well-established primary and secondary endpoints. Using the same drug in AN means applying a drug to a novel condition with a more diverse clinical presentation, different immunopathogenesis and heterogeneous or less well-defined quantitative outcome measures. Furthermore, regulatory concerns such as pre-existing patents that could impede commercialization of the repositioned drug need to be considered.

Notably, most of the presently discussed DMTs are established in RRMS or SPMS, as only ocrelizumab is currently approved as a DMT for PPMS and the other DTMs showed only limited treatment success.²¹⁸ Many CIDP patients also present with a pattern resembling a 'primary-progressive' disease course, with clinical features like PPMS. The heterogeneity of AN patient cohorts is also a consideration in the context of the translational therapeutic failures noted with some DMTs that may reflect different disease subtypes.^{219,220} This is highlighted by the fact that there are several clinical variants of CIDP including pure motor or sensory forms, multifocal motor-sensory neuropathy (Lewis-Sumner syndrome) and pure distal forms. Some patients only respond to steroids, while others show a better response to IVIg suggesting differences in the immunopathogenesis of the disease.219

Several pathogenic factors which are the target for DMTs in NMOSD and MS are shared in AN, especially CIDP: production of immunogenic antibodies against a known or unknown antigen by B cells, infiltration of inflammatory cells like macrophages, disruption of the BBB or BNB, respectively, as wells as complement activation, a pathological hallmark in NMOSD (Table 1 and Figure 1). In both, AN and MS/NMOSD, inflammatory attacks induce demyelination and axonal damage. Chronical demyelination and axonal degeneration are believed to be the main driver of disease progression in PPMS and SPMS, but also in some CIDP patients.²²¹

The question as to which of the discussed drugs promise the highest benefit is, therefore, challenging especially since there is no standardization for this evaluation process or adequately weighing experimental and clinical data. Moreover, factors such as potential neurotoxicity, time to improvement and the possibility of the desired drug to be used as add-on therapy may further influence the selection process. Accordingly, by applying these criteria, many of the DMTs can be already excluded. Interferons and fingolimod are not applicable because of the negative evidence-based data of RCTs.^{16,17,112} GA also is not suitable, as its mechanism of action is based on its resemblance to MBP, which is a non-relevant antigen in EAN and AN.³⁹ Teriflunomide may exert a beneficial mode of action, but its weak immunopathogenic

effect relevant to CIDP and other AN and the possibility of association with peripheral neuropathy are not favourable factors. Likewise, although there are promising preclinical data that suggest laquinimod may work for CIDP, the unresolved issue of long-term safety will prevent its further consideration as a potential treatment option for AN. Experimental data also suggest a beneficial effect of natalizumab; however, the available clinical data and its safety profile with the risk of development PML in JC-virus-positive patients¹⁴² probably argue against its further exploration in AN.

In contrast, cladribine seems to be a good candidate for a trial in AN patients. This view is also supported by promising results in anti-MAG neuropathy patients. Anti-CD20 agents also appear attractive, based on the pivotal role of certain autoantibodies, such as MAG and gangliosides, and the clinical experience with rituximab as off-label drug. At present, a controlled study with rituximab has started in Italy for CIDP patients.²²² The anti-CD20 antibodies differ as mentioned by their targeted epitope and their potential to activate ADCC. As B-cell depletion is described sufficiently and reliable for all agents, and no head-to-head studies are available, similar translational results to CIDP should be expected. Anti-CD19 therapies like inebilizumab also target mature B cells like anti-CD20 agents; however, CD19 is expressed throughout B-cell maturation and also on secreting plasmablasts and plasma cells.²²³ Hence, anti-CD19 agents might provide an additional benefit by directly targeting the sources of pathogenic autoantibody production, plasmablasts and plasma cells. Obexelimab is another antibody on the horizon, targeting CD19 along with the inhibitory FcyRIIb receptor.²²⁴ Obexelimab is designed to inhibit B-cell function without destroying the immune cells,²²⁵ potentially reducing susceptibility to infections as seen by long-lasting B-cell depletion. Comparative clinical studies regarding autoimmunity of the CNS are currently missing to support this hypothesis. The strong biological plausibility and the comparable side-effect profile compared with the anti-CD20 agents should strongly encourage RCTs in AN, especially in the IgG4-related nodopathies which do not respond to IVIg.²²⁶ A compelling alternative to anti-CD20 antibodies, despite the lack of preclinical data, are BTKIs. The potential reversibility after treatment discontinuation and the well-tolerability as well as the low incidence of opportunistic infections encourages further exploration for AN.

Preclinical and clinical data regarding complement also imply a potential role of anti-complement agents. Advantageously, data from an RCT already demonstrated that the parallel treatment of IVIg and eculizumab does not diminish efficacy of anti-complement activity.²⁰⁴ Complement is, however, no treatment target in IgG4nodopathy CIDP patients as they do not cause complement-fixing or macrophage-mediated demyelination.^{226,227} The role of IL-6 and hence the use of IL-6 receptor antagonists are not well explored, and there is no evidence in favour or against its use in CIDP or other AN.

Taken together, repurposing DMTs, which are well established in MS and NMOSD, is an attractive option for AN to expand the therapeutic landscape, provided a careful selection process has been employed implementing objective assessment of the available clinical and experimental data. Based on careful comparative clinical and safety assessments, encouraging data for new clinical trials in AN derive from B cell-targeted therapies (either antibodies or novel approaches such as BTK inhibition), complement-targeting DMTs and cladribine. The anti-FcRn inhibitors, currently explored in both NMOSD and CIDP, may be additional options.

Declarations

Ethics approval and consent to participate Not applicable.

Consent for publication Not applicable.

Author contributions

Felix Kohle: Conceptualization; Data curation; Investigation; Methodology; Visualization; Writing – original draft; Writing – review & editing.

Marinos C. Dalakas: Conceptualization; Investigation; Supervision; Validation; Writing – review & editing.

Helmar C. Lehmann: Conceptualization; Investigation; Supervision; Validation; Visualization; Writing – review & editing. Acknowledgements Not applicable.

Funding

The authors received no financial support for the research, authorship and/or publication of this article.

Competing interests

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: FK reports no potential competing interests. MCD has received consultancy fees from Baxter (data and safety monitoring board and lecture fees); Grifols/Talecris, Novartis, Octapharma (lecture fees and serving on DSMB); Alexion, Argenx and Dysimmune Diseases Foundation (consulting fees). He serves as an Associate Editor for Neurology (N2) and TAND. HCL received honoraria for speaking and advisory board engagement or academic research support by Akcea, Alnylam, Biogen, Celgene, CSL Behring, Grifols, Gruenenthal, LFB Pharma, Takeda and UCB.

Availability of data and materials Not applicable.

ORCID iDs

Felix Kohle https://orcid.org/0000-0002-4429-0367

Marinos C. Dalakas D https://orcid.org/0000-0001-7070-1134

Helmar C. Lehmann D https://orcid.org/0000-0001-6205-2293

References

- Dalakas MC. Potential biomarkers for monitoring therapeutic response in patients with CIDP. *J Peripher Nerv Syst* 2011; 16(Suppl. 1): 63–67.
- 2. Van den Bergh PYK, van Doorn PA, Hadden RDM, *et al.* European Academy of Neurology/ Peripheral Nerve Society guideline on diagnosis and treatment of chronic inflammatory demyelinating polyradiculoneuropathy: report of a joint Task Force – Second revision. *J Perip Nerv Syst* 2021; 26: 242–268.
- 3. Wallin MT, Culpepper WJ, Nichols E, *et al.* Global, regional, and national burden of multiple sclerosis 1990–2016: a systematic analysis for the

Global Burden of Disease Study 2016. Lancet Neurol 2019; 18: 269–285.

