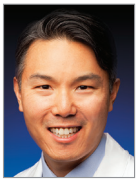
AntiCD20$^+$ Agents

AntiCD20$^+$ agents are among the highest efficacy treatments for multiple sclerosis.

By Brian Barry, MD and Robert K. Shin, MD

B-cell depletion has been used worldwide as a treatment strategy for multiple sclerosis (MS) for over a decade. Clinical trials have repeatedly demonstrated that antiCD20$^+$ monoclonal antibodies have robust efficacy in preventing MS relapses, reducing new T2 and gadolinium-enhancing (Gd$^+$) lesions on MRI, and slowing disability progression. These results have upended earlier assumptions that inflammation in MS is predominantly mediated by T cells. Although, ocrelizumab is the antiCD20$^+$ drug approved by the Food and Drug Administration (FDA) for treatment of MS, rituximab has been widely used off-label, and successful phase 3 clinical trials of subcutaneously injected ofatumumab have been completed. Ublituximab, another infused antiCD20$^+$ therapy is being evaluated in 2 phase 3 studies that are expected to read out later this year (Table 1).

Possible Mechanisms of Action

Although CD20 is a B-cell marker, not all cells in the B-cell lineage express it. Circulating CD20$^+$ B cells are rapidly depleted in the periphery after administration of antiCD20+ agents; whereas, hematopoietic stem cells in bone marrow and antibody-producing plasma cells remain largely unaffected. It is believed that this selective B-cell depletion allows for efficacy in treating MS without significantly increasing the clinical risk of immunosuppression.

TABLE 1. ANTICD20+ B-CELL DEPLETING AGENTS FOR MULTIPLE SCLEROSIS

Drug	Structure	Brand names	Dosing
Ublituximab	Chimeric	none[a]	450 mg IV[a]
Rituximab	Chimeric	Rituxan, Truxima, Ruxience	Variable (500-2000 mg every 6 months)
Ocrelizumab	Humanized	Ocrevus	300 mg IV at week 0 and 2, then 600 mg IV every 6 months[b]
Ofatumumab	Human	Arzerra	20 mg subcutaneous injection at day 1, 7, 14, then 20 mg every 4 weeks

[a] investigational [b] dosing used in ASCLEPIOS trial. Abbreviations: IV, intravenous.

The exact mechanism by which B-cell depletion has efficacy for treating MS remains unknown. Production of antibodies is only 1 of many important B-cell functions, and it is likely that the disruption of other functions contributes to the efficacy of antiCD20$^+$ drugs.[1,2] Among antigen-presenting cells, B cells are unique because of the specificity of their surface immunoglobulin antigen receptor. In individuals with MS, this antigen receptor may be targeted against central nervous system (CNS) antigens, and B cells may drive inflammation by presenting CNS antigens to T cells in the context of major histocompatibility class (MHC) II molecules.[3] B cells are also found in active MS plaques where they produce inflammatory cytokines (eg, interleukin [IL]-6, granulocyte-macrophage colony-stimulating factor [GM-CSF] and tumor necrosis factor-α [TNF-α] that stimulate T cells to drive the autoimmune response.[2] Finally, clusters of inflammatory cells, including B cells, have been found in the meninges of individuals with progressive MS (PMS) and have been suggested as a contributor to cortical inflammation and disability in PMS.[1,4,5]

Hematopoietic stem cells in the bone marrow are CD20$^-$ and B-cell precursors are continuously repopulated. This allows for immunologic recovery if treatment is interrupted. At the other end of the B-cell development stages, antibody-producing plasma cells are also CD20$^-$ and thus preexisting humoral immunity is largely unaffected by short-term treatment. Although circulating CD20$^+$ B cells are reduced to levels that cannot be detected, they may persist in the bone marrow, lymph nodes, and CNS after treatment.[3] AntiCD20$^+$ therapy has generally shown a good safety profile.[6] If CNS resident B cells and plasma cells are involved in the pathophysiology of PMS, then persistence of B cells in the CNS after treatment may explain the relatively modest effect of antiCD20$^+$ agents for PMS.[3,6]

Clinical Use in Relapsing Multiple Sclerosis

In general, B-cell depletion appears to be a highly effective and relatively safe treatment option for the treatment

of relapsing forms of MS. Whether one antiCD20+ agent is superior to another for relapsing MS is debatable.

