Genentech's Ocrevus heralds new chapter in MS treatment

The widely anticipated FDA approval of Genentech's CD20-targeting antibody Ocrevus (ocrelizumab) for treating both relapsing and primary progressive forms of multiple sclerosis (MS), on March 28, marks the beginning of a new era in MS therapy. For the first time, patients with primary progressive MS, which is characterized by a steady deterioration in neurologic function, have access to a disease-modifying drug that offers a tangible, if modest, benefit. For patients with relapsing MS, who experience intermittent disease flare-ups punctuated by periods of remission, Ocrevus represents a highly promising addition to an already lengthy list of disease-modifying drugs (**Table 1**). To many observers, Ocrevus looks like a game changer, not least because Genentech, a subsidiary of Basel, Switzerland–based Roche, has challenged its competitors by pricing the drug at $65,000 annually, which represents a significant discount on current prices for MS drugs. What's more, its B-cell-depletion mechanism overturns a long-held dogma that T cells were the main autoimmune actors in MS and were primarily responsible for demyelinating neurons within the central nervous system. Ocrevus is resetting the research as well as the clinical agenda in MS.

Even though the market for relapsing MS drugs is now quite crowded—with products that have differing immunosuppressive mechanisms and varying risk–benefit profiles—Ocrevus has attracted multi-billion-dollar forecasts on the strength of its efficacy and its apparently favorable safety profile. As with any new MS therapy, it will take several years of follow-up study in a large patient population before a fuller understanding of its safety profile will emerge. But for now, Ocrevus is the only approved drug to treat MS by targeting CD20, a mechanism long used for treating other autoimmune conditions, such as rheumatoid arthritis, and B-cell malignancies.

In MS, the new era has been a long time coming. More than a decade ago, a group led by Stephen Hauser at the University of California, San Francisco, found that Genentech's Rituxan (rituximab), a chimeric anti-CD20 antibody first approved in 1997 for treating non-Hodgkin's lymphoma and approved in 2006 for treating rheumatoid arthritis, also had dramatic effects in a phase 2 trial in MS. Shortly afterwards, Basel, Switzerland–based Roche became the outright owner of Genentech and terminated the program in favor of a newer, humanized successor with a longer patent life (*Mult. Scler.* **21**, 8–21, 2015). Off-label use of Rituxan in MS treatment has continued, particularly in Sweden, where the drug has delivered on its initial promise, even if the supporting evidence base (*Neurology* **87**, 2074–2081, 2016) is at this point much thinner than that underpinning Ocrevus, which has completed a comprehensive development program.

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The immune system attacks myelin sheaths in multiple sclerosis, but the precise role played by B cells remains poorly understood.

In two phase 3 registration trials in patients with relapsing MS, Ocrevus proved to be markedly more effective than Rebif (interferon β-1a), long a mainstay of therapy. Relapse rates for patients on Ocrevus were 46–47% lower than they were for those on Rebif (*N. Engl. J. Med.* **376**, 221–234, 2017). The benefit in primary progressive MS was more marginal: after 12 weeks of therapy, 32.9% of those on Ocrevus had confirmed disability progression, as compared with 39.3% of those on placebo (*N. Engl. J. Med.* **376**, 209–220, 2017).

"The effects are not absolutely stunning," says Hartmut Wekerle, senior professor of neuroimmunology at the Max Planck Institute of Neurobiology in Martinsried, Germany. The data may be of more theoretical than clinical value, he says. At the very least, they challenge the view that progressive MS is radically different from relapsing MS and requires a totally different approach to treatment, based on tackling neurodegeneration rather than inflammation. Basel, Switzerland–based Novartis last year reported a similar outcome in a phase 3 trial of siponimod, an oral sphingosine 1-phosphate receptor modulator, in patients with secondary progressive MS, in which the acute events associated with relapsing MS give way to a steady decline in function that is akin to the primary progressive pathology. "That, in principle, means, even in the progressive stage, there is a window of opportunity for immuno-modulatory, immuno-suppressive therapies," says Hans Lassmann, head of the neuroimmunology department at the Medical University of Vienna, in Austria. "The border between relapsing and progressive MS is not a sharp line," he added. Genentech and Novartis both recruited progressive MS patients with active inflammation at baseline, who may have contributed disproportionately to the modest efficacy signals that were detected. On the primary endpoint, a reduction in disability progression, only male primary-progressive-MS patients appeared to benefit from Ocrevus—there was no substantial difference between female patients on Ocrevus or on placebo with respect to disability progression, the US Food and Drug Administration (FDA) noted on the drug's label. Hideki Garran, group medical director, neuroscience, at Genentech, notes that the study was "not powered to demonstrate efficacy differences in gender subgroups, and no firm conclusions can be drawn based on these exploratory subgroup analyses." When additional parameters were taken into account, such as reductions in relapse rates and changes in the volume of existing brain lesions or in the development of new lesions, Ocrevus did confer benefit across the entire study population.

