

B-cell–targeted therapies in relapsing forms of MS

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ABSTRACT

In recent years, there has been a significant increase in the therapeutic options available for the management of relapsing forms of MS. Therapies primarily targeting B cells, including therapeutic anti-CD20 monoclonal antibodies, have been evaluated in phase I, phase II, and phase III clinical trials. Results of these trials have shown their efficacy and relatively tolerable adverse effect profiles, suggesting a favorable benefit-to-risk ratio. In this review, we discuss the pathogenic role of B cells in MS and the rationale behind the utilization of B-cell depletion as a therapeutic cellular option. We also discuss the data of clinical trials for anti-CD20 antibodies in relapsing forms of MS and existing evidence for other B-cell-directed therapeutic strategies. *Neurol Neuroimmunol Neuroinflamm* 2017;4:e405; doi: 10.1212/NXI.0000000000000405

GLOSSARY

ADCC = antibody-dependent cell-mediated cytotoxicity; **APRIL** = a proliferation-inducing ligand; **APC** = antigen-presenting cell; **CDC** = complement-dependent cytotoxicity; **DC** = dendritic cell; **DMT** = disease-modifying therapy; **Ig** = immunoglobulin; **OCB** = oligoclonal band; **OCB** = ocrelizumab; **OFT** = ofatumumab; **PML** = progressive multifocal leukoencephalopathy; **PPMS** = primary progressive MS; **RA** = rheumatoid arthritis; **RTX** = rituximab; **SLE** = systemic lupus erythematosus; **SPMS** = secondary progressive MS.

Understanding of the role of B cells in the pathogenesis of MS continues to evolve.¹ The presence of oligoclonal bands (OCBs), dominant B-cell clonotypes, plasma cells and plasmablasts in the CSF, antigen-dependent affinity maturation of antibodies, immunoglobulin (Ig), and complement deposition in lesions, the presence of B-cell follicle–like structures in the meninges, and efficacy of disease-modifying therapies (DMTs) targeting B cells are all indicators of the significance of B cells in disease pathogenesis.²

OCBs are intrathecally produced clonally expanded antibodies.^{3,4} They are used in clinical practice as a very sensitive but relatively nonspecific disease biomarker, especially in the diagnosis of progressive forms of MS. The cognate antigen for these clonally expanded antibodies still remains elusive.⁵ Transcriptome analysis of clonally expanded B cells in CSF has shown that they are responsible for OCB production.^{4,6} In addition, it was shown that the transcriptomes of these B cells overlap with B cells in the MS lesions, perhaps suggesting a pathogenic contribution. B cells in MS lesions also show somatic hypermutation, implying antigen-driven expansion.⁷

Further evidence for the potential role of antibodies and B cells in the pathogenesis of MS is derived from the presence of Ig and complement deposition in the most prevalent subtype of demyelinating MS plaques.⁸ In addition, B-cell follicle–like structures have been described in the meninges of patients with primary progressive MS (PPMS).⁹ Of note, the IgG repertoire of extraparenchymal meningeal B-cell clones is highly similar to that of B cells found in brain lesion.¹⁰

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Various cytokines and chemokines, including B-cell survival factor tumor necrosis factor superfamily 13b (B-cell-activating factor [BAFF]), CXCL13, and the chemokine (C-C motif) ligand 19 (CCL19) have been identified in the CSF and lesions of patients with MS, and were proposed as key chemoattractants for other immunocompetent cells.¹¹ The increased intrathecal Ig production and the activation of B cells and plasmablasts have all been associated with increased CXCL13 and CCL19 levels. In addition, increased CSF expression of CXCL13 has been associated with relapses suggesting the importance of B-cell recruitment in MS relapses and disease progression.

