MILESTONE 8

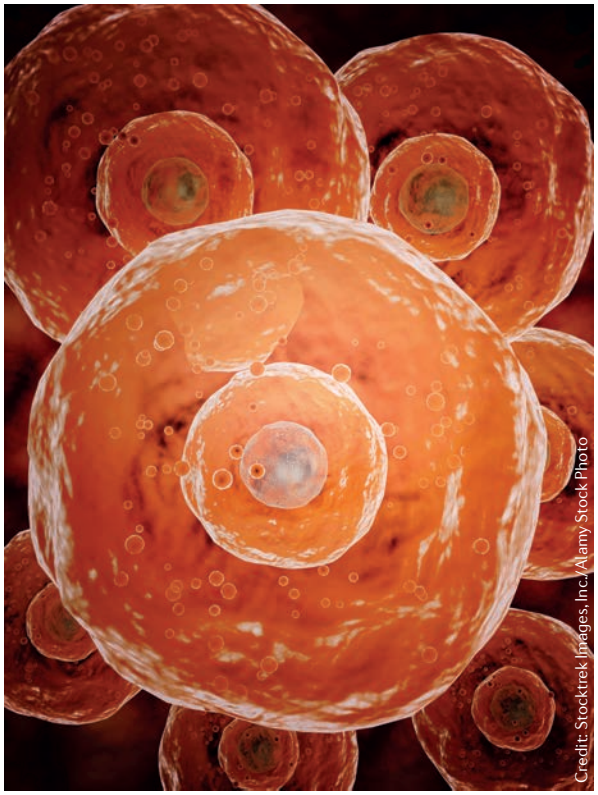
Targeting B cells leads to breakthrough therapy

Traditionally, T cell-mediated neuroinflammation has been considered central to the pathogenesis of multiple sclerosis (MS). Over the past few years, however, B cells have also emerged as key players in the MS disease process and are providing an important focus for the development of new disease-modifying therapies for both relapsing and progressive forms of the condition.

In MS, the inflammatory environment in the brain is thought to promote the proliferation, maturation and survival of B cells — effects mediated by trophic factors such as BAFF (B cell-activating factor of the TNF family) and APRIL (a proliferation-inducing ligand). B cells can produce both pro-inflammatory and anti-inflammatory cytokines, but their pro-inflammatory function seems to predominate in MS. B cells also produce immunoglobulin that forms oligoclonal bands in the cerebrospinal fluid — one of the principal diagnostic features of MS.

Several established MS therapies, including interferon-β (IFNβ), natalizumab and fingolimod, have been found to exert their beneficial effects partially through modulation of B cell function. In light of this knowledge, the B cell-specific monoclonal antibodies rituximab and ocrelizumab have recently been tested in MS. These antibodies selectively deplete circulating B cells by targeting the CD20 antigen, which is expressed on developing and mature B cells.

Rituximab was the first anti-CD20 monoclonal antibody to be licensed for use in humans, and has been approved for the treatment of various conditions, including non-Hodgkin lymphoma, chronic lymphocytic leukaemia and rheumatoid arthritis. In 2008, a phase II placebo-controlled trial of rituximab in patients with relapsing–remitting MS (RRMS) was published. Over the 48-week study period, patients who received rituximab experienced fewer relapses and had fewer gadolinium-enhancing lesions in the brain than those who received placebo.



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> “the efficacy of anti-CD20 B cell-depleting therapies in RRMS and PPMS represents a breakthrough”

Despite the early promise of rituximab, no phase III trials of this drug in patients with MS have yet been published. Consequently, rituximab is not approved by the FDA for the treatment of MS, although it is frequently prescribed off-label for this indication.

The year 2017 saw the publication of OPERA I and OPERA II, two pivotal phase III trials that tested the efficacy and safety of ocrelizumab versus IFNβ-1a in patients with RRMS. The trials had identical designs but were conducted at different locations. Both trials showed that ocrelizumab was more effective than IFNβ-1a at reducing MS disease activity and progression over a 96-week period. A third phase III trial, ORATORIO, demonstrated the benefits of ocrelizumab in patients with primary progressive MS (PPMS; MILESTONE 9).

On the basis of the OPERA I, OPERA II and ORATORIO data, the FDA approved ocrelizumab for the treatment of RRMS and PPMS in March 2017, and the European Medicines Agency followed suit in November 2017.

In all three phase III trials of ocrelizumab, the overall safety profile of the treatment was good. However, in comparison with IFNβ-1a in OPERA I and OPERA II and with placebo in ORATORIO, ocrelizumab treatment was associated with a slight increase in the risk of neoplasms. Furthermore, although no cases of progressive multifocal leukoencephalopathy (PML; MILESTONE 3) occurred in the trials, some cases of PML associated with ocrelizumab therapy have been reported since its approval. For these reasons, ongoing monitoring of the real-world safety of ocrelizumab is needed.

Despite these potential drawbacks, the efficacy of anti-CD20 B cell-depleting therapies in RRMS and PPMS represents a breakthrough. By taking the first steps into previously uncharted territory, this development has further expanded the therapeutic options for RRMS.

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Nature Reviews Neurology

ORIGINAL ARTICLES Hauser, S. L. et al. B-cell depletion with rituximab in relapsing–remitting multiple sclerosis. *N. Engl. J. Med.* **358**, 676–688 (2008) | Hauser, S. L. et al. Ocrelizumab versus interferon beta-1a in relapsing multiple sclerosis. *N. Engl. J. Med.* **376**, 221–234 (2017) | Gelfand, J. M. et al. Ocrelizumab and other CD20$^+$ B-cell-depleting therapies in multiple sclerosis. *Neurotherapeutics* **14**, 835–841 (2017) | FDA approves new drug to treat multiple sclerosis. *FDA* https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm549325.htm (2017) | Ocrelizumab recommended for licensing by European Medicines Agency. *Multiple Sclerosis Trust* https://www.mstrust.org.uk/news/news-about-ms/ocrelizumab-recommended-licensing-european-medicines-agency (2017)

FURTHER READING Krumbholz, M. et al. B cells and antibodies in multiple sclerosis pathogenesis and therapy. *Nat. Rev. Neurol.* **8**, 613–623 (2012)