- Gold R, Hartung HP and Toyka KV. Animal models for autoimmune demyelinating disorders of the nervous system. *Mol Med Today* 2000; 6: 88–91.
- Gold R, Linington C and Lassmann H. Understanding pathogenesis and therapy of multiple sclerosis via animal models: 70 years of merits and culprits in experimental autoimmune encephalomyelitis research. *Brain* 2006; 129(Pt 8): 1953–1971.
- Duan T and Verkman AS. Experimental animal models of aquaporin-4-IgG-seropositive neuromyelitis optica spectrum disorders: progress and shortcomings. *Brain Pathol* 2020; 30: 13–25.
- Samuel CE. Antiviral actions of interferons. *Clin* Microbiol Rev 2001; 14: 778–809.
- Haji Abdolvahab M, Mofrad MRK and Schellekens H. Chapter eight – interferon beta: from molecular level to therapeutic effects. In: Jeon KW and Galluzzi L (eds) *International review of cell and molecular biology*. New York: Academic Press, 2016, pp. 343–372.
- Hebenstreit D, Horejs-Hoeck J and Duschl A. JAK/STAT-dependent gene regulation by cytokines. *Drug News Perspect* 2005; 18: 243– 249.
- Ghafouri-Fard S, Hussen BM, Nicknafs F, et al. Expression analysis of protein inhibitor of activated STAT in inflammatory demyelinating polyradiculoneuropathy. *Front Immunol* 2021; 12: 659038.
- Stark GR, Kerr IM, Williams BR, et al. How cells respond to interferons. Annu Rev Biochem 1998; 67: 227–264.
- Guo B, Chang EY and Cheng G. The type I IFN induction pathway constrains Th17mediated autoimmune inflammation in mice. *J Clin Invest* 2008; 118: 1680–1690.
- Huang H, Ito K, Dangond F, et al. Effect of interferon beta-1a on B7.1 and B7.2 B-cell expression and its impact on T-cell proliferation. *Journal of Neuroimmunology* 2013; 258: 27–31.
- Vriesendorp FJ, Flynn RE, Khan M, et al. Oral administration of type I interferon modulates the course of experimental allergic neuritis. *Autoimmunity* 1996; 24: 157–165.
- 15. Zou LP, Ma DH, Wei L, *et al.* IFN-beta suppresses experimental autoimmune neuritis in Lewis rats by inhibiting the migration of

inflammatory cells into peripheral nervous tissue. *J Neurosci Res* 1999; 56: 123–130.

- Hadden RD, Sharrack B, Bensa S, *et al.* Randomized trial of interferon beta-1a in chronic inflammatory demyelinating polyradiculoneuropathy. *Neurology* 1999; 53: 57–61.
- Hughes RA, Gorson KC, Cros D, et al. Intramuscular interferon beta-1a in chronic inflammatory demyelinating polyradiculoneuropathy. *Neurology* 2010; 74: 651–657.
- Matsuse D, Ochi H, Tashiro K, et al. Exacerbation of chronic inflammatory demyelinating polyradiculoneuropathy during interferonbeta-1b therapy in a patient with childhood-onset multiple sclerosis. *Intern Med* 2005; 44: 68–72.
- 19. Jones MR, Urits I, Wolf J, *et al.* Drug-induced peripheral neuropathy: a narrative review. *Curr Clin Pharmacol* 2020; 15: 38–48.
- Ekstein D, Linetsky E, Abramsky O, et al. Polyneuropathy associated with interferon beta treatment in patients with multiple sclerosis. *Neurology* 2005; 65: 456–458.
- Van den Berg-Vos RM, Van den Berg LH, Franssen H, *et al.* Treatment of multifocal motor neuropathy with interferon-beta1A. *Neurology* 2000; 54: 1518–1521.
- 22. Martina IS, van Doorn PA, Schmitz PI, et al. Chronic motor neuropathies: response to interferon-beta1a after failure of conventional therapies. J Neurol Neurosurg Psychiatry 1999; 66: 197–201.
- Kursula P. Structural properties of proteins specific to the myelin sheath. *Amino Acids* 2008; 34: 175–185.
- 24. Fridkis-Hareli M, Teitelbaum D, Gurevich E, et al. Direct binding of myelin basic protein and synthetic copolymer 1 to class II major histocompatibility complex molecules on living antigen-presenting cells–specificity and promiscuity. *Proc Nat Acad Sci USA* 1994; 91: 4872–4876.
- 25. Neuhaus O, Farina C, Wekerle H, *et al.* Mechanisms of action of glatiramer acetate in multiple sclerosis. *Neurology* 2001; 56: 702–708.
- Vieira PL, Heystek HC, Wormmeester J, et al. Glatiramer acetate (copolymer-1, copaxone) promotes Th2 cell development and increased IL-10 production through modulation of dendritic cells. J Immunol 2003; 170: 4483–4488.

- Weber MS, Starck M, Wagenpfeil S, *et al.* Multiple sclerosis: glatiramer acetate inhibits monocyte reactivity in vitro and in vivo. *Brain* 2004; 127(Pt 6): 1370–1378.
- Duda PW, Schmied MC, Cook SL, et al. Glatiramer acetate (Copaxone) induces degenerate, Th2-polarized immune responses in patients with multiple sclerosis. *J Clin Invest* 2000; 105: 967–976.
- Hong J, Li N, Zhang X, *et al.* Induction of CD4⁺CD25⁺ regulatory T cells by copolymer-I through activation of transcription factor Foxp3. *Proc Nat Acad Sci USA* 2005; 102: 6449–6454.
- Aharoni R, Teitelbaum D, Arnon R, et al. Copolymer 1 acts against the immunodominant epitope 82–100 of myelin basic protein by T cell receptor antagonism in addition to major histocompatibility complex blocking. Proc Nat Acad Sci USA 1999; 96: 634–639.
- Greenfield S, Brostoff SW and Hogan EL. Characterization of the basic proteins from rodent peripheral nervous system myelin. *β Neurochem* 1980; 34: 453–455.
- Boggs JM. Myelin basic protein: a multifunctional protein. *Cell Mol Life Sci* 2006; 63: 1945–1961.
- 33. Aharoni R. The mechanism of action of glatiramer acetate in multiple sclerosis and beyond. *Autoimmun Rev* 2013; 12: 543–553.
- Aharoni R, Meshorer A, Sela M, et al. Oral treatment of mice with copolymer 1 (glatiramer acetate) results in the accumulation of specific Th2 cells in the central nervous system. *J Neuroimmunol* 2002; 126: 58–68.
- Liu J, Johnson TV, Lin J, et al. T cell independent mechanism for copolymer-1induced neuroprotection. Eur J Immunol 2007; 37: 3143–3154.
- Zhang CJ, Zhai H, Yan Y, et al. Glatiramer acetate ameliorates experimental autoimmune neuritis. *Immunol Cell Biol* 2014; 92: 164–169.
- Aronovich R, Katzav A and Chapman J. The strategies used for treatment of experimental autoimmune neuritis (EAN): a beneficial effect of Glatiramer acetate administered intraperitoneally. *Clin Rev Allergy Immunol* 2012; 42: 181–188.
- Staudt M, Diederich JM, Meisel C, et al. Differences in peripheral myelin antigen-specific T cell responses and T memory subsets in atypical versus typical CIDP. BMC Neurology 2017; 17: 81.