The CD4⁺ T helper 1 (Th1) and 17 (TH17) cell subsets have been shown to play a central role in experimental autoimmune encephalomyelitis (EAE) as well as MS pathogenesis.^{12,13} Activation of these cell types requires antigen presentation via MHC class II molecules, which are expressed on B cells as well as dendritic cells (DCs) and monocytes.⁵ Although DCs are considered the most effective antigen-presenting cells (APCs), B cells are specialized to serve as efficient APCs and have a unique potential to present the antigen that is available at only very low amounts because of their ability to capture a specific antigen via their B cell receptor. The activation of autoreactive CD4⁺ T cells occurs twice, initially in the periphery, and again later in the CNS.¹⁴ Autoreactive B cells can function as APC and activate autoreactive T cells through the trimolecular complex of T cell receptor/MHCII/antigen and costimulatory molecules. Reciprocal activation of B cells by activated T cells via CD40L and interleukin-4 (IL-4) provides B cells with the capability to activate T cells in turn.¹⁵ Such an interplay between B cells and T cells results in simultaneous expansion of antigen-specific B cells and T cells, which enhances proinflammatory immune response and disease progression or relapse.

B cells may also serve as regulatory functions, mediated, for example, via the secretion of interleukin-10.¹⁶ Studies have shown that mice containing B cells that cannot produce IL-10 failed to recover from EAE.¹⁷ Of interest, in an EAE model induced by

myelin-oligodendrocyte peptide 35–55, naive B-cell depletion was associated with increased polarizing capacity of myeloid APCs.¹⁸ CD-20 therapy has also been shown to correlate with an increase in relative frequency and function of monocytes in treated patients.¹⁹ These findings suggest that B-cell function and contribution in CNS autoimmunity is complex, and selective inhibition of B-cell function may serve as an efficacious target for disease modification.

PLASMAPHERESIS Plasmapheresis, which is thought to remove proinflammatory Ig's and cytokines, has been used for the management of acute relapse.⁵ Keegan et al.²⁰ showed that patients with type II (antibody-/complement-associated demyelination) MS lesions⁸ had the most favorable response to plasma exchange. None of the patients with other subtype I or III had favorable outcomes. This suggests that the efficacy of plasma exchange in the management of acute MS exacerbation may be related to its effects on B cells, Ig's, and cytokines, and specifically their downstream roles as inflammatory mediators within the CNS.²⁰ Although it is not feasible to obtain histologic evaluations before deciding on a therapeutic intervention, certain radiologic factors such as ring-enhancing lesion or tumefactive demyelination suggestive of humoral pathogenic mechanisms may be helpful in guiding therapeutic decision making.²¹

ANTI-CD20 MONOCLONAL ANTIBODIES Currently, 15 DMTs are approved for patients with MS, and many more are in clinical development (table 1).^{22,23} Most of the approved agents target B cells to varying degrees. With the advent of therapeutic recombinant monoclonal antibodies (mAbs), therapeutic modalities have emerged that allow targeting of specific B-cell populations on the basis of distinct molecular targets (table 2).^{13,23,24} These antibodies mediate depletion of their cellular target via antibody binding and complement-dependent cytotoxicity (CDC), antibody-dependent cell-mediated cytotoxicity (ADCC), or induction of apoptosis.¹³

Rituximab. Rituximab (RTX) is a chimeric IgG1 Ab that binds to the CD20 cell surface epitope expressed on cells of the B-lymphocyte lineage (pre-B cells, immature B cells, mature B cells, and some memory B cells).¹³ It causes B-cell depletion via ADCC, CDC, and apoptosis.²⁵ Pleuripotent stem cells, pre-B cells, and differential plasma cells do not express CD20.^{1,26} Therefore, B-cell reconstitution capability and humoral immunity are preserved with the use of anti-CD20 mAbs. It is currently thought that B-cell depletion may eventually also reduce total antibody

