

EDITORIAL



B-Cell Depletion — A Frontier in Monoclonal Antibodies for Multiple Sclerosis

Peter A. Calabresi, M.D.

Multiple sclerosis is a disabling autoimmune disease in which immune cells target central nervous system (CNS) antigens, leading to demyelination, glial activation, and subsequent loss of neurons and axons.¹ There are three main subtypes of multiple sclerosis: relapsing–remitting, in which patients recover partly or fully from attacks but go on to have others; secondary progressive, in which patients with relapsing–remitting disease have progression of disability between attacks; and primary progressive, in which patients have continual progression from the time of onset of the disease.² Over the past two decades, a remarkable number of new therapies have been developed that reduce the rate of relapses, reduce accumulation of lesions seen on magnetic resonance imaging (MRI), and modestly slow disability, but these are effective almost exclusively in relapsing multiple sclerosis.³

Most therapies for multiple sclerosis target T-cell activation, the trafficking of these cells into the CNS, and effector functions of the lymphocytes, but many have concomitant effects on B cells. Because B cells also migrate from the peripheral blood into the CNS in patients with multiple sclerosis and these cells produce immunoglobulins, which are a characteristic finding in the cerebrospinal fluid, several phase 1b and 2 studies have tested the efficacy of the B-cell–depleting chimeric anti-CD20 monoclonal antibody rituximab.^{4,7} This therapy has reduced relapses and MRI activity in patients with relapsing–remitting multiple sclerosis but has not slowed the progression of disability in patients with primary progressive multiple sclerosis, except in a post hoc analysis of patients younger than 51 years of age and

with gadolinium-enhancing lesions on MRI. Hauser et al.⁸ and Montalban et al.⁹ now report in the *Journal* the results of phase 3 trials of a new and fully humanized monoclonal anti-CD20 antibody, ocrelizumab, in two clinical trials in relapsing multiple sclerosis and one trial in primary progressive multiple sclerosis.

In the identical trials involving patients with relapsing multiple sclerosis, called OPERA I and OPERA II, Hauser et al. compared ocrelizumab at a dose of 600 mg every 24 weeks versus interferon beta-1a at a dose of 44 μ g three times a week for 96 weeks. Both trials showed a significant effect of ocrelizumab on the primary outcome of annualized relapse rate, with ocrelizumab resulting in a 46% or 47% lower rate than with interferon beta-1a. The percentage of patients with disability progression and the number of lesions on MRI were also significantly lower in the ocrelizumab group. Remarkably, in the ORATORIO trial by Montalban et al. involving patients with primary progressive multiple sclerosis, a previously untreatable subtype of the disease, the relative risk of disability progression was approximately 25% lower among patients who received 600 mg of ocrelizumab every 24 weeks for at least 120 weeks than among those who received placebo. In addition, the total volume of brain lesions on T₂-weighted MRI decreased with ocrelizumab and increased with placebo. This is the first drug to show a significant effect in slowing disability progression in a phase 3 trial in primary progressive multiple sclerosis, and therefore the trial represents a landmark study in the field.

The mechanism by which B-cell depletion achieves these effects is not fully understood but

may be multifunctional, because B cells have important roles in antibody secretion, antigen presentation, and the release of effector cytokines. Although there are several other antigen-presenting cells, such as dendritic cells and monocytes, B cells by virtue of their number may be important antigen-presenting cells in multiple sclerosis. Previous studies have shown that rituximab rapidly reduced secretion of the inflammatory cytokines interferon- γ and interleukin-17 from T cells in patients with multiple sclerosis, findings that are consistent with the early reduction of active gadolinium-enhancing lesions observed with anti-CD20 therapy.¹⁰ In addition, the B cell is a reservoir for Epstein–Barr virus, which has been implicated in the pathogenesis of multiple sclerosis by virtue of its high sequence homology with myelin basic protein, and it is interesting to speculate that B-cell depletion may eliminate this reservoir, thereby decreasing autoreactivity, although this has not been proven.^{11,12}

