Role of B Cells in Multiple Sclerosis and Related Disorders

Giancarlo Comi, MD,[1] Amit Bar-Or, MD,[2] Hans Lassmann, MD,[3] Antonio Uccelli, MD,[4] Hans-Peter Hartung, MD,[5] Xavier Montalban, MD,[6] Per Solberg Sørensen, MD,[7] Reinhard Hohlfeld, MD,[8] and Stephen L. Hauser, MD,[9]

Expert Panel of the 27th Annual Meeting of the European Charcot Foundation

The success of clinical trials of selective B-cell depletion in patients with relapsing multiple sclerosis (MS) and primary progressive MS has led to a conceptual shift in the understanding of MS pathogenesis, away from the classical model in which T cells were the sole central actors and toward a more complex paradigm with B cells having an essential role in both the inflammatory and neurodegenerative components of the disease process. The role of B cells in MS was selected as the topic of the 27th Annual Meeting of the European Charcot Foundation. Results of the meeting are presented in this concise review, which recaps current concepts underlying the biology and therapeutic rationale behind B-cell–directed therapeutics in MS, and proposes strategies to optimize the use of existing anti–B-cell treatments and provide future directions for research in this area.

ANN NEUROL 2021;89:13–23

From November 21 to 23, 2019, the 27th Annual Meeting of the European Charcot Foundation was held in Baveno, Italy. "The role of B cells in multiple sclerosis (MS)" was selected as this year's theme. The meeting gathered 500 onsite delegates and provided an opportunity for scientists, clinicians, industry leaders, patients, and other health care experts to review existing evidence on the mechanisms of action of B cells in MS and other neuroinflammatory conditions such as neuromyelitis optica spectrum disorder (NMOSD), and discuss current and emerging therapeutic strategies of treatments targeting B cells.

The understanding of the role of B cells in MS has evolved substantially in recent years, shifting from the classical model (T cells being central players) to a mechanism in which the interplay between B and T cells is a central feature of the disease pathogenesis.[1] This shift was mostly driven by the success of clinical trials of selective B-cell depletion in patients with relapsing MS (RMS) and also primary progressive MS (PPMS), indicating that B cells are essential contributors to immune responses involved in MS. This changed the MS treatment landscape substantially; B-cell therapies represent a significant conceptual advance in treating all forms of MS and in understanding the biology of this complex disease and will hopefully lead to development of even more selective, effective, and safe therapeutics.

A wide range of topics were discussed at the meeting, including but not limited to the role of intrathecal

View this article online at wileyonlinelibrary.com. DOI: 10.1002/ana.25927

Received Jul 3, 2020, and in revised form Oct 5, 2020. Accepted for publication Oct 5, 2020.

Address correspondence to Dr Comi, Institute of Experimental Neurology, Ospedale San Raffaele, Via Olgettina 48, 20132 Milan, Italy. E-mail: comi.giancarlo@hsr.it

From the [1]Institute of Experimental Neurology, San Raffaele Hospital, Milan, Italy; [2]Department of Neurology, Center for Neuroinflammation and Neurotherapeutics, University of Pennsylvania, Philadelphia, PA; [3]Department of Neuroimmunology (Center for Brain Research), University Hospital Vienna, Vienna, Austria; [4]Department of Neuroscience, Genetic Ophthalmology, and Infant Maternity Science, San Martino Polyclinic Hospital, Genoa, Italy; [5]Department of Neurology, Medical Faculty, Heinrich Heine University Düsseldorf, Düsseldorf, Germany; [6]Neurology-Neuroimmunology Department and Neurorehabilitation Unit, Multiple Sclerosis Center of Catalonia, Vall d'Hebron Barcelona Hospital Campus, Barcelona, Spain; [7]Department of Neurology, Danish Multiple Sclerosis Center, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark; [8]Institute of Clinical Neuroimmunology, Ludwig Maximilians University of Munich and Munich Cluster for Systems Neurology (SyNergy), Munich, Germany; and [9]Department of Neurology, UCSF Weill Institute for Neurosciences, University of California, San Francisco, San Francisco, CA

Additional supporting information can be found in the online version of this article.

antibodies in demyelinating diseases, therapeutic experience with anti-CD20 monoclonal antibodies, approaches to monitor efficacy, and safety of B-cell–directed therapies. This concise review recaps current concepts underlying the biology and therapeutic rationale behind B-cell–directed therapeutics in MS and proposes future directions that could impact today's unmet need, preventing and treating MS progression.

Impact of B Cells on the Pathophysiology of MS

B Cells as Immunomodulators in MS

Though T cells are widely considered to be major contributors to inflammatory demyelination in MS, growing evidence suggests a significant role for B cells in disease pathogenesis. Both antibody-dependent and antibody-independent mechanisms are thought to underlie B-cell–mediated central nervous system (CNS) injury in MS. In addition to antibody secretion by plasmablasts and plasma cells, B-cell functions implicated in pathogenesis include (1) antigen presentation to T cells and driving autoproliferation of brain-homing T cells (presumably by memory B cells), (2) production of proinflammatory cytokines and chemokines that propagate inflammation, (3) production of soluble toxic factors contributing to oligodendrocyte and neuronal injury, (4) contribution to the formation of ectopic lymphoid aggregates in the meninges, and (5) providing a reservoir for Epstein–Barr virus (EBV) infection.[2–6] These B-cell actions may contribute to both MS relapses and disease progression.

The importance of B cells in MS is underscored through clinical trials revealing that anti-CD20 monoclonal antibodies are highly effective in limiting new relapsing disease activity.[7–10] Of note, this therapy does not directly target plasma cells, nor does it appear to significantly impact the abnormal cerebrospinal fluid (CSF) antibody profile.[7] Peripheral B cells of MS patients exhibit aberrant proinflammatory cytokine responses, including exaggerated lymphotoxin-α, tumor necrosis factor α, interleukin (IL)-6, and granulocyte-macrophage colony–stimulating factor secretion. B-cell depletion results in significantly diminished proinflammatory responses of CD4+ and CD8+ T cells, as well as myeloid cells.[11,12] It is noteworthy that a small proportion of circulating T cells express CD20, and these are also depleted with anti-CD20 therapy; however, because anti-CD19 therapy also seemed effective in MS, the robust effects of anti-CD20 in MS are not likely to be exclusively mediated by removal of CD20-expressing T cells.[13]

In addition, B cells have the capacity to produce anti-inflammatory cytokines such as transforming growth factor β1, IL-35, and IL-10.[1] In mice with experimental autoimmune encephalomyelitis (EAE), gut-derived immunoglobulin A (IgA) + B cells are mobilized to the CNS, where they attenuate neuroinflammation through expression of IL-10.[14] Studies in MS patients indicate that their B cells are deficient in IL-10 production compared to healthy controls, which may imply that B cells of patients are less capable of downregulating immune responses. Consistent with such a role, MS patients who are infected with parasites harbor higher frequencies of IL-10–expressing B cells and appear to have less disease activity than uninfected MS patients.[14]