Table 1 Clinical trials for B-cell-depleting anti-CD20 monoclonal antibodies

Anti-CD20 mAb	Intervention arm/control arm	Patients	ARR [relative reduction] (p value)	Mean no. of new CELs (p value)	Mean no. of new T2 lesions (p value)	Sustained disability accumulation risk reduction (p value)
RTX (HERMES trial, phase II) ³¹	IV RTX	69	0.20 [20%] (p = 0.04)	4.5 (p < 0.001)	Mean no. NS	NS
	Placebo	35	0.40	0.2	175.4 mm ³ (mean volume) (p = 0.004) 417.8 mm ³	NS
OCT (phase II) ⁴¹	Low-dose OCT	55	0.13 [79%] (p = 0.0005)	0.8 (p < 0.0001)	0.0 (p < 0.0001)	NS
	High-dose OCT	55	0.17 [73%] (p = 0.0014)	0.8 (p < 0.0001)	0.0 (p < 0.0001)	NS
	IFNβ-1a	54	0.36 [43%] (p = 0.07)	7.2	1.8	NS
	Placebo	54	0.64	6.6	1.4	NS
OFT (phase II) ³⁵	OFT/placebo	26	NS	8-24 wks	8-24 wks	NS
				0.04 (p < 0.001)	0.12 (p < 0.001)	
				24-48 wks	24-48 wks	NS
	Placebo/OFT	12	NS	8-24 wks	8-24 wks	NS
				9.69	10.67	
				24-48 wks	24-48 wks	NS
OCT (OPERA I, phase III) ³⁴	OCT	410	0.156 [46%] (p < 0.0001)	0.016 [94%] (p < 0.0001)	0.323 [77%] (p < 0.0001)	12 wks 4.7 [43%] (p < 0.05)
	IFNβ-1a	411	0.292	0.286	1.413	24 wks 4.1 [43%] (p < 0.05)
OCT (OPERA II, phase III) ³⁴	OCT	417	0.155 [47%] (p < 0.0001)	0.291 [95%] (p < 0.0001)	0.325 [83%] (p < 0.0001)	12 wks 6.4 [37%] (p < 0.05)
	IFNβ-1a	418	0.290	0.416	1.904	24 wks 5.0 [37%] (p < 0.05)

Abbreviations: ARR = annualized relapse rate; CEL = contrast-enhancing lesion; IFNβ-1a = interferon β1-a; mAb = monoclonal antibody; NS = not specified; OCT = ocrelizumab; OFT = ofatumumab.

production. However, studies have suggested that clinical effects of RTX are mainly mediated through effects on cytokine networks and T-cell activation.²⁷ The first biosimilar monoclonal antibody, CT-P10 (Truxima), physiochemically and pharmacodynamically similar to RTX was approved by the European Medicines Agency for use in diffuse large B-cell non-Hodgkin lymphoma, follicular lymphoma, chronic lymphocytic leukemia, rheumatoid arthritis (RA), granulomatosis with polyangiitis, and microscopic polyangiitis.²⁸ Biosimilar agents provide an opportunity to lower health care cost and promote wider utilization of these therapies in developing countries.²⁹

Clinical trials. In 2005, the index case of the use of RTX in a patient with very aggressive relapsing-remitting MS was published that provided the proof of principle for the use of anti-CD20 therapy in patients with this disorder.³⁰ In 2008, Hauser et al.³¹ published the results of a phase II, double-blind, placebo-controlled trial that enrolled 104 patients with RRMS randomly assigned in 2:1 ratio to RTX (a single course administered IV 1,000 mg on days 1 and 15), or placebo. The number of new contrast-

enhancing lesions (CELs) at 12, 16, 20, and 24 weeks was significantly reduced in the RTX group compared with the placebo group. At the end of 48 weeks, there was also a significant reduction in the ARR in the RTX arm (20.3%) compared with the placebo (40%).

Another phase II trial used RTX as an add-on therapy in RRMS patients with standard injectable DMTs.³² Thirty patients with at least 1 relapse in the previous 18 months or new CELs on previous 3 MRIs were included in the study. Patients who received RTX as an add-on therapy had a significant reduction in new CELs (74% vs 26%). There was also improvement in MSFC, but the EDSS remained stable.