- Csurhes PA, Sullivan AA, Green K, et al. T cell reactivity to P0, P2, PMP-22, and myelin basic protein in patients with Guillain-Barre syndrome and chronic inflammatory demyelinating polyradiculoneuropathy. *J Neurol Neurosurg Psychiatry* 2005; 76: 1431–1439.
- Schimrigk S, Brune N, Hellwig K, et al. Oral fumaric acid esters for the treatment of active multiple sclerosis: an open-label, baselinecontrolled pilot study. Eur J Neurol 2006; 13: 604–610.
- 41. Linker RA and Gold R. Dimethyl fumarate for treatment of multiple sclerosis: mechanism of action, effectiveness, and side effects. *Curr Neurol Neurosci Rep* 2013; 13: 394.
- de Jong R, Bezemer AC, Zomerdijk TP, et al. Selective stimulation of T helper 2 cytokine responses by the anti-psoriasis agent monomethylfumarate. Eur J Immunol 1996; 26: 2067–2074.
- Litjens NH, Rademaker M, Ravensbergen B, et al. Monomethylfumarate affects polarization of monocyte-derived dendritic cells resulting in down-regulated Th1 lymphocyte responses. Eur *J Immunol* 2004; 34: 565–575.
- 44. Longbrake EE, Cantoni C, Chahin S, *et al.* Dimethyl fumarate induces changes in B- and T-lymphocyte function independent of the effects on absolute lymphocyte count. *Mult Scler* 2018; 24: 728–738.
- Diebold M, Sievers C, Bantug G, et al. Dimethyl fumarate influences innate and adaptive immunity in multiple sclerosis. *J Autoimmun* 2018; 86: 39–50.
- Schulze-Topphoff U, Varrin-Doyer M, Pekarek K, et al. Dimethyl fumarate treatment induces adaptive and innate immune modulation independent of Nrf2. Proc Natl Acad Sci U S A 2016; 113: 4777–4782.
- Hosseini A, Masjedi A, Baradaran B, et al. Dimethyl fumarate: regulatory effects on the immune system in the treatment of multiple sclerosis. *J Cell Physiol* 2019; 234: 9943–9955.
- Fleischer V, Friedrich M, Rezk A, et al. Treatment response to dimethyl fumarate is characterized by disproportionate CD8+ T cell reduction in MS. *Mult Scler* 2018; 24: 632–641.
- Spencer CM, Crabtree-Hartman EC, Lehmann-Horn K, et al. Reduction of CD8(+) T lymphocytes in multiple sclerosis patients treated with dimethyl fumarate. *Neurol Neuroimmunol Neuroinflamm* 2015; 2: e76.

- Smith MD, Martin KA, Calabresi PA, et al. Dimethyl fumarate alters B-cell memory and cytokine production in MS patients. Ann Clin Transl Neurol 2017; 4: 351–355.
- Linker RA, Lee DH, Ryan S, *et al.* Fumaric acid esters exert neuroprotective effects in neuroinflammation via activation of the Nrf2 antioxidant pathway. *Brain* 2011; 134(Pt 3): 678–692.
- Chen H, Assmann JC, Krenz A, et al. Hydroxycarboxylic acid receptor 2 mediates dimethyl fumarate's protective effect in EAE. J Clin Invest 2014; 124: 2188–2192.
- Han R, Xiao J, Zhai H, *et al.* Dimethyl fumarate attenuates experimental autoimmune neuritis through the nuclear factor erythroid-derived 2-related factor 2/hemoxygenase-1 pathway by altering the balance of M1/M2 macrophages. *J Neuroinflamm* 2016; 13: 97.
- 54. Pitarokoili K, Bachir H, Sgodzai M, *et al.* Induction of regulatory properties in the intestinal immune system by dimethyl fumarate in Lewis rat experimental autoimmune neuritis. *Front Immunol* 2019; 10: 2132.
- Pitarokoili K, Ambrosius B, Meyer D, *et al.* Dimethyl fumarate ameliorates Lewis rat experimental autoimmune neuritis and mediates axonal protection. *PLoS ONE* 2015; 10: e0143416.
- 56. Thompson MT, Virginia D, Nick B, et al. Adherence and discontinuation rates in patients on Tecfidera[™] (dimethyl fumarate): long-term Canadian experience from the Biogen ONE[™] support program. Multi Scler Relat Disorder 2022; 67: 104080.
- 57. Naismith RT, Wundes A, Ziemssen T, et al. Diroximel fumarate demonstrates an improved gastrointestinal tolerability profile compared with dimethyl fumarate in patients with relapsing-remitting multiple sclerosis: results from the randomized, double-blind, phase III EVOLVE-MS-2 study. CNS Drugs 2020; 34: 185–196.
- Aly L, Hemmer B and Korn T. From leflunomide to teriflunomide: drug development and immunosuppressive oral drugs in the treatment of multiple sclerosis. *Curr Neuropharmacol* 2017; 15: 874–891.
- 59. Fairbanks LD, Bofill M, Ruckemann K, et al. Importance of ribonucleotide availability to proliferating T-lymphocytes from healthy humans. Disproportionate expansion of pyrimidine pools and contrasting effects of de novo synthesis inhibitors. *J Biol Chem* 1995; 270: 29682–2968.

- Löffler M, Klein A, Hayek-Ouassini M, et al. Dihydroorotate dehydrogenase mRNA and protein expression analysis in normal and drugresistant cells. Nucleosides Nucleotides Nucleic Acids 2004; 23: 1281–1285.
- 61. Klotz L, Eschborn M, Lindner M, *et al.* Teriflunomide treatment for multiple sclerosis modulates T cell mitochondrial respiration with affinity-dependent effects. *Sci Transl Med* 2019; 11: eaao5563.
- Dimitrova P, Skapenko A, Herrmann ML, et al. Restriction of de novo pyrimidine biosynthesis inhibits Th1 cell activation and promotes Th2 cell differentiation. *f Immunol* 2002; 169: 3392–3399.
- 63. Ringheim GE, Lee L, Laws-Ricker L, *et al.* Teriflunomide attenuates immunopathological changes in the dark agouti rat model of experimental autoimmune encephalomyelitis. *Front Neurol* 2013; 4: 169.
- 64. Merrill JE, Hanak S, Pu SF, *et al.* Teriflunomide reduces behavioral, electrophysiological, and histopathological deficits in the Dark Agouti rat model of experimental autoimmune encephalomyelitis. *J Neurol* 2009; 256: 89–103.
- Ochoa-Repáraz J, Colpitts SL, Kircher C, et al. Induction of gut regulatory CD39(+) T cells by teriflunomide protects against EAE. Neurol Neuroimmunol Neuroinflamm 2016; 3: e291.
- Korn T, Toyka K, Hartung HP, et al. Suppression of experimental autoimmune neuritis by leflunomide. *Brain* 2001; 124(Pt 9): 1791–1802.
- 67. Richards BL, Spies J, McGill N, *et al.* Effect of leflunomide on the peripheral nerves in rheumatoid arthritis. *Intern Med J* 2007; 37: 101–107.
- 68. Miller AE, Olsson TP, Wolinsky JS, *et al.* Longterm safety and efficacy of teriflunomide in patients with relapsing multiple sclerosis: results from the TOWER extension study. *Mult Scler Relat Disord* 2020; 46: 102438.
- Confavreux C, O'Connor P, Comi G, et al. Oral teriflunomide for patients with relapsing multiple sclerosis (TOWER): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Neurol* 2014; 13: 247–256.
- Colaianna M, Ilmjärv S, Peterson H, et al. Fingerprinting of neurotoxic compounds using a mouse embryonic stem cell dual luminescence reporter assay. Arch Toxicol 2017; 91: 365–391.
- 71. Cambridge: Genzyme Corporation aSc. AUBAGIO prescribing information, https://

products.sanofi.us/aubagio/aubagio.html (2012, accessed 23 February 2022).