B-Cell Trafficking in the CNS

Molecular analysis of B-cell populations in the CNS and periphery of MS patients points to bidirectional trafficking of B cells. Relatively little is known about the molecular mechanisms that underlie human B-cell migration into, and retention within, the CNS.[3,15] ex vivo studies found that B-cell migration across the blood–brain barrier (BBB) endothelial cells is significantly inhibited by blocking antibodies to the adhesion molecules intercellular adhesion molecule-1 and leukocyte very late antigen-4 (VLA-4).[16,17] Activated leukocyte cell adhesion molecule (ALCAM; CD166) on human and mouse brain endothelial cells has also been assigned a role in transmigration across the BBB. ALCAM promotes the recruitment of proinflammatory B cells across the BBB and blood–meningeal barrier. Blocking ALCAM reduced disease severity in animals affected by a B-cell–dependent form of EAE, and the proportion of ALCAM+ B cells was increased in the peripheral blood and within brain lesions of MS patients.[18]

These mechanisms raise the prospect of novel therapeutic targets for limiting CNS B-cell infiltration and could predict how therapies currently developed to target T-cell migration, such as anti–VLA-4 antibodies, may impact B-cell trafficking. B-cell retention within the chronically inflamed CNS may be mediated by both immune and brain cells. For example, Th17 cells known to be present in the CNS of both MS patients and EAE models have been shown to induce robust tertiary lymphoid tissue formation within the brain meninges in EAE, where these B-cell–rich immune aggregates were associated with local demyelination.[19] Activated glial cells (such as astrocytes) within the inflamed MS CNS may also secret factors that support B-cell survival and persistence within the CNS.[20,21]

B Cells in the MS CNS Compartment

Neuropathological studies provided evidence for a significant contribution of B cells in the CNS of MS patients. B

cells in the inflammatory infiltrates are more abundant in MS—particularly in patients with active disease—in comparison to other inflammatory brain diseases. B cells are mainly located in the meninges and in the large perivascular spaces around the cerebral ventricles. In early and active lesions, CD20+ B cells dominate and may have proinflammatory functions, whereas at later stages plasma cells with possible anti-inflammatory functions increase in number.[22]

Within the brain, there is a local production of cytokines, which support homing, survival, and functional activation of B cells.[23] The intrathecal production of these cytokines is stimulated by the proinflammatory environment in the MS lesion, and their action is controlled by shedding of their receptors (B-cell maturation antigen, transmembrane activator, and CAML interactor [TACI]) from the surface of B cells by gamma-secretase.[20] Shed survival receptors, liberated into the CSF, may become promising biomarkers for disease activity.[24]

Prominent B-cell–rich inflammatory aggregates with features of tertiary lymph follicles reside in the meninges of MS patients, and especially within deep cortical sulci. Their abundance correlates with the amount and size of cortical lesions, with the degree of neurodegeneration in the cortex, and with the accrual of disability.[25,26] Meningeal infiltrates are the source of cytokines and chemokines in the CSF and correlate topographically with the presence and size of cortical lesions, the degree of neurodegeneration in the cortex, and the liberation of neurofilament light (NFL) protein into the CSF, which is an established biomarker for neurodegeneration.[27,28]

To date, meningeal inflammation can be detected—at least in part—by high-resolution magnetic resonance imaging (MRI), because it is associated with blood–meningeal barrier impairment, visualized by gadolinium enhancement. Through direct correlation between MRI and pathology, it was shown that meningeal enhancement is associated with inflammation and the presence of cortical lesions.[29] Similarly, in EAE mouse models meningeal enhancement discloses areas of meningeal inflammation.[30] Some data describe an association between meningeal enhancement in MRI and the degree of cortical atrophy, but this has to be validated in larger patient cohorts.[31]

Autoantibody Involvement in MS and NMOSD

The importance of antibody-producing B cells and the potential role of autoantibodies in MS have been a topic of interest for many years. The establishment of reliable biomarkers for diagnosis, prognosis, and treatment of MS has proven to be very difficult. Autoantibodies are formed against different CNS cell types, including neurons, oligodendrocytes, astrocytes, and even immune cells; however, none of them has been validated so far for clinical use in MS.[32,33]

Many active MS lesions are characterized by deposition of IgG and activated complement products.[34] Oligoclonal IgG bands (OCBs) are clonally expanded antibodies produced intrathecally and one of the few biomarkers in CSF included in the diagnostic criteria of MS.[35] Their presence remains relatively stable over time, although it has been shown that some therapeutic interventions could mildly affect OCB production.[36,37] OCBs as well as the presence of intrathecal IgM synthesis have some prognostic value in MS at the time of diagnosis.[38–42] Some OCB antibodies recognize conformational epitopes of ubiquitous intracellular proteins, indicating that part of the OCB response may occur secondary to tissue damage.[43] OCB production and expanded intrathecal plasmablast clones can be observed even at the earliest prodromal stages of MS, as revealed in MS-discordant monozygotic twin pairs, where the clinically unaffected cotwin may show CSF changes of "subclinical neuroinflammation."[44]

In addition to identifying relevant target antigens of B-cell and antibody responses in MS, understanding the repertoire of pathogenic B cells and how they differentiate, as well as their location in the CNS and peripheral immune system, has become a central issue in MS pathogenesis.[45] Some immunophenotyping studies have focused on alterations in composition of B-cell subsets. Rituximab in rheumatoid arthritis (RA), for example, effectively depletes B cells and skews the B-cell compartment. Repopulation occurred mainly with naive mature and immature B cells. Patients whose RA relapsed on return of B cells tended to show repopulation with higher numbers of memory B cells.[46–48] In patients with MS, restoration of regulatory B cells was observed following cladribine and alemtuzumab treatment, suggesting that these cells might serve as surrogate markers for disease activity.[49,50] However, these are preliminary findings that will require confirmation. Standardized multisite cytomics data could provide further understanding of treatment impact on MS immunophenotype and pave the way toward monitoring B cells to personalize treatment.[51]

Pathogenic Autoantibodies

Several approaches for antigen-hunting in MS have been conducted. Antibodies such as aquaporin 4 (AQP4) and myelin oligodendrocyte glycoprotein (MOG) have helped to classify and define subgroups previously included under the umbrella of MS but that are now identified as distinct diseases with different prognostic and therapeutic implications (Table 1).[54] Despite the vast effort that has been expended over the past decades in the field, the pursuit for the antigen(s) in MS is still open.