In a large retrospective observational study, using a Swedish MS registry, 822 RTX-treated patients with MS were identified. The mean duration of follow-up was 21.8 months (SD 14.3 months).³³ The majority of these patients had RRMS (557) followed by secondary progressive MS (SPMS) (198) and PPMS (67). The annualized relapse rates were 0.044, 0.038, and 0.015 in RRMS, SPMS, and PPMS, respectively. Among the patients with RRMS,

Table 2 Summary of the effect of various approved disease-modifying therapies of B and T cells, their adverse effects, and effect on vaccine response

Drugs	Mechanism of action for B cells	Mechanism of action for T cells	Adverse effects	Vaccine response
Interferon beta⁵⁹	Impaired antigen presentation; increased BAFF (relative increase in transitional B cells but decrease in memory B cells in circulation); decreased expression of costimulatory molecules (CD 40 and CD 80); increased anti-inflammatory cytokines (IL-10); and inhibits proinflammatory cytokines (e.g., IL-1 β and IL-23)	Reduced activation of T cells due to increased expression of anti-inflammatory cytokines and decreased expression of proinflammatory cytokines	Flu-like symptoms, transient worsening of MS symptoms; depression (unconfirmed), anemia, thyroid dysfunction, and hepatotoxicity	Unchanged
Glatiramer acetate²	Impaired antigen presentation; decreased BAFF (decreased total number of circulating B cells); reduced expression of costimulatory molecules (CD80 and CD86); increased anti-inflammatory cytokines (IL-4, IL-10, and IL-13); inhibits proinflammatory cytokines (e.g., TNF- α , IL-17, and IL-6); and decreased expression of the chemokine receptor, CXCR5, and elevated BDNF expression	Reduced activation of T cells due to increased expression of anti-inflammatory cytokines and decreased expression of proinflammatory cytokines; increased production of BDNF	Injection site reaction, flushing, urticaria, skin necrosis, and chest pain	Impaired
Dimethyl fumarate²²	Reduced proportion of CD27 ⁺ memory B cells was decreased, but increase immunoregulatory CD24 ⁺ CD38 ⁺ transition 2 marginal zone precursor and CD43 ⁺ CD27 ⁺ B1 B cells increase IL-10	Increased expression of anti-inflammatory cytokines and reduced expression of proinflammatory cytokines; increased production of reduced glutathione	Abdominal pain, diarrhea, nausea, vomiting, flushing, and lymphopenia	Unknown
Fingolimod⁶⁰	Sequesters B cells in lymphoid tissue; decreased number of circulating B cells and reduced entry into the CNS; enhances the capacity of regulatory B cells to transmigrate across the blood-brain barrier; reduced expression of costimulatory molecules (CD 80 and CD 86); increased anti-inflammatory cytokines (IL-10); reduced proinflammatory cytokines (e.g., TNF- α)	Sequesters T cells in lymphoid tissue	Bradycardias, macular edema, hepatic transaminitis, basal cell carcinomas, varicella zoster virus reactivation, and herpes encephalitis	Impaired
Teriflunomide²	Potent inhibitor of dihydroorotate dehydrogenase, which is needed for B-cell proliferation, reduced number of activated B cells, and less infiltration into the CNS	Reduces T-cell proliferation by inhibition of dihydroorotate dehydrogenase	Potentially teratogenic, gastrointestinal disturbances, hepatotoxicity, lymphopenia, thrombocytopenia, high blood pressure, and opportunistic infections	Marginally diminished
Natalizumab¹³	α -4 integrin antagonist; impairs transmigration into the CNS and other tissues; relative decrease in naive B cells, but regulatory B cells, and marginal zone-like B cells increase	α -4 integrin antagonist, prevents leukocyte migration, induces apoptosis via interaction with fibronectin	Infusion reaction, liver disease, fever, joint pain, PML, and melanoma	Impaired (data unclear)
Alemtuzumab²³	Increased BAFF, temporary depletion of B cells via ADCC, CDC, and apoptosis with subsequent reconstitution	Long-term depletion of T cells via ADCC, CDC, and apoptosis	Infusion reaction, infections, autoimmune disorders (thyroiditis, ITP, and glomerulonephritis)	Normal
Daclizumab¹³	Decreased absolute memory B-cell numbers	Depletion of activated T cells via CD-25 antagonism and activation of CD56 natural killer cells	Infections, liver dysfunction, skin rash, depression, and malignancy	Normal
Mitoxantrone²	Potent inhibitor of type II topoisomerase subsequently reduces B-cell proliferation, especially CD27 ⁺ memory B cells; increased anti-inflammatory cytokines (IL-10)	Potent inhibitor of type II topoisomerase subsequently reduces T-cell proliferation, inhibits activation of naive T cells via inhibition of proinflammatory cytokines (e.g., TNF- α)	Congestive heart failure, acute myeloid leukemia, liver dysfunction, lymphopenia, and potentially teratogenic, discoloration of urine (purple or green)	Impaired
Anti-CD20 mAb (RTX, OFT, and ocrelizumab)¹³	Depletion of B cells in circulation and CNS via ADCC and/or CDC and increased anti-inflammatory cytokines (IL-10)	Reduced activation of naive T cells via reduction of antigen-presenting cells and inhibition of proinflammatory cytokines (GM-CSF)	Infusion reaction, infections, PML	Impaired