- 72. Beutler E. Cladribine (2-chlorodeoxyadenosine). Lancet 1992; 340: 952–956.
- Jacobs BM, Ammoscato F, Giovannoni G, et al. Cladribine: mechanisms and mysteries in multiple sclerosis. J Neurol Neurosurg Psychiatry 2018; 89: 1266–1271.
- Hunsucker SA, Mitchell BS and Spychala J. The 5'-nucleotidases as regulators of nucleotide and drug metabolism. *Pharmacol Ther* 2005; 107: 1–30.
- 75. Kawasaki H, Carrera CJ, Piro LD, et al. Relationship of deoxycytidine kinase and cytoplasmic 5'-nucleotidase to the chemotherapeutic efficacy of 2-chlorodeoxyadenosine. *Blood* 1993; 81: 597–601.
- 76. Baker D, Herrod SS, Alvarez-Gonzalez C, et al. Both cladribine and alemtuzumab may effect MS via B-cell depletion. Neurol Neuroimmunol Neuroinflamm 2017; 4: e360.
- 77. Genini D, Adachi S, Chao Q, et al. Deoxyadenosine analogs induce programmed cell death in chronic lymphocytic leukemia cells by damaging the DNA and by directly affecting the mitochondria. *Blood* 2000; 96: 3537–3543.
- Singh V, Prajeeth CK, Gudi V, et al.
 2-Chlorodeoxyadenosine (cladribine) induces apoptosis in human monocyte-derived dendritic cells. *Clin Exp Immunol* 2013; 173: 288–297.
- 79. Korsen M, Bragado Alonso S, Peix L, *et al.* Cladribine exposure results in a sustained modulation of the cytokine response in human peripheral blood mononuclear cells. *PLoS ONE* 2015; 10: e0129182.
- Kraus SH, Luessi F, Trinschek B, et al. Cladribine exerts an immunomodulatory effect on human and murine dendritic cells. *Int Immunopharmacol* 2014; 18: 347–357.
- Sarmiento MA, Neme D, Fornari MC, et al. Guillain-Barre syndrome following 2-chlorodeoxyadenosine treatment for Hairy Cell Leukemia. Leuk Lymphoma 2000; 39: 657–659.
- Kapoor P, Ansell SM, Fonseca R, et al. Diagnosis and management of Waldenström Macroglobulinemia: mayo stratification of macroglobulinemia and risk-adapted therapy (mSMART) guidelines 2016. JAMA Oncol 2017; 3: 1257–1265.
- 83. Niermeijer JM, Eurelings M, Lokhorst H, *et al.* Neurologic and hematologic response

to fludarabine treatment in IgM MGUS polyneuropathy. *Neurology* 2006; 67: 2076–2079.

- Dalakas MC. Advances in the diagnosis, immunopathogenesis and therapies of IgManti-MAG antibody-mediated neuropathies. *Ther Adv Neurol Disord* 2018; 11: 1756285617746640.
- Barkaoui MA, Queheille E, Aladjidi N, et al. Long-term follow-up of children with risk organ-negative Langerhans cell histiocytosis after 2-chlorodeoxyadenosine treatment. Br J Haematol 2020; 191: 825–834.
- Vahdat L, Wong ET, Wile MJ, et al. Therapeutic and neurotoxic effects of 2-chlorodeoxyadenosine in adults with acute myeloid leukemia. *Blood* 1994; 84: 3429–3434.
- Warzocha K, Krykowksi E, Góra-Tybor J, et al. Fulminant 2-chlorodeoxyadenosinerelated peripheral neuropathy in a patient with paraneoplastic neurological syndrome associated with lymphoma. *Leuk Lymphoma* 1996; 21: 343–346.
- Cook S, Leist T, Comi G, et al. Safety of cladribine tablets in the treatment of patients with multiple sclerosis: an integrated analysis. *Mult Scler Relat Disord* 2019; 29: 157–167.
- Adachi K, Kohara T, Nakao N, et al. Design, synthesis, and structure-activity relationships of 2-substituted-2-amino-1,3-propanediols: discovery of a novel immunosuppressant, FTY720. Bioorganic Med Chem Lett 1995; 5: 853–856.
- Enosawa S, Suzuki S, Kakefuda T, et al. Induction of selective cell death targeting on mature T-lymphocytes in rats by a novel immunosuppressant, FTY720. *Immunopharmacology* 1996; 34: 171–179.
- Brinkmann V, Davis MD, Heise CE, et al. The immune modulator FTY720 targets sphingosine 1-phosphate receptors. *β Biol Chem* 2002; 277: 21453–21457.
- Mandala S, Hajdu R, Bergstrom J, et al. Alteration of lymphocyte trafficking by sphingosine-1-phosphate receptor agonists. *Science* 2002; 296: 346–349.
- Fujino M, Funeshima N, Kitazawa Y, et al. Amelioration of experimental autoimmune encephalomyelitis in Lewis rats by FTY720 treatment. *J Pharmacol Exp Ther* 2003; 305: 70–77.
- 94. Webb M, Tham CS, Lin FF, *et al.* Sphingosine 1-phosphate receptor agonists attenuate

relapsing-remitting experimental autoimmune encephalitis in SJL mice. *J Neuroimmunol* 2004; 153: 108–121.