Rituximab

Rituximab is a chimeric monoclonal antibody that is administered intravenously. Although it is approved by the FDA for oncologic and rheumatologic indications, rituximab is not approved for any neurologic conditions. Nevertheless, rituximab or its biosimilar forms that were available have been used off-label to treat MS.

Trials of rituximab in MS showed promising effects but because of intellectual property considerations, phase 3 studies were not done. A phase 2 study demonstrated a dramatic reduction in new Gd+ MRI lesions at 48 weeks after a single course of rituximab vs placebo.[7] Although there was no phase 3 efficacy study for RMS, real-world experience has corroborated the efficacy of rituximab. In a large observational study of rituximab across 3 Swedish centers, the annualized relapse rate (ARR) was 0.04 in people with RMS treated with rituximab (approximately 1 relapse for every 23 years on treatment).[8] Rituximab is widely used in rural Sweden where biannual infusions are an appealing first-line strategy because of large travelling distances. Early use of rituximab in the rural cohort resulted in lower relapse rates compared with a Stockholm-based cohort for which an escalation strategy of injectable, oral, and infusion therapies was more commonly used.[9]

Because there is no FDA-approved dose for rituximab to treat RMS, there is significant variability in dosing reported by different centers. We find that 1000 mg every 6 months is effective and well-tolerated by most patients.

Ocrelizumab

Ocrelizumab was the first antiCD20+ monoclonal antibody approved for treatment of MS. Ocrelizumab demonstrated superior efficacy compared with interferon β-1a in people with RMS.[10] Ocrelizumab is a humanized monoclonal antibody that significantly decreased relapse rate (approximately 50%), slowed disability progression, dramatically reduced the number of new, enlarging, or enhancing MRI lesions (over 90%), and slowed brain volume loss compared to interferon β-1a.[10] Ocrelizumab is administered intravenously, 600 mg once every 6 months with the first round split into 2 doses of 300 mg each that are administered 2 weeks apart. Subcutaneous delivery of ocrelizumab is currently being explored.[11]

Ofatumumab

More recently, ofatumumab, a fully human antiCD20+ monoclonal antibody, demonstrated efficacy compared with teriflunomide.[a] After a loading dose, monthly subcutaneous injections of ofatumumab (20 mg) resulted in approximately 50% relapse reduction compared with teriflunomide. New Gd+ MRI lesions were reduced by more than 90% with ofatumumab vs teriflunomide. If approved, ofatumumab will be the first subcutaneously delivered antiCD20+ agent for MS.

Ublituximab

Ublituximab is a chimeric monoclonal antiCD20+ antibody that has been glycoengineered to enhance affinity for variants of FcγRIIIa receptors. Phase 3 trials are ongoing, and results are expected later in 2020.

Clinical Use in Progressive Multiple Sclerosis

Disease progression is among the greatest treatment challenges faced by MS clinicians. Disease progression can be defined as clinical worsening or accumulation of disability not due to relapse activity and can exist with or without concurrent relapsing disease. Individuals with PMS may worsen despite having no evidence of disease activity defined as clinical relapses or new or enhancing lesions on MRI.

When 4 courses of rituximab were administered to individuals with PMS over 96 weeks there was no significant difference in disability progression with rituximab vs placebo.[12] Nevertheless, there was significantly slowed progression in those who were less than age 51, and those who had Gd+ lesions at baseline, as well as an additive effect of age and presence of Gd+ lesions.

Treatment with ocrelizumab demonstrated significant reduction in confirmed disability progression compared with placebo (32.9% vs 39.3%; hazard ratio, 0.76; 95% CI, 0.59-0.98; *P*=.03).[13] Benefits for walking speed and slowing of brain volume loss were also seen. Compared to the rituximab trial, participants in the ocrelizumab trial were younger (mean age 44 vs 50), with about one-fourth of participants having Gd+ lesions on baseline MRI.