Abbreviations: ADCC = antibody-dependent cell-mediated cytotoxicity; BAFF = B-cell-activating factor of the tumor necrosis factor family; CDC = complement-dependent cytotoxicity; GM-CSF = granulocyte-macrophage colony-stimulating factor; IL = interleukin; ITP = immune thrombocytopenic purpura; OFT = ofatumumab; PML = progressive multifocal leukoencephalopathy; RTX = rituximab; TNF- α = tumor necrosis factor α .

the median EDSS remained unchanged over the period of follow-up, but it increased by 0.5 and 1.0 in SPMS and PPMS, respectively.

Because of the chimeric nature of RTX, 24.6% of patients developed anti-idiotypic antibodies in the HERMES trial.³¹ No clear impact of these antibodies

on efficacy or rate adverse effects has been proven. However, humanized or human anti-CD20 antibodies have much lower immunogenicity or rate of anti-idiotypic antibody formation.^{34,35}

Safety. Infusion-associated reactions are the most common adverse effect of RTX.^{13,31,32} The majority of patients (78%) who received RTX in the HERMES trial had infusion-associated reactions compared with 40% in the placebo group. Most of these reactions were mild to moderate in severity (92.6%).³¹ The administration of glucocorticoids and antihistaminic agents before the infusion and slowing down the rate of infusion may reduce the occurrence or severity of infusion-associated reactions.^{13,31} Other potential adverse effects commonly reported in the studies included headache, sinusitis, nausea, upper respiratory tract infections, and urinary tract infections. Malignant thyroid neoplasm was also diagnosed in one patient.^{31,32,36} In addition, in the Swedish MS registry study, 3 malignancies were detected, 2 basiliomas and 1 pyoderma gangrenosum.³³

The rate of infection following RTX administration has been reported as 18.1 per 100 patient-years. In one study that evaluated the efficacy and safety of RTX in different autoimmune diseases, 7 of 11 deaths were attributed to underlying infections.³⁷ There have been few cases of progressive multifocal leukoencephalopathy (PML) reported following administration of RTX in combination with other immunosuppressive agents in patients with lymphoproliferative disorders, RA, systemic lupus erythematosus (SLE), and autoimmune thrombocytopenia, but until now, no cases have been reported in patients with MS in clinical trial or with off-label usage.³⁸ It remains unclear whether there is a causal relationship between anti-CD20 treatment and development of PML or the underlying immunocompromised state (lymphoproliferative disorder) and cotreatment with other immunosuppressive medications contributed to development of this life-threatening infection. Among patients switched from natalizumab to either fingolimod or RTX due to John Cunningham virus seropositivity, RTX had better efficacy in reducing relapses as well as lowering adverse event rate.³⁹ Therefore, clinicians may have a preference to use anti-CD20 therapy in JC virus-seropositive patients. Because of rheumatology and oncology data on incidence of PML among RTX-treated individuals, CSF evaluation for JC virus infection should be considered before initiating anti-CD20 treatment.