- 95. Chiba K, Yanagawa Y, Masubuchi Y, et al. FTY720, a novel immunosuppressant, induces sequestration of circulating mature lymphocytes by acceleration of lymphocyte homing in rats. I. FTY720 selectively decreases the number of circulating mature lymphocytes by acceleration of lymphocyte homing. *J Immunol* 1998; 160: 5037–5044.
- Nakamura M, Matsuoka T, Chihara N, et al. Differential effects of fingolimod on B-cell populations in multiple sclerosis. *Mult Scler* 2014; 20: 1371–1380.
- 97. Jenne CN, Enders A, Rivera R, et al. T-betdependent S1P5 expression in NK cells promotes egress from lymph nodes and bone marrow. J Exp Med 2009; 206: 2469–2481.
- Chun J, Kihara Y, Jonnalagadda D, et al. Fingolimod: lessons learned and new opportunities for treating multiple sclerosis and other disorders. *Annu Rev Pharmacol Toxicol* 2019; 59: 149–170.
- Derfuss T, Mehling M, Papadopoulou A, et al. Advances in oral immunomodulating therapies in relapsing multiple sclerosis. *Lancet Neurol* 2020; 19: 336–347.
- 100. Ritter C, Svačina MK, Bobylev I, et al. Impact of age and polytherapy on fingolimod induced bradycardia: a preclinical study. J Neuroimmune Pharmacol 2017; 12: 204–209.
- 101. Kappos L, Bar-Or A, Cree BAC, et al. Siponimod versus placebo in secondary progressive multiple sclerosis (EXPAND): a double-blind, randomised, phase 3 study. Lancet 2018; 391: 1263–1273.
- 102. Comi G, Kappos L, Selmaj KW, et al. Safety and efficacy of ozanimod versus interferon beta-1a in relapsing multiple sclerosis (SUNBEAM): a multicentre, randomised, minimum 12-month, phase 3 trial. Lancet Neurol 2019; 18: 1009–1020.
- 103. Kappos L, Fox RJ, Burcklen M, et al. Ponesimod compared with teriflunomide in patients with relapsing multiple sclerosis in the active-comparator phase 3 OPTIMUM study: a randomized clinical trial. JAMA Neurology 2021; 78: 558–567.
- 104. Zhang Z, Zhang ZY, Fauser U, et al. FTY720 ameliorates experimental autoimmune neuritis by inhibition of lymphocyte and monocyte infiltration into peripheral nerves. Exp Neurol 2008; 210: 681–690.

- 105. Zhang ZY, Zhang Z and Schluesener HJ. FTY720 attenuates lesional interleukin-17(+) cell accumulation in rat experimental autoimmune neuritis. *Neuropathol Appl Neurobiol* 2009; 35: 487–495.
- 106. Brun S, Beaino W, Kremer L, et al. Characterization of a new rat model for chronic inflammatory demyelinating polyneuropathies. J Neuroimmunol 2015; 278: 1–10.
- 107. Kremer L, Taleb O, Boehm N, et al. FTY720 controls disease severity and attenuates sciatic nerve damage in chronic experimental autoimmune neuritis. *J Neuroinflammation* 2019; 16: 54.
- 108. Kim HJ, Jung CG, Dukala D, et al. Fingolimod and related compounds in a spontaneous autoimmune polyneuropathy. J Neuroimmunol 2009; 214: 93–100.
- 109. Huehnchen P, Boehmerle W and Endres M. Fingolimod therapy is not effective in a mouse model of spontaneous autoimmune peripheral polyneuropathy. *Sci Rep* 2018; 8: 5648–5648.
- 110. Heinen A, Beyer F, Tzekova N, et al. Fingolimod induces the transition to a nerve regeneration promoting Schwann cell phenotype. Exp Neurol 2015; 271: 25–35.
- 111. Köhne A, Stettner M, Jangouk P, et al. Fingolimod impedes Schwann cell-mediated myelination: implications for the treatment of immune neuropathies. Arch Neurol 2012; 69: 1280–1289.
- 112. Hughes R, Dalakas MC, Merkies I, et al. Oral fingolimod for chronic inflammatory demyelinating polyradiculoneuropathy (FORCIDP Trial): a double-blind, multicentre, randomised controlled trial. *Lancet Neurol* 2018; 17: 689–698.
- 113. Kang C and Blair HA. Ofatumumab: a review in relapsing forms of multiple sclerosis. *Drugs* 2022; 82:55–62.
- 114. Fox E, Lovett-Racke AE, Gormley M, *et al.* A phase 2 multicenter study of ublituximab, a novel glycoengineered anti-CD20 monoclonal antibody, in patients with relapsing forms of multiple sclerosis. *Mult Scler* 2021; 27: 420–429.
- 115. Klein C, Lammens A, Schäfer W, *et al.* Epitope interactions of monoclonal antibodies targeting CD20 and their relationship to functional properties. *Mabs* 2013; 5: 22–33.
- 116. Cragg MS, Morgan SM, Chan HT, *et al.* Complement-mediated lysis by anti-CD20 mAb correlates with segregation into lipid rafts. *Blood* 2003; 101: 1045–1052.

- 117. Sellebjerg F, Blinkenberg M and Sorensen PS. Anti-CD20 monoclonal antibodies for relapsing and progressive multiple sclerosis. CNS Drugs 2020; 34: 269–280.
- 118. Payandeh Z, Bahrami AA, Hoseinpoor R, et al. The applications of anti-CD20 antibodies to treat various B cells disorders. *Biomed Pharmacother* 2019; 109: 2415–2426.
- 119. 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.
- 120. Frampton JE. Inebilizumab: first approval. *Drugs* 2020; 80: 1259–1264.
- 121. Zhu Y, Bao L, Zhu S, *et al.* CD4 and CD8 T cells, but not B cells, are critical to the control of murine experimental autoimmune neuritis. *Exp Neurol* 2002; 177: 314–320.
- 122. Abraham PM, Quan SH, Dukala D, *et al.* CD19 as a therapeutic target in a spontaneous autoimmune polyneuropathy. *Clin Exp Immunol* 2014; 175: 181–191.
- 123. Smith CJ, Allard DE, Wang Y, et al. IL-10 paradoxically promotes autoimmune neuropathy through S1PR1-dependent CD4(+) T cell migration. *J Immunol* 2018; 200: 1580–1592.
- 124. Mahdi-Rogers M, Brassington R, Gunn AA, et al. Immunomodulatory treatment other than corticosteroids, immunoglobulin and plasma exchange for chronic inflammatory demyelinating polyradiculoneuropathy. *Cochrane Database Syst Rev* 2017; 5: CD003280003280.
- 125. Querol L, Rojas-García R, Diaz-Manera J, *et al.* Rituximab in treatment-resistant CIDP with antibodies against paranodal proteins. *Neurol Neuroimmunol Neuroinflamm* 2015; 2: e149.
- 126. Furman RR, Eradat HA, DiRienzo CG, et al. Once-weekly ofatumumab in untreated or relapsed Waldenström's macroglobulinaemia: an open-label, single-arm, phase 2 study. Lancet Haematol 2017; 4: e24–e34.
- Léger JM, Viala K, Nicolas G, et al. Placebocontrolled trial of rituximab in IgM anti-myelinassociated glycoprotein neuropathy. *Neurology* 2013; 80: 2217–2225.
- 128. Dalakas MC, Rakocevic G, Salajegheh M, *et al.* Placebo-controlled trial of rituximab in IgM anti-myelin-associated glycoprotein antibody demyelinating neuropathy. *Ann Neurol* 2009; 65: 286–293.