TABLE 1. Clinical Spectrum of Demyelinating Diseases

Characteristic	MS CNS-Directed T cells, B cells	AQP4-Ab+ CNS-Directed Ab	MOG-Ab+ CNS-Directed Ab
Target	Myelin?	Water channel expressed on astrocytes	Surface of oligodendrocytes and myelin in CNS
Clinical presentation	Brain, short TM, ON; chronic progressive	NMO, ON, LETM; relapsing	ON, TM, ADEM, cortical encephalitis; monophasic or relapsing
Onset age, yr	20–50	30–60	10–40
OCB positivity	>90%	11–20%	0–11%
CSF cell count[52]	Mononuclear +/−, polymorphonuclear −	Mononuclear ++, polymorphonuclear +	Mononuclear +, polymorphonuclear +/−
CSF protein	−	+	++
Cytokine profile[52]	IFNγ −, IL-6 −, IL-2 +++	IFNγ −, IL-6 +++, IL-2 −	IFNγ +, IL-6 +++, IL-10 −
Presence of MOG-IgG Ab[53]	3–10%; more frequent in children	Very rare	Yes
Presence of AQP4-IgG Ab[53]	Very rare	Yes	Very rare
Pathological features[34]	Confluent demyelination pattern; CD8+ dominant, complement activation, axonal injury	Edema, necrosis, AQP4 and GFAP loss, complement	Perivenous demyelination, CD4+ dominant, no complement deposition, cortical demyelination

Ab = antibody; ADEM = acute disseminated encephalomyelitis; AQP4 = aquaporin 4; CNS = central nervous system; CSF = cerebrospinal fluid; GFAP = glial fibrillary acidic protein; IFNγ = interferon gamma; Ig = immunoglobulin; IL = interleukin; LETM = longitudinally extensive transverse myelitis; MOG = myelin oligodendrocyte glycoprotein; MS = multiple sclerosis; NMO = neuromyelitis optica; OCB = oligoclonal band; ON = optic neuritis; TM = transverse myelitis.

The binding of pathogenic AQP4-specific autoantibodies to astrocytes is a key event in the formation of neuromyelitis optica (NMO) lesions. This has been well documented in animal models, and is supported by the pathology of NMO in humans.[55–57] NMO is an inflammatory demyelinating disease of the CNS caused by binding of pathogenic IgG autoantibodies to AQP4. Astrocyte damage and downstream inflammation require NMO-IgG effector function to initiate complement-dependent cytotoxicity (CDC) and antibody-dependent cell-mediated cytotoxicity (ADCC).[58–60] The discovery of AQP4 as a biomarker marked a breakthrough in the understanding of the pathogenesis of the disease.

MOG is expressed on the outermost layer of CNS myelin sheaths and on the extracellular surface of oligodendrocytes.[61] Although the pathogenic role of anti-MOG antibodies in EAE is undisputed, the exact role of anti-MOG antibodies in MS patients has been controversially discussed over decades.[33] It has been shown that myelin-specific MS antibodies cause oligodendrocyte loss and demyelination in organotypic cerebellar slices and display seminal features of active MS lesions. Myelin-specific antibodies may play an active role in MS lesion formation through CDC mechanisms.[62,63] Typical MS cases are largely anti-MOG negative.[64,65] In a small trial, initial detection of serum anti-MOG and anti–myelin basic protein antibodies has been shown to be correlated with early conversion from clinically isolated syndrome to definite MS.[66] Analysis of pathogenic antibodies could thereby be of value to estimate individual risk of early relapse. However, the association between anti-MOG antibodies and progression to MS has not been reproduced in other trials.[67]

With the use of different cell-based immunoassays more recently,[68] anti-MOG antibodies could be identified in a subset of inflammatory demyelinating diseases of the CNS clinically and pathologically distinct from MS and AQP4 antibody seropositive NMOSD, defined

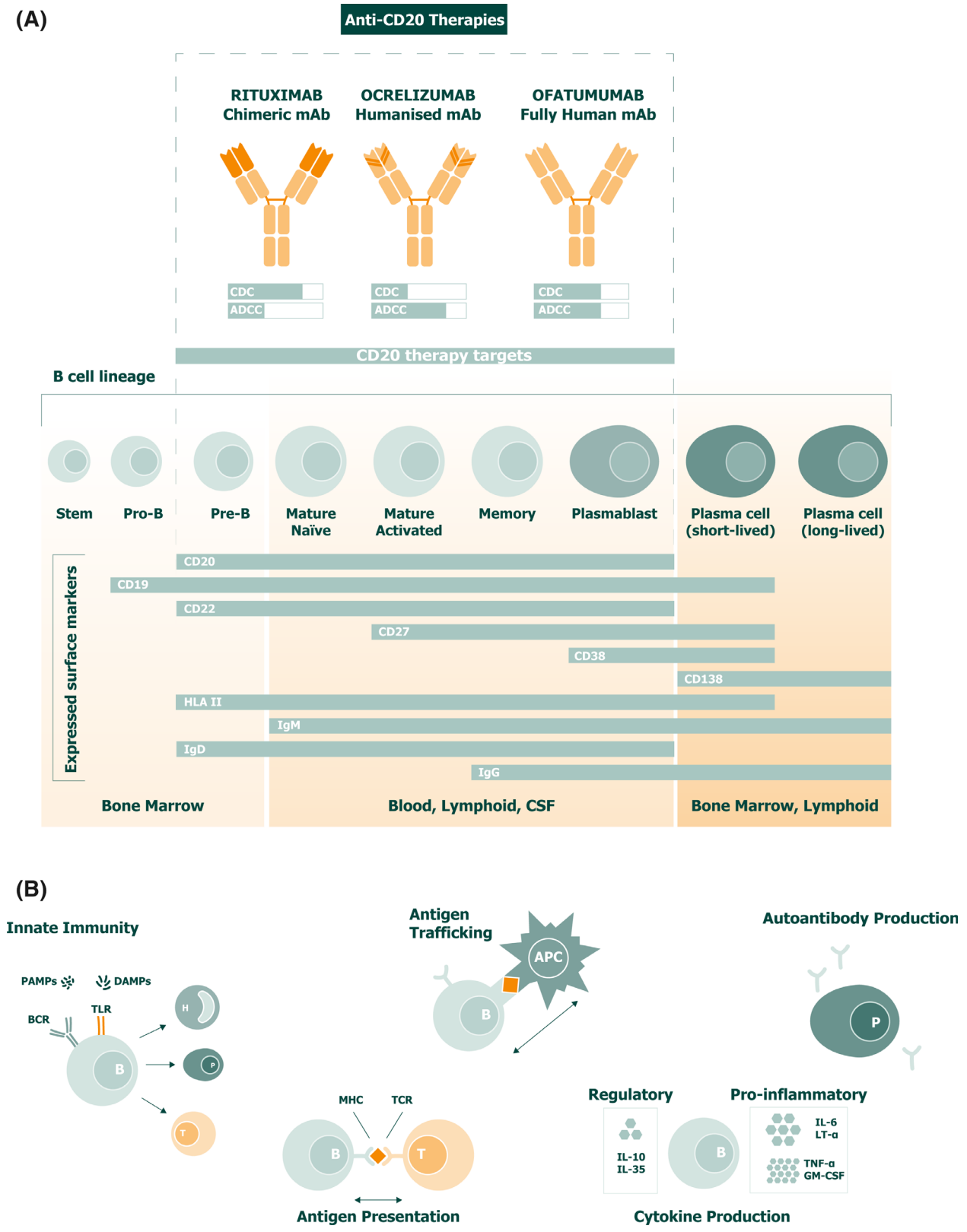

FIGURE: Anti-CD20 monoclonal antibodies: mechanisms of action and maturation stages. ADCC = antibody-dependent cell-mediated toxicity; APC = antigen-presenting cell; BCR = B-cell receptor; CDC = complement-dependent cytotoxicity; CSF = cerebrospinal fluid; DAMP = damage-associated molecular pattern molecule; GM-CSF = granulocyte-macrophage colony–stimulating factor; HLA = human leukocyte antigen; Ig = immunoglobulin; IL = interleukin; LT = lymphotoxin; mAb = monoclonal antibody; MHC = major histocompatibility complex; PAMP = pathogen-associated molecular pattern molecule; TCR = T-cell receptor; TLR = Toll-like receptor; TNF = tumor necrosis factor.