Ocrelizumab. Ocrelizumab (OCR) also targets and depletes CD20⁺ B cells. Compared with RTX, OCR is a humanized IgG1 mAb, and it is less immunogenic.⁴⁰ Therefore, it leads to fewer allergic reactions and development of anti-idiotypic antibodies.^{40,41}

It targets different but overlapping epitope than RTX with higher avidity. Its efficacy is mediated more by ADCC than by CDC.^{13,40} It induces rapid B-cell depletion following infusion; recovery of B cell occurs at 3 months.⁴² Given the lower immunogenicity and higher avidity for the epitope, OCR might have a more favorable risk-benefit profile than RTX.

Clinical trials. A phase II, randomized, double-blind, placebo-controlled trial comparing OCR with placebo and IFN β -1a was published in 2011.⁴¹ In this multicenter study (79 centers and 20 countries), patients were randomized 1:1:1:1 to receive placebo, low-dose OCR (600 mg), high-dose OCR (2,000 mg), or IFN β -1a (open-label, rater-blinded exploratory arm). After completion of the initial 24 weeks, patients in the placebo and IFN β -1a were switched to receive OCR. There was a significant reduction in the number of CELs; 89% and 96% in the low- and high-dose OCR treatment arms, respectively, compared with the placebo. The proportion of individuals free from new CELs was also significantly lower in the OCR groups compared with the placebo group (low-dose OCR: 77%, high-dose OCR: 82.7%, and placebo: 35%). The ARR in the placebo, low-dose OCR, high-dose OCR, and IFN β -1a groups was 30%, 5%, 7%, and 17%, respectively. The ARR was significantly lower in both the high-dose (7%) and low-dose (5%) OCR groups compared with the placebo (30%). There was a significant difference in the ARR between low-dose OCR (5%) and IFN β -1a (17%), but not between high-dose OCR and IFN β -1a.

Two phase III trials (OPERA I and II) with an identical design were recently published.³⁴ These were multicenter, randomized, double-blind, double-dummy, parallel-group trials to evaluate the efficacy and safety of OCR compared with IFN β -1a in patients with RRMS. In 2 trials enrolled (OPERA I: 821 and OPERA II: 835), patients were aged between 18 and 55 years, with a diagnosis of RRMS according to the 2010 revised McDonald criteria,⁴³ EDSS score <5.5 at screening, and at least 2 documented clinical attacks within the 2 years prior or 1 within 1 year before screening. Patients were randomized 1:1 to receive OCR (300 mg or 600 mg) intravenously every 24 weeks or IFN β -1a 44 μ g subcutaneously 3 times per week throughout a 96-week treatment period. EDSS raters were masked to the clinical and laboratory data, which could have been suggestive of either OCR or IFN β -1a group. In both studies, OPERA I and II, there was a significant reduction of ARR in the OCR treatment arms compared with IFN β -1a 46% and 47%, respectively. There was also a significant reduction in confirmed disability progression at 12 (OPERA I 43% and OPERA II 37%) and 24 weeks (OPERA I 43% and OPERA II 37%) compared with IFN β -1a. The

mean relative reduction in CELs with OCR treatment compared with IFN β -1a treatment at weeks 24, 48, and 96 was 94% and 95% in OPERA I and OPERA II, respectively. The number of new and/or enlarging T2 hyperintense lesions was also significantly reduced in the OCR-treated patients compared with IFN β -1a treatment: 77% in OPERA I and 83% in OPERA II. Relatively no evidence of disease activity,⁴⁴ defined as the absence of protocol-defined relapses, confirmed disability progression events, new or enlarging T2 lesions, and CELs from baseline to week 96, improvement of OCR treatment arms compared with IFN β -1a treatment arms in OPERA I (77%) and OPERA II (89%) was significantly higher. In both these studies, OCR treatment was also associated with the relative reduction in rates of brain volume loss compared with IFN β -1a, 23.5% and 23.8% in OPERA I and OPERA II, respectively.