Primary progressive multiple sclerosis is characterized by insidious progression of disability over years with no remission and low MRI activity, and it is generally considered less inflammatory and more neurodegenerative than relapsing multiple sclerosis. These features are cited as explanations for the failure of other immunosuppressive drugs to decrease disease progression in primary progressive multiple sclerosis. One possible explanation for the positive effects of ocrelizumab in the ORATORIO trial is that the patient population included younger patients (mean age, approximately 45 years) and those with active MRI scans (>25% had gadolinium-enhancing lesions), allowing for a measurable antiinflammatory effect of ocrelizumab in patients who had some inflammation at an early, reversible stage of the disease. Another possible explanation is that B cells may mediate pathologic processes by secretion of cytokines or by deposition of immunoglobulins after they enter the CNS. B cells and plasma cells secrete antibodies that may target CNS antigens such as myelin, neurons, and glia, which could accelerate neurodegeneration or inhibit myelin repair.¹³ The continued separation of disability progression curves in the ORATORIO trial beyond 52 weeks, when antiinflammatory effects have been maximized, and success in the relatively noninflammatory disorder of primary progressive multiple sclerosis suggest that additional mecha-

nisms of action may be operational, and further study is warranted.

Although ocrelizumab offers promise for patients with primary progressive multiple sclerosis, who are desperately in need of a therapy, side effects must also be considered. Agents that target the immune system often result in some degree of immune suppression, potentially rendering the host susceptible to infections and impaired immune surveillance of new cancer cells, which could increase the risk of neoplasms. Although the dreaded complication of other drugs for multiple sclerosis, infection with JC virus causing progressive multifocal leukoencephalopathy, has not been seen with B-cell depletion in multiple sclerosis to date, there does appear to be a higher-than-normal risk of herpes reactivation and of neoplasms, especially breast cancer. These side effects will need to be studied in future trials and in phase 4 monitoring in the community to understand the extent of the risk. Clinicians are urged to carefully consider which patients might benefit the most from ocrelizumab and to stay vigilant with regard to monitoring for side effects that could be managed effectively if detected early.

Disclosure forms provided by the authors are available with the full text of this editorial at NEJM.org.

From the Department of Neurology, Johns Hopkins University School of Medicine, Baltimore.

This editorial was published on December 21, 2016, at NEJM.org.

1. Frohman EM, Racke MK, Raine CS. Multiple sclerosis — the plaque and its pathogenesis. *N Engl J Med* 2006;354:942-55.
2. Lassmann H, van Horssen J, Mahad D. Progressive multiple sclerosis: pathology and pathogenesis. *Nat Rev Neurol* 2012;8:647-56.
3. Comi G, Radaelli M, Soelberg Sørensen P. Evolving concepts in the treatment of relapsing multiple sclerosis. *Lancet* 2016 November 23 (Epub ahead of print).
4. Franciotta D, Salvetti M, Lolli F, Serafini B, Aloisi F. B cells and multiple sclerosis. *Lancet Neurol* 2008;7:852-8.
5. Naismith RT, Piccio L, Lyons JA, et al. Rituximab add-on therapy for breakthrough relapsing multiple sclerosis: a 52-week phase II trial. *Neurology* 2010;74:1860-7.
6. 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;66:460-71.
7. Hauser SL, Waubant E, Arnold DL, et al. B-cell depletion with rituximab in relapsing-remitting multiple sclerosis. *N Engl J Med* 2008;358:676-88.
8. Hauser SL, Bar-Or A, Comi G, et al. Ocrelizumab versus interferon beta-1a in relapsing multiple sclerosis. *N Engl J Med*. DOI: 10.1056/NEJMoa1601277.
9. Montalban X, Hauser SL, Kappos L, et al. Ocrelizumab ver-

sus placebo in primary progressive multiple sclerosis. *N Engl J Med*. DOI: 10.1056/NEJMoa1606468.

10. 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;67:452-61.

11. Shannon-Lowe C, Rowe M. Epstein Barr virus entry; kissing and conjugation. *Curr Opin Virol* 2014;4:78-84.

12. Lünemann JD, Jelčić I, Roberts S, et al. EBNA1-specific T cells from patients with multiple sclerosis cross react with

myelin antigens and co-produce IFN-gamma and IL-2. *J Exp Med* 2008;205:1763-73.

13. Michel L, Touil H, Pikor NB, Gommerman JL, Prat A, Bar-Or A. B cells in the multiple sclerosis central nervous system: trafficking and contribution to cns-compartmentalized inflammation. *Front Immunol* 2015;6:636.

DOI: 10.1056/NEJMe1614717

Copyright © 2016 Massachusetts Medical Society.