TABLE 2. B-Cell–Targeted Therapies in MS

	Mechanism of Action	Compound	Structure and Route of Administration	Efficacy	Development Status in MS
RMS	Anti-CD20 monoclonal antibodies	Rituximab	Chimeric; IV	High efficacy in the phase 2 HERMES trial[7]	Phase 2; used off-label in MS
		Ocrelizumab	Humanized; IV	High efficacy in the phase 3 OPERA I and II trials[9,75,76]	Approved for RMS
		Ofatumumab	Human; SC	Phase 2 MIRROR[77]; phase 3 ASCLEPIOS I and II[78]	Phase 3 finished; pending approval by agencies
		Ublituximab	Chimeric/ glycoengineered; IV	Phase 2[74]	Phase 3 (ULTIMATE I and II) underway
	BTK inhibitor	Evobrutinib	Oral	Phase 2[79]	Phase 2; phase 3 underway
PPMS	Anti-CD20 monoclonal antibodies	Ocrelizumab	Humanized, IV	ORATORIO[10]	Approved for PPMS

BTK = Bruton tyrosine kinase; IV = intravenous; MS = multiple sclerosis; PPMS = primary progressive MS; RMS = relapsing MS; SC = subcutaneous.

as MOG antibody–associated disorder (MOGAD). MOGAD phenotypes are varied and range from classical NMO to acute disseminated encephalomyelitis and cortical encephalitis.[69–71] The diagnosis depends on using a reliable, specific, and sensitive assay of the antibody.[72] Clinical and imaging features of MOG-associated syndromes overlap with AQP4 antibody NMOSD but can usually be distinguished from MS; in particular, the silent lesions typical of MS that progressively increase lesion volume are rare in MOGAD.[73]

Therapeutic Depletion of B Cells in MS

Different therapeutic approaches are under investigation aiming to improve prognosis, prevent relapse, and minimize the extent of disability. Most MS therapies alter the frequency, phenotype, or homing of B cells in one way or another.

Treatment of RMS

CD20 is a transmembrane ion channel protein expressed on the surface of premature, immature, mature, and memory B cells. Several anti-CD20 monoclonal antibodies, each reacting with different epitopes of CD20, have been developed for RMS treatment, including rituximab, ocrelizumab, ublituximab, and ofatumumab, which are further detailed in Table 2 and the Figure. Anti-CD20 antibodies spare plasma cells (which do not express CD20), and their critical therapeutic target in MS are thought to be memory B cells.[80] In contrast, atacicept, a recombinant fusion protein of the extracellular domain of TACI and the human IgG1 Fc domain (TACI-Ig) does target plasma cells, although it tends to spare memory B cells. Of note, atacicept treatment resulted in dose-dependent exacerbations of MS disease activity, which may reflect its limited impact on proinflammatory memory B cells and potentially the removal of anti-inflammatory plasma cells.[81]

Administration of rituximab markedly reduced MRI evidence of MS disease activity and diminished the clinical relapse rate.[7] Ocrelizumab, a newer humanized anti-CD20 monoclonal antibody, was approved by the US Food and Drug Administration in March 2017 after the pivotal OPERA trials revealed dramatic effects on all key clinical and MRI outcomes versus interferon β1a in RMS.[9] Ofatumumab, a fully human anti-CD20 monoclonal antibody administered by subcutaneous injection at home, recently completed successful clinical trials in RMS.[78] Phase 3 testing of ublituximab, another anti-CD20, in RMS is currently in progress.

Anti-CD20 therapies rapidly and almost completely deplete circulating CD20+ B cells but have only limited effects in secondary lymphoid organs. Because the CD20 antigen is absent on the earliest B-cell precursors, stem cells, and pro-B cells in the bone marrow, and also on plasmablasts and plasma cells responsible for immunoglobulin production, B-cell repletion and pre-existing humoral immunity are largely preserved. These factors likely account for the favorable overall safety profile of anti-CD20

monotherapy. Anti-CD20 monoclonal antibodies cross the BBB poorly; they do partially reduce B-cell numbers in the CSF, although without a detectable effect observed so far on CSF IgG synthesis or OCBs.[82] Small-molecule therapies are being explored for their B-cell modulatory actions and could be beneficial due to higher BBB penetration and higher flexibility in treatment initiation and discontinuation. Reduction in enhancing lesions with evobrutinib, a Bruton tyrosine kinase (BTK) inhibitor, has recently been shown in a phase 2 trial.[79]

Treatment of Progressive MS

PPMS, which affects 10 to 15% of MS patients, has been a notoriously difficult form of MS to recognize and to treat.[83–88] Rituximab was tested in PPMS patients in the phase 2/3 OLYMPUS trial and failed to meet the primary endpoint; however, the trial may have been underpowered, and a positive trend was evident; subgroup analyses suggested that younger patients, particularly those with inflammatory lesions, may have responded favorably.[89] These results provided the rationale for the investigation of ocrelizumab in PPMS in the phase 3 ORATORIO trial. This was the first trial to show positive results in PPMS, persisting over a duration of up to 6.5 years in open-label extension observations, albeit with modestly favorable effects on the primary endpoint.[10,90] No evidence of progression, a novel composite endpoint tested post hoc, was also achieved more frequently in patients treated with ocrelizumab compared to placebo patients.[91] Ocrelizumab is the first and only approved treatment for PPMS and recommended as first-line therapy in the European Committee for Treatment and Research in Multiple Sclerosis–European Academy of Neurology guideline.[92] Nonetheless, the need for more effective therapies in PPMS remains.

A pilot trial with intrathecal rituximab in progressive MS did not show a convincing effect on the clinical course of MS or CSF biomarkers, including NFL.[93] Treatment was well tolerated but not without risks; a case of low-virulent bacterial meningitis was reported.

B-Cell Therapy in Pediatric MS

Pediatric MS is characterized by more prominent inflammatory activity but better capability to compensate for brain damage. Therefore, it should be treated early and efficiently.[94] A considerable experience with rituximab exists in many immune-mediated disorders of children and adolescents. Rituximab has also been found effective in open-label trials in pediatric patients with MS.[95,96] Clinical data with ocrelizumab and ofatumumab in children/adolescents are still lacking. Anti-CD20 therapy may represent an attractive option in pediatric MS, but safety issues such as the still incompletely known potential long-term risks should be kept in mind.