Safety. The most common adverse effects reported in the phase II studies included headache, infections, and infusion-associated events. There was 1 reported death in the high-dose OCR group due to systemic inflammatory response syndrome.

In the phase III studies, a higher proportion of OCR-treated patients (34.3%) developed infusion-related reaction compared with IFN β -1a-treated patients (9.7%). Because of infusion-related reactions during the first infusion, 1.3% of study participants withdrew from OCR treatment. The rates of infections between the OCR treatment arms and IFN β -1a arms were comparable, 58.4% and 52.4%, respectively. The most commonly reported and diagnosed infections were upper respiratory tract infections, nasopharyngitis, and urinary tract infections. Headache, back pain, joint pain, and psychiatric disorders were other common adverse effects. There was no significant difference in serious adverse effects reported (OCR treatment arm 6.9% vs IFN β -1a treatment arm 8.7%). Four malignancies were reported in the OCR arm, which does not prove a causal relationship: renal cell cancer (1), melanoma (1), and breast cancer (2); whereas 2 patients in the IFN β -1a arm were reported to have malignancies, squamous cell carcinoma (1), and mantle cell lymphoma (1). The number of malignancies was higher (11, 2.3%) in the study evaluating OCR for patients with progressive MS.⁴⁵ Three deaths were reported during OPERA trials, 2 in an IFN β -1a arm (1 suicide and 1 mechanical ileus) and 1 in an OCR arm (suicide).²⁴ A total of 1246 patients have been recruited in the OPERA open-label extension study to evaluate the long-term safety, tolerability, and efficacy of OCR. These patients are on a regimen of 600 mg OCR every 24 weeks.

Ofatumumab. Ofatumumab (OFT) is a fully human IgG1 mAb targeting CD20⁺ B cells.^{13,46} OFT

mediates B-cell depletion via CDC and ADCC.³⁵ OFT binds to a novel membrane-proximal epitope. The rate at which it dissociates from the epitope is slower than RTX, which results in improved CDC.^{46,47} As expected, OFT is less immunogenic than RTX.⁴⁸

Clinical trials. In 2014, a phase II, placebo-controlled, double-blind trial was published in which patients were randomized to receive either OFT or placebo infusions at 2-week intervals.³⁵ At 24 weeks, the treatment arms were switched so that patients receiving OFT were given placebo and vice versa. Thirty-eight patients were randomized to either OFT first and placebo later (n = 26) or placebo first and OFT later (n = 12) groups. The number of new CELs during 8–24 weeks and the total CELs in the OFT group were significantly reduced. The percentage reduction in the number of T1 CELs from 8 to 24 weeks was >99%. During the first 24 weeks, in the OFT arm, 19% of patients had a clinical relapse, whereas in the placebo arm, 25% of patients had a relapse. After the therapies were switched at 24 weeks, 1 patient who had initially been on OFT relapsed, but none of the patients switched from placebo to OFT developed relapses. No clinical significant difference in EDSS or MSFC scores were observed in the OFT arm compared with the placebo or compared with the baseline.

Safety. The most prevalent adverse effect was an infusion-related reaction on the first day of infusion more commonly found in the OFT treatment group compared with the placebo. One patient receiving OFT discontinued treatment because of development on pharyngeal edema, pruritus, and nasal congestion during the first infusion. It is important that none of the patients on OFT tested for human anti-chimeric antibody were seropositive at the end of 48 weeks, pointing toward lower immunogenicity of OFT compared with RTX.