- 129. Pestronk A, Florence J, Miller T, et al. Treatment of IgM antibody associated polyneuropathies using rituximab. J Neurol Neurosurg Psychiatry 2003; 74: 485–489.
- Stieglbauer K, Topakian R, Hinterberger G, et al. Beneficial effect of rituximab monotherapy in multifocal motor neuropathy. Neuromuscul Disord 2009; 19: 473–475.
- 131. Umapathi T, Hughes RA, Nobile-Orazio E, et al. Immunosuppressant and immunomodulatory treatments for multifocal motor neuropathy. *Cochrane Database Syst Rev* 2015; 2015: Cd003217.
- Collins MP and Hadden RD. The nonsystemic vasculitic neuropathies. *Nat Rev Neurol* 2017; 13: 302–316.
- 133. Warnke C, Stettner M, Lehmensiek V, et al. Natalizumab exerts a suppressive effect on surrogates of B cell function in blood and CSF. *Mult Scler* 2015; 21: 1036–1044.
- 134. Stüve O, Marra CM, Bar-Or A, et al. Altered CD4+/CD8+ T-cell ratios in cerebrospinal fluid of natalizumab-treated patients with multiple sclerosis. Arch Neurol 2006; 63: 1383–1387.
- Berger JR and Fox RJ. Reassessing the risk of natalizumab-associated PML. J Neurovirol 2016; 22: 533–535.
- 136. Khoy K, Mariotte D, Defer G, *et al.* Natalizumab in multiple sclerosis treatment: from biological effects to immune monitoring. *Front Immunol* 2020; 11: 549842.
- 137. Foley JF, Defer G, Ryerson LZ, et al. Comparison of switching to 6-week dosing of natalizumab versus continuing with 4-week dosing in patients with relapsing-remitting multiple sclerosis (NOVA): a randomised, controlled, open-label, phase 3b trial. Lancet Neurol 2022; 21: 608–619.
- 138. Enders U, Lobb R, Pepinsky RB, *et al.* The role of the very late antigen-4 and its counterligand vascular cell adhesion molecule-1 in the pathogenesis of experimental autoimmune neuritis of the Lewis rat. *Brain* 1998; 121(Pt 7): 1257–1266.
- 139. Leussink VI, Zettl UK, Jander S, *et al.* Blockade of signaling via the very late antigen (VLA-4) and its counterligand vascular cell adhesion molecule-1 (VCAM-1) causes increased T cell apoptosis in experimental autoimmune neuritis. *Acta Neuropathol* 2002; 103: 131–136.
- 140. Wolf C, Menge T, Stenner MP, *et al.* Natalizumab treatment in a patient with chronic

inflammatory demyelinating polyneuropathy. *Arch Neurol* 2010; 67: 881–883.

- 141. Vallat JM, Mathis S, Ghorab K, *et al.* Natalizumab as a disease–modifying therapy in chronic inflammatory demyelinating polyneuropathy – a report of three cases. *Eur Neurol* 2015; 73: 294–302.
- 142. Bloomgren G, Richman S, Hotermans C, et al. Risk of natalizumab-associated progressive multifocal leukoencephalopathy. N Engl J Med 2012; 366: 1870–1880.
- 143. Bruton OC. Agammaglobulinemia. *Pediatrics* 1952; 9: 722–728.
- 144. Vetrie D, Vorechovský I, Sideras P, *et al.* The gene involved in X-linked agammaglobulinaemia is a member of the Src family of protein-tyrosine kinases. *Nature* 1993; 361: 226–233.
- 145. Middendorp S, Dingjan GM, Maas A, et al. Function of Bruton's tyrosine kinase during B cell development is partially independent of its catalytic activity. *J Immunol* 2003; 171: 5988– 5996.
- 146. Cariappa A, Tang M, Parng C, et al. The follicular versus marginal zone B lymphocyte cell fate decision is regulated by Aiolos, Btk, and CD21. Immunity 2001; 14: 603–615.
- 147. Katewa A, Wang Y, Hackney JA, *et al.* Btk-specific inhibition blocks pathogenic plasma cell signatures and myeloid cell-associated damage in IFNα-driven lupus nephritis. *JCI Insight* 2017; 2: e90111.
- 148. Reich DS, Arnold DL, Vermersch P, et al. Safety and efficacy of tolebrutinib, an oral brainpenetrant BTK inhibitor, in relapsing multiple sclerosis: a phase 2b, randomised, double-blind, placebo-controlled trial. *Lancet Neurol* 2021; 20: 729–738.
- 149. Montalban X, Arnold DL, Weber MS, et al. Placebo-controlled trial of an oral BTK inhibitor in multiple sclerosis. N Eng J Med 2019; 380: 2406–2417.
- 150. Estupiñán HY, Berglöf A, Zain R, et al. Comparative analysis of BTK inhibitors and mechanisms underlying adverse effects. Front Cell Dev Biol 2021; 9: 630942.
- 151. Torke S, Pretzsch R, Häusler D, *et al.* Inhibition of Bruton's tyrosine kinase interferes with pathogenic B-cell development in inflammatory CNS demyelinating disease. *Acta Neuropathol* 2020; 140: 535–548.
- 152. Roche H-L. A study to investigate the efficacy of fenebrutinib in relapsing multiple sclerosis (RMS),

https://ClinicalTrials.gov/show/NCT05119569 (2021, accessed 13 September 2022).

- 153. García-Merino A. Bruton's Tyrosine Kinase inhibitors: a new generation of promising agents for multiple sclerosis therapy. *Cells* 2021; 10: 2560.
- 154. Metz M, Sussman G, Gagnon R, *et al.* Fenebrutinib in H(1) antihistamine-refractory chronic spontaneous urticaria: a randomized phase 2 trial. *Nat Med* 2021; 27: 1961–1969.
- 155. Beijing InnoCare Pharma Tech Co. A phase 2 study of orelabrutinib in patients with relapsing-remitting multiple sclerosis, https:// ClinicalTrials.gov/show/NCT04711148 (2021, accessed 8 September 2022).
- 156. Sanofi. Primary Progressive Multiple Sclerosis (PPMS) Study of Bruton's Tyrosine Kinase (BTK) Inhibitor Tolebrutinib (SAR442168), https://ClinicalTrials.gov/show/NCT04458051 (2020, accessed 8 September 2022).
- 157. Roche H-L. A study to evaluate the efficacy and safety of fenebrutinib compared with ocrelizumab in adult participants with primary progressive multiple sclerosis, https:// ClinicalTrials.gov/show/NCT04544449 (2020, accessed 13 September 2022).
- 158. Sanofi. Nonrelapsing secondary progressive multiple sclerosis (NRSPMS) study of Bruton's Tyrosine Kinase (BTK) Inhibitor Tolebrutinib (SAR442168), https://ClinicalTrials.gov/show/ NCT04411641 (2020, accessed 8 September 2022).
- 159. Xuanwu Hospital B. An open label study of the effects and safety of zanubrutinib in NMOSDs adult patients, https://ClinicalTrials.gov/show/ NCT05356858 (2022, accessed 13 September 2022).
- 160. Sanofi. Efficacy and safety of tolebrutinib (SAR442168) tablets in adult participants with generalized myasthenia gravis. https:// ClinicalTrials.gov/show/NCT05132569 (2021, accessed 8 September 2022).
- 161. Castellani F, Visentin A, Campagnolo M, et al. The Bruton tyrosine kinase inhibitor ibrutinib improves anti-MAG antibody polyneuropathy. *Neurol Neuroimmunol Neuroinflamm* 2020; 7: e720.
- 162. Roy B, Das A, Ashish K, *et al.* Neuropathy with vascular endothelial growth factor receptor tyrosine kinase inhibitors: a meta-analysis. *Neurology* 2019; 93: e143–e148.
- Bauer TM, Felip E, Solomon BJ, et al. Clinical management of adverse events associated with Lorlatinib. Oncologist 2019; 24: 1103–1110.