Monitoring of B Cells

Studies in experimental animal models reveal that anti-CD20 therapy efficiently depletes peripheral B cells, whereas a subset of CD27+ B cells persist in secondary lymphoid organs.[97] B-cell repletion starts in bone marrow and spleen, followed by blood. The reappearing B cells in animals possess an enhanced capacity to recognize and present autoantigen. Of interest is whether monitoring B cells, in particular memory B cells, in the peripheral blood of MS patients may be useful for assessing the individual benefit–risk of therapy and personalizing treatment accordingly. High inter- and intraindividual variability in B-cell repopulation is seen after anti-CD20 depletion therapy in patients, and repopulation of memory B cells is not proportional to repopulation of CD19+ cells. In NMO, monitoring CD19+ CD27+ memory B cells (instead of total B-cell counts) has been found to be a more reliable marker for relapses, although cutoffs to identify early repopulators are not yet validated, and the extent to which such an approach may be relevant to MS remains to be defined.[98] It is also possible that the beneficial effects of anti-CD20 on clinical and MRI disease activity persist for some time even after B-cell repletion occurs.[7,99] Until more is known about the pharmacodynamics of the various anti-CD20 therapies, as an initial schedule, adherence to the dosing regimens used in the clinical trials seems prudent.

Monitoring CD4+ T cells after depletion therapy in RA patients showed a correlation between clinical improvement and CD4+ count decrease.[100] This could be explained by memory B-cell–driven autoproliferation of CD4+ T cells.[101]

Conclusions and Future Perspectives

The demonstration that B cells play a central role in MS pathogenesis led directly to the discovery that their depletion in peripheral blood is a highly successful therapeutic strategy.[102] Nonetheless, several important questions and challenges exist regarding the role of B cells in MS and the optimal clinical approach to treatment.

Depletion of B cells by anti-CD20 antibodies is mediated through several molecular mechanisms, including CDC, ADCC, and antibody-dependent cellular phagocytosis.[103] B-cell depletion produces outstanding control of clinical relapses and focal inflammatory MS disease activity, but benefits against progressive MS are only partial. This could be due to inefficient depletion of CNS B-cell populations, especially in progressive MS, due to CNS compartmentalization of the B-cell response in progressive disease and inefficient transit of anti-CD20 monoclonal antibodies across the BBB. In this regard OCBs in

CSF, which are believed to be secreted by long-lived plasma cells that do not express CD20, also appear to be largely unaffected by B-cell–depleting interventions.[82]

The extent and duration of optimal depletion is not yet fully known but is likely to be partial and depends on the type of anti-CD20 therapy (different CDC or ADCC activities) and dose in combination with individual host factors such as genetics. Lymph node B cells are not fully depleted by anti-CD20 therapy, and this could also provide an ongoing source of peripherally maintained disease activity. Uncertainties regarding the application of anti-CD20 therapies in medical practice include when to initiate treatment (early treatment might be more effective) and optimal dosing as well as duration (development of biomarkers to guide the need for continued therapy).

In addition, postmarketing surveillance is essential to fully uncover the effects on long-term disability and safety and will be essential to help position anti-CD20 therapies within the greater context of available MS disease-modifying therapies. The generally favorable safety profile of anti-CD20 therapy likely results from the large B-cell reservoir remaining even after repeated and chronic administration. Nevertheless, the long-term risk of infection or other adverse outcomes remains an important consideration, given the profound and sustained depletion of circulating B cells that is the hallmark of these agents.

Although therapies that target humoral immune system cells more broadly than anti-CD20 could possibly offer a higher level of efficacy, especially against progression, a less favorable safety profile could be a consequence, due to a greater degree of elimination of noncirculating B cells, depletion of earlier precursors in the bone marrow, or reducing antibody-producing plasma cells. Small molecules that target B-cell signaling (through BTK, PI3 kinase, or Janus kinases), the proteasome involved in plasma cell differentiation, or EBV, which infects B cells and is believed to be involved in MS etiology, may provide novel mechanisms to target B cells, increase the therapeutic effect, and better clarify the humoral immune pathogenesis of MS.

Acknowledgment

We thank N. Kim for editorial and graphical assistance, which was funded by the European Charcot Foundation, a nonprofit foundation and organizer of the 27th Annual Meeting at Baveno, Italy, which was sponsored by Biogen, Celgene, MedDay, Merck, Novartis, Roche, Sanofi Genzyme, and Teva.

Author Contributions

All authors wrote or critically reviewed the manuscript, including data acquisition, analysis, and creating the figure, and approved the final version. Members of the Expert Panel of the 27th European Charcot Foundation Annual Meeting who are not authors are listed with their institutional affiliations in the supplementary online table.

Potential Conflicts of Interest

The following companies are involved in MS drug development: Actelion (Ac), Alexion (Al), Annexon (An), Atara Bio (AB), Bayer (Ba), Biogen (Bi), Bionure (Bn), Celgene/BMS (Ce), Forward Pharma (FP), GeNeuro (GN), GlaxoSmithKline (GS), Janssen/Johnson-Johnson (JJ), MedDay Pharmaceuticals (MP), Merck (Me), Molecular Stethoscope (Mo), NervGen (NG), Neurona Therapeutics (Ne), Novartis (No), Octapharma (Oa), Roche/Genentech (Ro), Sanofi/Genzyme (Sa), Teva (Te), TG Therapeutics (TG), and Viela Bio (VB). G.C. has received personal compensation for consulting and speaking fees from No, Te, Sa, Me, Ce, Bi, Ro, FP, MP, and Excemed. A.B.-O. has served on scientific advisory boards for AB, Bi, Ce, JJ, Me, No, Ro, and Sa, and has sponsored research agreements with Bi, Me, No, and Ro. H.L. has received honoraria for lectures from No, Bi, Sa, Me, Ro, and MP. A.U. has received consultancy fees from Bi, Sa, Me, No, Ro, and Te and research support from Bi, Me, and No. H.-P.H. has received fees for serving on steering committees, data monitoring committees, and scientific advisory boards from Ba, Bi, Ce, GN, Me, No, Oa, Ro, Sa, Te, TG, and VB with approval by the Rector of Heinrich Heine University. X.M. has received speaking honoraria and travel expenses for scientific meetings, has been a steering committee member of clinical trials, or has participated on advisory boards of clinical trials in the past 3 years with Ac, Al, Ba, Bi, Ce, Me, Excemed, Sa, MP, Multiple Sclerosis International Federation, NG, National Multiple Sclerosis Society, No, Ro, Te, and TG. P.S.S. has received personal compensation for serving on scientific advisory boards, steering committees, or independent data monitoring committees or speaker honoraria from Bi, Me, No, Te, GS, and Ce. R.H. has received honoraria and grant support from No, Sa, Bi, Te, Me, JJ, and Ro. S.L.-H. currently serves on the scientific advisory board of Symbiotix, An, Bn, and Mo and on the board of trustees of Ne. S.L.H. also has received travel reimbursement and writing assistance from Ro and No for CD20-related meetings and presentations.