These results have led to the use of B-cell depleting agents in people with PMS or suspected PMS, especially those under age 51 with more active disease. Whether the results from trials in people with primary MS (PPMS) can be generalized to people with secondary PMS is unknown, but it has been our observation that it is often difficult to ascertain whether an individual's disease course started first with progression or relapses, meaning that it is possible that the distinction between PPMS and SPMS may not be clinically meaningful.[14] (see Point Counterpoint: *Food and Drug Administration Multiple Sclerosis Categorization Changes* p. 44 of this issue)

Safety and Monitoring

Decades of experience with rituximab show that B-cell depletion is well tolerated, even when treatment extends over many years. The safety profile of rituximab is bolstered by years of use not only in neurologic indications, but also by extensive use in oncology and rheumatology. Obviously,

a. A Study to Investigate the Pharmacokinetics, Safety, And Tolerability of Subcutaneous Ocrelizumab Administration in Patients with Multiple Sclerosis. (NCT03972306)

caution is warranted in extending lessons learned from rituximab to other B-cell depleting therapies, and safety concerns exist. Label warnings for rituximab include rare fatal infusion reactions, severe mucocutaneous reactions, hepatitis B reactivation and progressive multifocal leukoencephalopathy (PML).[15]

Screening

Prior to starting an antiCD20+ agent, screening for hepatitis B is mandatory, specifically checking for hepatitis B core antibodies (HBCAb), hepatitis surface antibodies (HBSAb) and hepatitis surface antigen (HBSAg). In practice, we expand screening labs to include other latent and treatable infections (Table 2). Because there is evidence that B-cell depletion may impair the efficacy of some vaccinations,[15] we recommend updating immunizations before initiating therapy, an approach informed by recently updated American Academy of Neurology guidelines.[16] If an individual is not immune to hepatitis B or varicella zoster based on screening tests, vaccination against these viruses can be offered prior to treatment. Immunization against pneumococcus could also be considered.

Pretreatment and Treatment

With both rituximab and ocrelizumab infusions, reactions are most likely to occur during the first infusion, with severity of reactions ranging from mild to life-threatening. The first dose of ocrelizumab is split into half doses administered 2 weeks apart to mitigate the risk of infusion reactions. Before treatment with rituximab or ocrelizumab, we recommend pretreatment 30 minutes before antibody infusion with intravenous methylprednisolone (125 mg), oral acetaminophen, and oral diphenhydramine. Mild symptoms of urticaria are managed with intravenous fluids and by slowing or pausing the infusion. Retreating with steroids, acetaminophen and diphenhydramine is also an option. Hypoxia, shock, or anaphylaxis merit discontinuation of infusion and appropriate management.

Clinical trial data suggest that severe reactions from subcutaneous injection of ofatumumab are rare.[11]

Potential Side-Effects

Based on clinical trial experience, mild infections may occur at a somewhat higher rate after treatment with antiCD20+ agents.[16,17] No increased risk of severe infections was seen in participants receiving ocrelizumab or ofatumumab during clinical trials for MS.[17]

In people treated with rituximab who had prior or concurrent immunosuppression, PML has been rarely reported.[15] A single case of PML has been attributed to ocrelizumab treatment in a person with pre-existing lymphopenia, and multiple cases of carryover PML have been seen in people previously treated with natalizumab. Appropriate vigilance for PML is advisable for any person using any antiCD20+ agent, especially those with recent exposure to natalizumab. We do not, however, recommend checking JC virus antibody titers prior to or during use of antiCD20+ agents, because the test provides no useful information in this context.

More cases of breast cancer were diagnosed among

TABLE 2. SCREENING BEFORE STARTING ANTICD20+ THERAPY

Screening step	Lab	Action Item
Hepatitis B	Hepatitis B surface antigen[a] Hepatitis B core antibody[a]	B-cell depletion is contraindicated in people with active hepatitis B; refer to liver specialist if surface antigen or core antibody is present[a]
Hepatitis B	Hepatitis B surface antibody	Consider vaccination against hepatitis B prior to starting B-cell depletion if not immune
Hepatitis C	Hepatitis C screen	Refer to liver specialist for treatment of hepatitis C
Lymphocyte count	CBC with differential	Consider risks and benefits of B-cell depletion in patients with baseline low lymphocyte counts
HIV	HIV screen	Consider risks versus benefits of B-cell depletion in patients with HIV.
Immunoglobulin levels	IgG, IgM, IgA levels	Consider risks versus benefits in patients with baseline hypogammaglobulinemia
Varicella	Varicella zoster virus IgG	Vaccinate against varicella prior to starting B-cell depletion if not immune
TB screening	QuantiFERON TB Gold or tuberculin skin test	Referral to infectious disease for treatment of latent TB
Immunization	N/A	Review immunization record for all recommended vaccines. Consider vaccination against pneumococcus