OTHER B-CELL-TARGETING THERAPIES The CD19 molecule is expressed on B cells that express CD20, and also on some antibody-producing plasmablasts, which makes it another potential therapeutic target for patients with RRMS. One therapeutic agent in development that targets CD19 is inebilizumab (MEDI-551), a humanized recombinant mAb.²⁶ It has been evaluated in a phase I trial for patients with relapsing forms of MS (NCT01585766). The study is completed, but no study results are available. Of importance, inebilizumab has demonstrated equal or better efficacy in depletion of human primary B cells in autologous ADCC assays, as well as longer-lasting B-cell depletion compared with RTX.^{1,26}

Epratuzumab is a monoclonal antibody targeting CD22, a B-cell transmembrane glycoprotein mostly

expressed on mature B cells that act as an accessory-signaling component of the B-cell antigen receptor. Epratuzumab has been evaluated in patients with SLE and non-Hodgkin lymphoma,⁴⁹ but no studies are currently under way in MS.

The BAFF receptor, which promotes cell survival through various developmental stages of B cells, is another therapeutic target of interest.¹¹ It is present on B-cell subsets in secondary lymphoid organs, as well as on a small subset of T cells.^{11,50} Of interest, a study testing a recombinant fusion protein neutralizing BAFF and a proliferation-inducing ligand (APRIL), another B-cell stimulator showed an increased inflammatory activity in patients with MS.⁵¹ Reasons for these counterintuitive results are unclear, but it could be secondary to the effect of anti-BAFF/APRIL (Atacicept) on CD27-negative naive B cells while having a little effect on memory B cells.⁵²

Tabalumab, a human IgG4 mAb that targets and neutralizes both soluble and membrane-bound BAFF,⁵³ was evaluated in a phase II clinical trial (NCT00882999). The trial was initiated in April 2009, but subsequently canceled in 2011. Whether the termination was due to safety issues, inefficacy, increased disease activity, or other reasons remains unknown.

Another human IgG1 mAb targeting receptor for BAFF (VAY736) was evaluated in a phase II trial for patients with RRMS.¹ VAY736 is hypothesized to cause B cell and serum Ig depletion. The study was completed, but no details or results are available thus far.

Tocilizumab is a humanized monoclonal IgG1 antibody targeting the IL-6 receptor and is FDA approved for the management of RA, polyarticular juvenile idiopathic arthritis, and active systemic juvenile idiopathic arthritis.⁵⁴ IL-6 drives the differentiation of B-cell subsets, including plasmablasts.⁵⁵ This mAb has also shown potential efficacy in the management of patients with neuromyelitis optica disorder refractory to RTX. It is another potential therapeutic option that may be evaluated in patients with MS in the near future.

Bortezomib, a proteasome inhibitor which preferentially affects plasma cell differentiation and survival, and predisposes them to apoptotic cell death, has been used in the management of multiple myeloma.^{56,57} Patients with refractory NMDA receptor encephalitis have also shown a favorable response, suggesting its utility in disorders with cell-mediated and antibody-mediated mechanisms.⁵⁸ Currently, there are no data on the use of bortezomib for MS, but in the future, these agents might prove to be useful for the management of refractory cases.

CONCLUSIONS Recently published data from OCR phase III trials further lend support to efficacy and

safety of B-cell-depleting therapies in RRMS and have resulted in the first approved B-cell-specific therapy for MS.³⁴ Agents that target other B-cell-associated molecules are also currently in clinical development.^{1,13} These trials aim to target B-cell subsets more specifically or more cell subsets of the B-cell lineage.

Some failed study initiatives illustrate the heterogeneous role of B-cell subsets. A better understanding of the biology of disease stage-specific and compartment-specific B-cell subsets will be required to further improve B-cell-targeted therapies.

AUTHOR CONTRIBUTIONS

Divyanshu Dubey: drafting/revising the manuscript, study concept or design, and analysis or interpretation of data. Thomas Forsthuber: drafting/revising the manuscript. Eoin P. Flanagan: drafting/revising the manuscript and analysis or interpretation of data. Sean J. Pittock: drafting/revising the manuscript. Olaf Stüve: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, and study supervision.

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DISCLOSURE

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