References

1. Li R, Patterson KR, Bar-Or A. Reassessing B cell contributions in multiple sclerosis. Nat Immunol 2018;19:696–707.
2. van Sechel AC, Bajramovic JJ, van Stipdonk MJ, et al. EBV-induced expression and HLA-DR-restricted presentation by human B cells of

alpha B-crystallin, a candidate autoantigen in multiple sclerosis. J Immunol 1999;162:129–135.

3. Palanichamy A, Apeltsin L, Kuo TC, et al. Immunoglobulin class-switched B cells form an active immune axis between CNS and periphery in multiple sclerosis. Sci Transl Med 2014;6:248ra106.
4. Lisak RP, Nedelkoska L, Benjamins JA, et al. B cells from patients with multiple sclerosis induce cell death via apoptosis in neurons in vitro. J Neuroimmunol 2017;309:88–99.
5. Lisak RP, Benjamins JA, Nedelkoska L, et al. Secretory products of multiple sclerosis B cells are cytotoxic to oligodendroglia in vitro. J Neuroimmunol 2012;246:85–95.
6. Serafini B, Rosicarelli B, Franciotta D, et al. Dysregulated Epstein-Barr virus infection in the multiple sclerosis brain. J Exp Med 2007; 204:2899–2912.
7. Hauser SL, Waubant E, Arnold DL, et al. B-cell depletion with rituximab in relapsing-remitting multiple sclerosis. N Engl J Med 2008;358:676–688.
8. Salzer J, Svenningsson R, Alping P, et al. Rituximab in multiple sclerosis: a retrospective observational study on safety and efficacy. Neurology 2016;87:2074–2081.
9. Hauser SL, Bar-Or A, Comi G, et al. Ocrelizumab versus interferon Beta-1a in relapsing multiple sclerosis. N Engl J Med 2017;376: 221–234.
10. Montalban X, Hauser SL, Kappos L, et al. Ocrelizumab versus placebo in primary progressive multiple sclerosis. N Engl J Med 2017; 376:209–220.
11. Bar-Or A, Fawaz L, Fan B, et al. Abnormal B-cell cytokine responses a trigger of T-cell-mediated disease in MS? Ann Neurol 2010;67: 452–461.
12. Li R, Rezk A, Miyazaki Y, et al. Proinflammatory GM-CSF-producing B cells in multiple sclerosis and B cell depletion therapy. Sci Transl Med 2015;7:310ra166.
13. Sabatino JJ Jr, Wilson MR, Calabresi PA, et al. Anti-CD20 therapy depletes activated myelin-specific CD8(+) T cells in multiple sclerosis. Proc Natl Acad Sci U S A 2019;116:25800–25807.
14. Correale J, Farez M, Razzitte G. Helminth infections associated with multiple sclerosis induce regulatory B cells. Ann Neurol 2008;64: 187–199.
15. Stern JNH, Yaari G, Vander Heiden JA, et al. B cells populating the multiple sclerosis brain mature in the draining cervical lymph nodes. Sci Transl Med 2014;6:248ra107.
16. Alter A, Duddy M, Hebert S, et al. Determinants of human B cell migration across brain endothelial cells. J Immunol 2003;170: 4497–1505.
17. Bar-Or A, Nuttall RK, Duddy M, et al. Analyses of all matrix metalloproteinase members in leukocytes emphasize monocytes as major inflammatory mediators in multiple sclerosis. Brain 2003;126: 2738–2749.
18. Michel L, Grasmuck C, Charabati M, et al. Activated leukocyte cell adhesion molecule regulates B lymphocyte migration across central nervous system barriers. Sci Transl Med 2019;11:eaaw0475.
19. Pikor NB, Astarita JL, Summers-Deluca L, et al. Integration of Th17- and lymphotoxin-derived signals initiates meningeal-resident stromal cell remodeling to propagate neuroinflammation. Immunity 2015;43:1160–1173.
20. Krumbholz M, Theil D, Derfuss T, et al. BAFF is produced by astrocytes and up-regulated in multiple sclerosis lesions and primary central nervous system lymphoma. J Exp Med 2005;201:195–200.
21. Touil H, Kobert A, Lebeurrier N, et al. Human central nervous system astrocytes support survival and activation of B cells: implications for MS pathogenesis. J Neuroinflammation 2018;15:114.
22. Machado-Santos J, Saji E, Tröscher AR, et al. The compartmentalized inflammatory response in the multiple sclerosis brain is composed of tissue-resident CD8+ T lymphocytes and B cells. Brain 2018;141:2066–2082.
23. Meinl E, Krumbholz M, Hohlfeld R. B lineage cells in the inflammatory central nervous system environment: migration, maintenance, local antibody production, and therapeutic modulation. Ann Neurol 2006;59:880–892.
24. Thaler FS, Laurent SA, Huber M, et al. Soluble TACI and soluble BCMA as biomarkers in primary central nervous system lymphoma. Neuro Oncol 2017;19:1618–1627.
25. Aloisi F, Pujol-Borrell R. Lymphoid neogenesis in chronic inflammatory diseases. Nat Rev Immunol 2006;6:205–217.
26. Magliozzi R, Howell O, Vora A, et al. Meningeal B-cell follicles in secondary progressive multiple sclerosis associate with early onset of disease and severe cortical pathology. Brain 2007;130: 1089–1104.
27. Magliozzi R, Hametner S, Facchiano F, et al. Iron homeostasis, complement, and coagulation cascade as CSF signature of cortical lesions in early multiple sclerosis. Ann Clin Transl Neurol 2019;6: 2150–2163.
28. Magliozzi R, Howell OW, Nicholas R, et al. Inflammatory intrathecal profiles and cortical damage in multiple sclerosis. Ann Neurol 2018; 83:739–755.
29. Absinta M, Vuolo L, Rao A, et al. Gadolinium-based MRI characterization of leptomeningeal inflammation in multiple sclerosis. Neurology 2015;85:18–28.
30. Pol S, Schweser F, Bertolino N, et al. Characterization of leptomeningeal inflammation in rodent experimental autoimmune encephalomyelitis (EAE) model of multiple sclerosis. Exp Neurol 2019;314:82–90.
31. Absinta M, Reich DS. Imaging of meningeal inflammation should become part of the routine MRI protocol—yes. Mult Scler 2019;25: 330–331.
32. Fraussen J, Claes N, de Bock L, Somers V. Targets of the humoral autoimmune response in multiple sclerosis. Autoimmun Rev 2014; 13:1126–1137.
33. Hohlfeld R, Dornmair K, Meinl E, Wekerle H. The search for the target antigens of multiple sclerosis, part 2: CD8+ T cells, B cells, and antibodies in the focus of reverse-translational research. Lancet Neurol 2016;15:317–331.
34. Lucchinetti C, Brück W, Parisi J, et al. Heterogeneity of multiple sclerosis lesions: implications for the pathogenesis of demyelination. Ann Neurol 2000;47:707–717.
35. Obermeier B, Mentele R, Malotka J, et al. Matching of oligoclonal immunoglobulin transcriptomes and proteomes of cerebrospinal fluid in multiple sclerosis. Nat Med 2008;14:688–693.
36. Larsson D, Åkerfeldt T, Carlson K, Burman J. Intrathecal immunoglobulins and neurofilament light after autologous haematopoietic stem cell transplantation for multiple sclerosis. Mult Scler 2019;26: 1352458519863983.
37. Rejdak K, Stelmasiak Z, Grieb P. Cladribine induces long lasting oligoclonal bands disappearance in relapsing multiple sclerosis patients: 10-year observational study. Mult Scler Relat Disord 2019; 27:117–120.
38. Farina G, Magliozzi R, Pitteri M, et al. Increased cortical lesion load and intrathecal inflammation is associated with oligoclonal bands in multiple sclerosis patients: a combined CSF and MRI study. J Neuroinflammation 2017;14:40.
39. Kuhle J, Disanto G, Dobson R, et al. Conversion from clinically isolated syndrome to multiple sclerosis: a large multicentre study. Mult Scler 2015;21:1013–1024.
40. Villar LM, Masjuan J, González-Porqué P, et al. Intrathecal IgM synthesis is a prognostic factor in multiple sclerosis. Ann Neurol 2003; 53:222–226.