a per labels for rituximab and ocrelizumab. Abbreviations: TB, tuberculosis

women who received ocrelizumab vs placebo or interferon β-1a in clinical trials. As a result, the ocrelizumab label contains a statement that an increased risk of malignancy including breast cancer may exist.[18] Updated data from ongoing ocrelizumab clinical trials and open-label extension are reassuring, and over time and with greater numbers of treated individuals, rates of all malignancies, including breast cancer, in those exposed to ocrelizumab appears no different than the background cancer risk.[19] The FDA recommendation is that "patients should follow standard breast cancer screening guidelines." We counsel all patients to maintain all age-appropriate cancer screenings with their primary care physician, but we do not feel that any additional breast cancer screening is necessary with ocrelizumab specifically. There has been no suggestion of increased breast cancer risk with rituximab[3] or ofatumumab.

Long-Term Considerations

As a class, antiCD20$^+$ agents are considered among the highest efficacy treatments for MS. Although these drugs are well tolerated in general, the long-term safety profile is incompletely characterized for all agents.

Iatrogenic hypogammaglobulinemia is a known complication in a minority of people receiving long-term rituximab treatment for nonneurologic indications[19,20] as well as in MS.[21,22] In people receiving ocrelizumab during clinical trial extensions and open-label follow-up, low IgG levels were seen rarely after 2 years of treatment, correlating with a small increase in infection rates.[23] We recommend checking IgG levels at least at baseline and at 2 years in those using antiCD20+ agents and in anyone experiencing unexplained infections. Dose adjustment or extended interval dosing may be an option in patients with mild hypogammaglobulinemia. Treatment discontinuation and immunoglobulin replacement therapy can be used in the rare event of severe hypogammaglobulinemia.

The optimal dose and dosing interval for antiCD20$^+$ agents may vary depending on individual factors (eg, age, weight, sex, and immunologic biomarkers) but these factors each need further exploration. It has been suggested that early repopulation of peripheral CD19$^+$ B cells over time may indicate that more frequent or higher dosing of antiCD20$^+$ agents might be required, but definitive evidence supporting this strategy is lacking. We do not currently recommend tracking B cell subsets.

Future Directions

Additional questions remain. Although antiCD20$^+$ agents can be used as first-line MS treatment, it is difficult to know which patients would benefit most from B-cell depletion early in their treatment course. Similarly, after many years of B-cell depletion, it is not known whether de-escalation to lower efficacy drugs should be recommended, or when it is safe to discontinue therapy altogether.[3,6] Finally, for people in a progressive phase of their disease without recent relapses or MRI changes, better biomarkers are needed to help clinicians weigh benefits of prolonged treatment against potential risks. ■