- 164. Castillo JJ. AstraZeneca and Dana-Farber Cancer I. ACALA-R in anti-MAG neuropathy mediated neuropathy, https://ClinicalTrials.gov/ show/NCT05065554 (2021, accessed 1 June 2022).
- Brück W and Wegner C. Insight into the mechanism of laquinimod action. *J Neurol Sci* 2011; 306: 173–179.
- 166. Comi G, Jeffery D, Kappos L, et al. Placebocontrolled trial of oral laquinimod for multiple sclerosis. N Engl J Med 2012; 366: 1000–1009.
- 167. Thöne J and Linker RA. Laquinimod in the treatment of multiple sclerosis: a review of the data so far. *Drug Des Devel Ther* 2016; 10: 1111–1118.
- 168. Kaye J, Piryatinsky V, Birnberg T, et al. Laquinimod arrests experimental autoimmune encephalomyelitis by activating the aryl hydrocarbon receptor. Proc Nat Acad Sci USA 2016; 113: E61456152.
- 169. Abdullah A, Maged M, Hairul-Islam MI, et al. Activation of aryl hydrocarbon receptor signaling by a novel agonist ameliorates autoimmune encephalomyelitis. PLoS ONE 2019; 14: e021598.
- 170. Thöne J, Ellrichmann G, Seubert S, et al. Modulation of autoimmune demyelination by laquinimod via induction of brain-derived neurotrophic factor. Am J Pathol 2012; 180: 267–274.
- 171. Berg J, Mahmoudjanlou Y, Duscha A, et al. The immunomodulatory effect of laquinimod in CNS autoimmunity is mediated by the aryl hydrocarbon receptor. J Neuroimmunol 2016; 298: 9–15.
- 172. Zou LP, Abbas N, Volkmann I, *et al.* Suppression of experimental autoimmune neuritis by ABR-215062 is associated with altered Th1/Th2 balance and inhibited migration of inflammatory cells into the peripheral nerve tissue. *Neuropharmacology* 2002; 42: 731–739.
- 173. Pitarokoili K, Ambrosius B, Schrewe L, et al. Laquinimod exerts strong clinical and immunomodulatory effects in Lewis rat experimental autoimmune neuritis. Journal of Neuroimmunology 2014; 274: 38–45.
- 174. Duchow A and Bellmann-Strobl J. Satralizumab in the treatment of neuromyelitis optica spectrum disorder. *Neurodegenerative Disease Management* 2021; 11: 49–59.
- 175. Araki M, Matsuoka T, Miyamoto K, *et al.* Efficacy of the anti–IL-6 receptor antibody

tocilizumab in neuromyelitis optica. A pilot study. *Neurology* 2014; 82: 1302–1306.

- 176. Ringelstein M, Ayzenberg I, Harmel J, et al. Long-term therapy with interleukin 6 receptor blockade in highly active neuromyelitis optica spectrum disorder. *JAMA Neurol* 2015; 72: 756–763.
- 177. Zhang C, Zhang M, Qiu W, et al. Safety and efficacy of tocilizumab versus azathioprine in highly relapsing neuromyelitis optica spectrum disorder (TANGO): an open-label, multicentre, randomised, phase 2 trial. *Lancet Neurol* 2020; 19: 391–401.
- 178. Traboulsee A, Greenberg BM, Bennett JL, *et al.* Safety and efficacy of satralizumab monotherapy in neuromyelitis optica spectrum disorder: a randomised, double-blind, multicentre, placebocontrolled phase 3 trial. *Lancet Neurol* 2020; 19: 402–412.
- 179. Yamamura T, Kleiter I, Fujihara K, *et al.* Trial of satralizumab in neuromyelitis optica spectrum disorder. *N Engl J Med* 2019; 381: 2114–2124.
- 180. Içöz S, Tüzün E, Kürtüncü M, et al. Enhanced IL-6 production in aquaporin-4 antibody positive neuromyelitis optica patients. Int J Neurosci 2010; 120: 71–75.
- 181. Uzawa A, Mori M, Ito M, et al. Markedly increased CSF interleukin-6 levels in neuromyelitis optica, but not in multiple sclerosis. J Neurol 2009; 256: 2082–2084.
- 182. Takeshita Y, Obermeier B, Cotleur AC, et al. Effects of neuromyelitis optica–IgG at the blood–brain barrier in vitro. Neurol Neuroimmunol Neuroinflamm 2017; 4: e311.
- 183. Chihara N, Aranami T, Sato W, et al. Interleukin 6 signaling promotes anti-aquaporin 4 autoantibody production from plasmablasts in neuromyelitis optica. Proceedings of the National Academy of Sciences 2011; 108: 3701–3706.
- 184. Zhu J, Bai XF, Mix E, et al. Cytokine dichotomy in peripheral nervous system influences the outcome of experimental allergic neuritis: dynamics of mRNA expression for IL-1 beta, IL-6, IL-10, IL-12, TNF-alpha, TNF-beta, and cytolysin. *Clin Immunol Immunopathol* 1997; 84: 85–94.
- 185. Deretzi G, Pelidou S, Zou L, et al. Suppression of chronic experimental autoimmune neuritis by nasally administered recombinant rat interleukin-6. Immunology 1999; 97: 69–76.
- 186. Maimone D, Annunziata P, Simone IL, et al. Interleukin-6 levels in the cerebrospinal fluid and serum of patients with Guillain-Barré syndrome

Volume 16

and chronic inflammatory demyelinating polyradiculoneuropathy. *J Neuroimmunol* 1993; 47: 55–61.

- 187. Sainaghi PP, Collimedaglia L, Alciato F, et al. The expression pattern of inflammatory mediators in cerebrospinal fluid differentiates Guillain-Barré syndrome from chronic inflammatory demyelinating polyneuropathy. *Cytokine* 2010; 51: 138–143.
- 188. Yamamoto M, Ito Y, Mitsuma N, et al. Parallel expression of neurotrophic factors and their receptors in chronic inflammatory demyelinating polyneuropathy. *Muscle Nerve* 2002; 25: 601–604.
- Gklinos P, Papadopoulou M, Stanulovic V, et al. Monoclonal antibodies as neurological therapeutics. *Pharmaceuticals (Basel)* 2021; 14: 92.
- 190. McKeage K. Ravulizumab: first global approval. *Drugs* 2019; 79: 347–352.
- 191. Dalakas MC, Alexopoulos H and Spaeth PJ. Complement in neurological disorders and emerging complement-targeted therapeutics. *Nat Rev Neurol* 2020; 16: 601–617.
- 192. Wang H, Wang K, Wang C, et al. Increased soluble C5b-9 in CSF of neuromyelitis optica. Scand J Immunol 2014; 79: 127–130.
- 193. Susuki K, Rasband MN, Tohyama K, et al. Anti-GM1 antibodies cause complementmediated disruption of sodium channel clusters in peripheral motor nerve fibers. *J Neurosci* 2007; 27: 3956–3967.
- 194. Vriesendorp FJ, Flynn RE, Pappolla MA, et al. Complement depletion affects demyelination and inflammation in experimental allergic neuritis. J Neuroimmunol 1995; 58: 157–165.
- 195. Feasby TE, Gilbert JJ, Hahn AF, et al. Complement depletion suppresses Lewis rat experimental allergic neuritis. Brain Res 1987; 419: 97–103.
- 196. Yan WX, Taylor J, Andrias-Kauba S, et al. Passive transfer of demyelination by serum or IgG from chronic inflammatory demyelinating polyneuropathy patients. Ann Neurol 2000; 47: 765–775.
- 197. Dalakas MC and Engel WK. Immunoglobulin and complement deposits in nerves of patients with chronic relapsing polyneuropathy. *Arch Neurol* 1980; 37: 637–640.
- 198. Quast I, Keller CW, Hiepe F, *et al.* Terminal complement activation is increased and associated with disease severity in CIDP. *Ann Clin Transl Neurol* 2016; 3: 730–735.