41. Pfuhl C, Grittner U, Gieß RM, et al. Intrathecal IgM production is a strong risk factor for early conversion to multiple sclerosis. Neurology 2019;93:e1439–e1451.
42. Casanova B, Lacruz L, Villar ML, et al. Different clinical response to interferon beta and glatiramer acetate related to the presence of oligoclonal IgM bands in CSF in multiple sclerosis patients. Neurol Sci 2018;39:1423–1430.
43. Brandle SM, Obermeier B, Senel M, et al. Distinct oligoclonal band antibodies in multiple sclerosis recognize ubiquitous self-proteins. Proc Natl Acad Sci U S A 2016;113:7864–7869.
44. Beltran E, Gerdes LA, Hansen J, et al. Early adaptive immune activation detected in monozygotic twins with prodromal multiple sclerosis. J Clin Invest 2019;129:4758–4768.
45. von Budingen HC, Kuo TC, Sirota M, et al. B cell exchange across the blood-brain barrier in multiple sclerosis. J Clin Invest 2012;122: 4533–4543.
46. Palanichamy A, Muhammad K, Roll P, et al. Rituximab therapy leads to reduced imprints of receptor revision in immunoglobulin kappa and lambda light chains. J Rheumatol 2012;39:1130–1138.
47. Roll P, Palanichamy A, Kneitz C, et al. Regeneration of B cell subsets after transient B cell depletion using anti-CD20 antibodies in rheumatoid arthritis. Arthritis Rheum 2006;54:2377–2386.
48. Leandro MJ, Cambridge G, Ehrenstein MR, Edwards JC. Reconstitution of peripheral blood B cells after depletion with rituximab in patients with rheumatoid arthritis. Arthritis Rheum 2006;54: 613–620.
49. Ceronie B, Jacobs BM, Baker D, et al. Cladribine treatment of multiple sclerosis is associated with depletion of memory B cells. J Neurol 2018;265:1199–1209.
50. Kim Y, Kim G, Shin H-J, et al. Restoration of regulatory B cell deficiency following alemtuzumab therapy in patients with relapsing multiple sclerosis. J Neuroinflammation 2018;15:300.
51. Cellerino M, Ivaldi F, Pardini M, et al. Impact of treatment on cellular immunophenotype in MS: a cross-sectional study. Neurol Neuroimmunol Neuroinflamm 2020;7:e693.
52. Kaneko K, Sato DK, Nakashima I, et al. CSF cytokine profile in MOG-IgG+ neurological disease is similar to AQP4-IgG+ NMOSD but distinct from MS: a cross-sectional study and potential therapeutic implications. J Neurol Neurosurg Psychiatry 2018;89: 927–936.
53. Mader S, Gredler V, Schanda K, et al. Complement activating antibodies to myelin oligodendrocyte glycoprotein in neuromyelitis optica and related disorders. J Neuroinflammation 2011;8:184.
54. Hohlfeld R, Dornmair K, Meinl E, Wekerle H. The search for the target antigens of multiple sclerosis, part 1: autoreactive CD4+ T lymphocytes as pathogenic effectors and therapeutic targets. Lancet Neurol 2016;15:198–209.
55. Hillebrand S, Schanda K, Nigritinou M, et al. Circulating AQP4-specific auto-antibodies alone can induce neuromyelitis optica spectrum disorder in the rat. Acta Neuropathol 2019;137: 467–485.
56. Pittock SJ, Berthele A, Fujihara K, et al. Eculizumab in aquaporin-4-positive neuromyelitis optica spectrum disorder. N Engl J Med 2019;381:614–625.
57. Misu T, Hoftberger R, Fujihara K, et al. Presence of six different lesion types suggests diverse mechanisms of tissue injury in neuromyelitis optica. Acta Neuropathol 2013;125:815–827.
58. Soltys J, Liu Y, Ritchie A, et al. Membrane assembly of aquaporin-4 autoantibodies regulates classical complement activation in neuromyelitis optica. J Clin Invest 2019;129:2000–2013.
59. Hinson SR, Clift IC, Luo N, et al. Autoantibody-induced internalization of CNS AQP4 water channel and EAAT2 glutamate transporter requires astrocytic Fc receptor. Proc Natl Acad Sci U S A 2017;114: 5491–5496.
60. Ratelade J, Asavapanumas N, Ritchie AM, et al. Involvement of antibody-dependent cell-mediated cytotoxicity in inflammatory demyelination in a mouse model of neuromyelitis optica. Acta Neuropathol 2013;126:699–709.
61. Peschl P, Schanda K, Zeka B, et al. Human antibodies against the myelin oligodendrocyte glycoprotein can cause complement-dependent demyelination. J Neuroinflammation 2017;14:208.
62. Spadaro M, Winklmeier S, Beltrán E, et al. Pathogenicity of human antibodies against myelin oligodendrocyte glycoprotein. Ann Neurol 2018;84:315–328.
63. Liu Y, Given KS, Harlow DE, et al. Myelin-specific multiple sclerosis antibodies cause complement-dependent oligodendrocyte loss and demyelination. Acta Neuropathol Commun 2017;5:25.
64. Hoftberger R, Guo Y, Flanagan EP, et al. The pathology of central nervous system inflammatory demyelinating disease accompanying myelin oligodendrocyte glycoprotein autoantibody. Acta Neuropathol 2020;139:875–892.
65. Fujihara K. Neuromyelitis optica spectrum disorders: still evolving and broadening. Curr Opin Neurol 2019;32:385–394.
66. Berger T, Rubner P, Schautzer F, et al. Antimyelin antibodies as a predictor of clinically definite multiple sclerosis after a first demyelinating event. N Engl J Med 2003;349:139–145.
67. Kuhle J, Pohl C, Mehling M, et al. Lack of association between antimyelin antibodies and progression to multiple sclerosis. N Engl J Med 2007;356:371–378.
68. Reindl M, Waters P. Myelin oligodendrocyte glycoprotein antibodies in neurological disease. Nat Rev Neurol 2019;15:89–102.
69. Jurynczyk M, Messina S, Woodhall MR, et al. Clinical presentation and prognosis in MOG-antibody disease: a UK study. Brain 2017; 140:3128–3138.
70. Mariano R, Messina S, Kumar K, et al. Comparison of clinical outcomes of transverse myelitis among adults with myelin oligodendrocyte glycoprotein antibody vs aquaporin-4 antibody disease. JAMA Netw Open 2019;2:e1912732.
71. Wingerchuk DM, Banwell B, Bennett JL, et al. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. Neurology 2015;85:177–189.
72. Waters P, Woodhall M, O'Connor KC, et al. MOG cell-based assay detects non-MS patients with inflammatory neurologic disease. Neurol Neuroimmunol Neuroinflamm 2015;2:e89.
73. Juryńczyk M, Jacob A, Fujihara K, Palace J. Myelin oligodendrocyte glycoprotein (MOG) antibody-associated disease: practical considerations. Pract Neurol 2019;19:187–195.
74. 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 2020;1352458520918375. https://pubmed.ncbi.nlm.nih.gov/32351164/, online ahead of print.
75. Barkhof F, Kappos L, Wolinsky JS, et al. Onset of clinical and MRI efficacy of ocrelizumab in relapsing multiple sclerosis. Neurology 2019;93:e1778–e1786.
76. Havrdová E, Arnold DL, Bar-Or A, et al. No evidence of disease activity (NEDA) analysis by epochs in patients with relapsing multiple sclerosis treated with ocrelizumab vs interferon beta-1a. Mult Scler J Exp Transl Clin 2018;4:2055217318760642.
77. Bar-Or A, Grove RA, Austin DJ, et al. Subcutaneous ofatumumab in patients with relapsing-remitting multiple sclerosis: the MIRROR study. Neurology 2018;90:e1805–e1814.
78. Hauser SL, Bar-Or A, Cohen JA, et al. Ofatumumab versus teriflunomide in multiple sclerosis. N Engl J Med 2020;383: 546–557.
79. Montalban X, Arnold DL, Weber MS, et al. Placebo-controlled trial of an oral BTK inhibitor in multiple sclerosis. N Engl J Med 2019; 380:2406–2417.