1. Mitsdoerffer M, Peters A. Tertiary lymphoid organs in central nervous system autoimmunity. *Front Immunol*. 2016;7:451.
2. Li R, Rezk A, Healy L, et al. Cytokine-defined B cell responses as therapeutic targets in multiple sclerosis. *Front Immunol*. 2016;(6):626.
3. Greenfield A, Hauser S. B-cell therapy for multiple sclerosis: entering an era. *Ann Neurol*. 2018;83(1):13-26.
4. Serafini B, Rosicarelli B, Magliozzi R, Stigliano E, Aloisi F. Detection of ectopic B-cell follicles with germinal centers in the meninges of patients with secondary progressive multiple sclerosis. *Brain Pathol*. 2004;14(2):164-174.
5. 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(4):1089-1104.
6. Gelfand J, Cree B, Hauser S. Ocrelizumab and other CD20+ B-cell depleting therapies in multiple sclerosis. *Neurotherapeutics*. 2017;14:835-841.
7. Hauser S, Waubant E, Arnold D, et al. B-cell depletion with rituximab in relapsing-remitting multiple sclerosis. *N Eng J Med*. 2008;358:676-688.
8. Salzer J, Svenningsson R, Alping P. Rituximab in multiple sclerosis: a retrospective observational study on safety and efficacy. *Neurology*. 2016;87(20):2074-2081.
9. Granqvuist M, Boremalm M, Poorghobad A, et al. Comparative effectiveness of rituximab and other initial treatment choices for multiple sclerosis. *JAMA Neurol*. 2018;75(3):320-327.
10. Hauser S, Bar-Or A, Comi G, et al. Ocrelizumab versus interferon beta-1a in relapsing multiple sclerosis. *N Eng J Med*. 2017;376:221-234.
11. Hauser S, Bar-Or A, Cohen J, et al. *Efficacy and safety of ofatumumab versus teriflunomide in relapsing multiple sclerosis: results of the phase 3 ASCLEPIOS I and II trials*. Scientific Session at ECTRIMS Annual Meeting. Stockholm, Sweden. Sep 13, 2019. 279581;336.
12. Hawker K, O'Connor P, Freedman M, et al. Rituximab in patients with primary progressive multiple sclerosis: results of a randomized double-blind placebo-controlled multicenter trial. *Ann Neurol*. 2009;66(4):460-471.
13. Montalban X, Hauser S, Kappos L, et al. Ocrelizumab versus placebo in primary progressive multiple sclerosis. *N Eng J Med*. 2017; 376:209-20.
14. Lublin F, Reingold S, Cohen J, et al. Defining the clinical course of multiple sclerosis: the 2013 revisions. *Neurology*. 2014;83:278-86.
15. Rituxan [Prescribing information]. South San Francisco (CA): Genentech, Inc; 2019. Available from: https://www.gene.com/download/pdf/rituxan_prescribing.pdf.
16. Farez M, Correale J, Armstrong M. et al. Practice guideline update summary: vaccine-preventable infections and immunization in multiple sclerosis. *Neurology*. 2019;93:584-94.
17. Ocrevus [Prescribing information]. South San Francisco (CA): Genentech, Inc; 2019. Available from: https://www.gene.com/download/pdf/ocrevus_prescribing.pdf.
18. Hauser S, Kappos L, Montalban X, et al. *Safety of ocrelizumab in multiple sclerosis: updated analysis in patients with relapsing and primary progressive multiple sclerosis*. Poster session at ECTRIMS Annual Meeting. Stockholm, Sweden. Sep 11, 2019. 279008; P648.
19. Casulo C, Maragulia J, Zelenetz A. Incidence of hypogammaglobulinemia in patients receiving rituximab and the use of intravenous immunoglobulin for recurrent infections. Clin Lymphoma Myeloma Leuk. 2013;13(2):106-11.
20. Makatsori M, Kiani-Alikhan S, Manson A, et al. Hypogammaglobulinaemia after rituximab treatment—incidence and outcomes. *QJM*. 2014;107(10):821–28.
21. Zoehner G, Miclea A, Salmen A, et al. Reduced serum immunoglobulin G concentrations in multiple sclerosis: prevalence and association with disease-modifying therapy and disease course. Ther Adv Neurol Disord. 2019;12:1756286419878340.
22. Hallberg S, Boremalm M, Evertsson B, et at. *Risk of hypogammaglobulinemia in long-term treatment with rituximab in multiple sclerosis*. Scientific Session at ECTRIMS Annual Meeting. Stockholm, Sweden. Sep 11, 2019. 279398; 64.
23. Derfuss T, Weber M, Hughes R, et al. *Serum immunoglobulin levels and risk of serious infections in the pivotal phase III trials of ocrelizumab in multiple sclerosis and their open-label extensions*. Scientific Session at ECTRIMS Annual Meeting. Stockholm, Sweden. Sep 11, 2019; 279399; 65.

Brian Barry, MD
Department of Neurology
MedStar Georgetown University Hospital
Washington, DC

Robert K. Shin, MD
Professor
Department of Neurology
MedStar Georgetown University Hospital
Washington, DC

Disclosures
BB reports no disclosures; RKS has disclosures at www.practicalneurology.com