- 199. Koike H, Fukami Y, Nishi R, et al. Ultrastructural mechanisms of macrophageinduced demyelination in Guillain-Barré syndrome. J Neurol Neurosurg Psychiatry 2020; 91: 650–659.
- 200. Querol LA, Hartung HP, Lewis RA, *et al.* The role of the complement system in chronic inflammatory demyelinating polyneuropathy: implications for complement-targeted therapies. *Neurotherapeutics* 2022; 19: 864–873.
- 201. Bioverativ aSc and Sanofi. Proof-of-concept Study for BIVV020 in Chronic Inflammatory Demyelinating Polyneuropathy (CIDP), https:// ClinicalTrials.gov/show/NCT04658472 (2020, accessed 1 June 2022).
- 202. Fitzpatrick AM, Mann CA, Barry S, et al. An open label clinical trial of complement inhibition in multifocal motor neuropathy. *J Peripher Nerv* Syst 2011; 16: 84–91.
- 203. argenx. A clinical trial to investigate the safety and tolerability, efficacy, pharmacokinetics, pharmacodynamics and immunogenicity of 2 dose regimens of ARGX-117 in adults with multifocal motor neuropathy, https:// ClinicalTrials.gov/show/NCT05225675 (2022, accessed 1 June 2022).
- 204. Misawa S, Kuwabara S, Sato Y, *et al.* Safety and efficacy of eculizumab in Guillain-Barré syndrome: a multicentre, double-blind, randomised phase 2 trial. *Lancet Neurol* 2018; 17: 519–529.
- 205. Davidson AI, Halstead SK, Goodfellow JA, et al. Inhibition of complement in Guillain-Barré syndrome: the ICA-GBS study. J Peripher Nerv Syst 2017; 22: 4–12.
- 206. Alexion P. A study to evaluate the efficacy and safety of eculizumab in Guillain-Barré syndrome, https://ClinicalTrials.gov/show/ NCT04752566 (2021, accessed 1 June 2022).
- 207. Annexon I. Efficacy and safety of ANX005 in subjects with Guillain-Barré syndrome, https:// ClinicalTrials.gov/show/NCT04701164 (2021, accessed 1 June 2022).
- 208. Dalakas MC and Spaeth PJ. The importance of FcRn in neuro-immunotherapies: from IgG catabolism, FCGRT gene polymorphisms, IVIg dosing and efficiency to specific FcRn inhibitors. *Ther Adv Neurol Disord* 2021; 14: 1756286421997381.
- 209. SRLUB. A study to evaluate rozanolixizumab in study participants with generalized myasthenia gravis, https://ClinicalTrials.gov/show/

NCT04650854 (2020, accessed 13 September 2022).

- 210. Janssen Research Development. A study of nipocalimab administered to adults with generalized myasthenia gravis, https:// ClinicalTrials.gov/show/NCT04951622 (2021, accessed 8 September 2022).
- 211. Immunovant. Phase 3 study to assess the efficacy and safety of batoclimab as induction and maintenance therapy in adult participants with generalized myasthenia gravis, https:// ClinicalTrials.gov/show/NCT05403541 (2022, accessed 8 September 2022).
- 212. Remlinger J, Madarasz A, Guse K, *et al.* Antineonatal Fc receptor antibody treatment ameliorates MOG-IgG-associated experimental autoimmune encephalomyelitis. *Neurol Neuroimmunol Neuroinflamm* 2022; 9: e1134.
- 213. argenx. A study to assess the safety and efficacy of a subcutaneous formulation of efgartigimod in adults with chronic inflammatory demyelinating polyneuropathy (CIDP, an autoimmune disorder that affects the peripheral nerves), https://ClinicalTrials.gov/show/NCT04281472 (2020, accessed 1 June 2022).
- 214. Janssen Research & Development. Efficacy and safety study of nipocalimab for adults with chronic inflammatory demyelinating polyneuropathy (CIDP), https://ClinicalTrials. gov/show/NCT05327114 (2022, accessed 8 September 2022).
- 215. Peter HH, Ochs HD, Cunningham-Rundles C, et al. Targeting FcRn for immunomodulation: benefits, risks, and practical considerations. J Allergy Clin Immunol 2020; 146: 479–491.
- 216. Langedijk J, Mantel-Teeuwisse AK, Slijkerman DS, *et al.* Drug repositioning and repurposing: terminology and definitions in literature. *Drug Discov Today* 2015; 20: 1027–1034.
- 217. Pushpakom S, Iorio F, Eyers PA, et al. Drug repurposing: progress, challenges and recommendations. Nat Rev Drug Discov 2019; 18: 41–58.

- 218. Portaccio E, Fonderico M, Iaffaldano P, *et al.* Disease-modifying treatments and time to loss of ambulatory function in patients with primary progressive multiple sclerosis. *JAMA Neurol* 2022; 79: 869–878.
- 219. Dalakas MC. Advances in the diagnosis, pathogenesis and treatment of CIDP. *Nat Rev Neurol* 2011; 7: 507–517.
- 220. Köller H, Kieseier BC, Jander S, *et al.* Chronic inflammatory demyelinating polyneuropathy. *N Engl J Med* 2005; 352: 1343–1356.
- 221. Simkins TJ, Duncan GJ and Bourdette D. Chronic demyelination and axonal degeneration in multiple sclerosis: pathogenesis and therapeutic implications. *Curr Neurol Neurosci Rep* 2021; 21: 26.
- 222. EUCTR2017-005034-36-IT. Study evaluating the effect of rituximab in patients with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), https:// www.clinicaltrialsregister.eu/ctr-search/ search?query=eudract_number:2017-005034-36 (2020, accessed 1 June 2022).
- 223. Forsthuber TG, Cimbora DM, Ratchford JN, et al. B cell-based therapies in CNS autoimmunity: differentiating CD19 and CD20 as therapeutic targets. *Ther Adv Neurol Disord* 2018; 11: 1756286418761697.
- 224. Szili D, Cserhalmi M, Bankó Z, et al. Suppression of innate and adaptive B cell activation pathways by antibody coengagement of FcγRIIb and CD19. Mabs 2014; 6: 991–999.
- 225. Zhao Q. Bispecific antibodies for autoimmune and inflammatory diseases: clinical progress to date. *Biodrugs* 2020; 34: 111–119.
- 226. Dalakas MC. IgG4-mediated neurologic autoimmunities. *Neurol Neuroimmunol Neuroinflamm* 2022; 9: e1116.
- 227. Manso C, Querol L, Lleixà C, et al. Anti-Neurofascin-155 IgG4 antibodies prevent paranodal complex formation in vivo. J Clin Invest 2019; 129: 2222–2236.

Visit SAGE journals online journals.sagepub.com/ home/tan

SAGE journals