80. Baker D, Marta M, Pryce G, et al. Memory B cells are major targets for effective immunotherapy in relapsing multiple sclerosis. EBioMedicine 2017;16:41–50.

81. Kappos L, Hartung HP, Freedman MS, et al. Atacicept in multiple sclerosis (ATAMS): a randomised, placebo-controlled, double-blind, phase 2 trial. Lancet Neurol 2014;13:353–363.

82. Cross AH, Stark JL, Lauber J, et al. Rituximab reduces B cells and T cells in cerebrospinal fluid of multiple sclerosis patients. J Neuroimmunol 2006;180:63–70.

83. Comi G. Disease-modifying treatments for progressive multiple sclerosis. Mult Scler 2013;19:1428–1436.

84. Wolinsky JS, Narayana PA, O'Connor P, et al. Glatiramer acetate in primary progressive multiple sclerosis: results of a multinational, multicenter, double-blind, placebo-controlled trial. Ann Neurol 2007;61:14–24.

85. Lublin F, Miller DH, Freedman MS, et al. Oral fingolimod in primary progressive multiple sclerosis (INFORMS): a phase 3, randomised, double-blind, placebo-controlled trial. Lancet 2016;387:1075–1084.

86. Montalban X, Sastre-Garriga J, Tintoré M, et al. A single-center, randomized, double-blind, placebo-controlled study of interferon beta-1b on primary progressive and transitional multiple sclerosis. Mult Scler 2009;15:1195–1205.

87. Tur C, Montalban X, Tintoré M, et al. Interferon β-1b for the treatment of primary progressive multiple sclerosis: five-year clinical trial follow-up. Arch Neurol 2011;68:1421–1427.

88. Lublin FD, Reingold SC, Cohen JA, et al. Defining the clinical course of multiple sclerosis: the 2013 revisions. Neurology 2014;83: 278–286.

89. Hawker K, O'Connor P, Freedman MS, et al. Rituximab in patients with primary progressive multiple sclerosis: results of a randomized double-blind placebo-controlled multicenter trial. Ann Neurol 2009; 66:460–471.

90. Wolinsky JS, Brochet B, Hartung HP, et al. Sustained reduction in confirmed disability progression in patients with primary progressive multiple sclerosis treated with ocrelizumab in the open-label extension period of the phase III ORATORIO trial: 6.5-study year follow-up data (Abstract 159). Paper presented at: 35th Annual Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS); September 11–13, 2019; Stockholm, Sweden.

91. Wolinsky JS, Montalban X, Hauser SL, et al. Evaluation of no evidence of progression or active disease (NEPAD) in patients with primary progressive multiple sclerosis in the ORATORIO trial. Ann Neurol 2018;84:527–536.

92. Montalban X, Gold R, Thompson AJ, et al. ECTRIMS/EAN guideline on the pharmacological treatment of people with multiple sclerosis. Eur J Neurol 2018;25:215–237.

93. Bergman J, Burman J, Gilthorpe JD, et al. Intrathecal treatment trial of rituximab in progressive MS: an open-label phase 1b study. Neurology 2018;91:e1893–e1901.

94. Ghezzi A, Baroncini D, Zaffaroni M, Comi G. Pediatric versus adult MS: similar or different? Mult Scler Demyelinating Disord 2017;2:5.

95. Beres SJ, Graves J, Waubant E. Rituximab use in pediatric central demyelinating disease. Pediatr Neurol 2014;51:114–118.

96. Salzer J, Lycke J, Wickstrom R, et al. Rituximab in paediatric onset multiple sclerosis: a case series. J Neurol 2016;263:322–326.

97. Hausler D, Hausser-Kinzel S, Feldmann L, et al. Functional characterization of reappearing B cells after anti-CD20 treatment of CNS autoimmune disease. Proc Natl Acad Sci U S A 2018;115: 9773–9778.

98. Cohen M, Romero G, Bas J, et al. Monitoring CD27+ memory B-cells in neuromyelitis optica spectrum disorders patients treated with rituximab: results from a bicentric study. J Neurol Sci 2017; 373:335–338.

99. Kappos L, Li D, Calabresi PA, et al. Ocrelizumab in relapsing-remitting multiple sclerosis: a phase 2, randomised, placebo-controlled, multicentre trial. Lancet 2011;378:1779–1787.

100. Bensalem A, Mulleman D, Thibault G, et al. CD4+ count-dependent concentration-effect relationship of rituximab in rheumatoid arthritis. Br J Clin Pharmacol 2019;85:2747–2758.

101. Jelcic I, Al Nimer F, Wang J, et al. Memory B cells activate brain-homing, autoreactive CD4(+) T cells in multiple sclerosis. Cell 2018; 175:85–100.e23.

102. Hauser SL. Progress in multiple sclerosis research: an example of bedside to bench. JAMA 2020;324:841–842.

103. Silverman GJ, Weisman S. Rituximab therapy and autoimmune disorders: prospects for anti-B cell therapy. Arthritis Rheum 2003;48: 1484–1492.