The delay in getting an effective anti-CD20 therapy to MS patients was not solely due to commercial considerations related to patent protection. "The resistance to the idea that B cells could be involved in MS was quite fierce," says Tim Coetzee, chief advocacy, services and research officer, at the National Multiple

Table 1 Approved disease-modifying MS therapies

Drug	Company	Mechanism	Average wholesale price ($)	2016 sales ($ millions)	FDA approval
Betaseron/Betaferon (interferon β-1b)	Bayer (Leverkusen, Germany)	Incompletely understood immunomodulatory mechanism	91,261	690[a]	7/23/93
Avonex (interferon β-1a)/ Plegridy (peginterferon β-1a)	Biogen	Incompletely understood immunomodulatory mechanism	86,308	2,794	5/17/96
Copaxone (glatiramer acetate)	Teva (Petach Tikva, Israel)	Incompletely understood immunomodulatory mechanism	91,401	1,015	12/20/96
Rebif (interferon β-1a)	EMD Serono (Darmstadt, Germany)	Incompletely understood immunomodulatory mechanism	91,005	1,637[a]	3/7/02
Tysabri (natalizumab)	Biogen	α4β1/α4β7-integrin inhibitor that prevents trafficking of T cells into the central nervous system	82,368	1,964	11/23/04
Extavia (interferon β-1b)	Novartis (Basel, Switzerland)	Incompletely understood immunomodulatory mechanism	76,201	NA	8/14/09
Gilenya (fingolomid)	Novartis	Oral sphingosine 1-phosphate (S1P) receptor modulator that reduces levels of circulating lymphocytes by sequestering them within lymph nodes	91,836	3,109	9/21/10
Aubagio (teriflunomide)	Sanofi (Paris)	Oral dihydroorotate dehydrogenase inhibitor that reduces lymphocyte proliferation by disrupting pyrimidine synthesis	80,902	1,217[a]	12/12/12
Tecfidera (dimethyl fumarate)	Biogen	Incompletely understood immunomodulatory mechanism	87,623	3,968	3/27/13
Lemtrada (alemtuzumab)	Sanofi	Cytolytic CD52 inhibitor that depletes circulating T-cells and B-cells	73,039	400[a]	11/14/14
Glatopa (glatiramer acetate)	Sandoz unit of Novartis	Incompletely understood immunomodulatory mechanism	66,731	NA	4/16/15
Zinbryta (daclizumab)	Biogen, AbbVie (North Chicago, Illinois)	Targets the a- subunit (CD25) of the interleukin 2 receptor and blocks T-cell activation by IL-2 receptor signaling	86,592	NA	5/27/16
Ocrevus (ocrelizumab)	Genentech, Biogen	Cytolytic CD20 inhibitor that depletes B cells	65,000	NA	3/28/17

NA, not available. [a]Sales figures converted from €734 million (Betaferon/Betaseron) €1,741 million (Rebif); €1295 million (Aubagio); €425 million (Lemtrada). Sources: company websites; FDA; Dennis Bourdette & Daniel Hartung, Oregon Health & Science University

Sclerosis Society, a New York–based patient advocacy group. There is also a more prosaic explanation: that interrogating T-cell biology was simply easier and doing so also yielded dividends. "B cells have been neglected in MS for trivial reasons. T cells were more accessible for experimental manipulation," says Wekerle. The precise role that B cells play in the disease process remains unclear, but the success of Ocrevus in MS has prompted some scientists to examine the effect on B cells of other MS drugs that operate through poorly understood mechanisms. For example, Amit Bar-Or, of McGill University in Montreal, Quebec, and colleagues recently reported that Tecfidera (dimethyl fumarate), the best-selling drug marketed by Biogen, of Cambridge, Massachusetts, altered the inflammatory profiles of a subset of B cells, leading to a reduction in the expression of several pro-inflammatory cytokines (*J. Immunol.* **198**, 691–698, 2017).

Dissecting out the precise mode of action of any MS drug is a challenge, however. Even Ocrevus does not have a completely clean mechanism. "Anti-CD20 antibodies do not deplete B cells exclusively. There are also CD20-positive T cells," Wekerle says. "We don't know what they contribute to the disease, but they may be players." The converse also holds with respect to other MS drugs, such as Gilenya (fingolimid), Lemtrada (alemtuzumab) and Tysabri (natalizumab). "All of those affect not only T cells but also B cells," says Lassmann. "The reality is we haven't completely sorted out all the immune pathways in MS," Coetzee says. In immunology, answers to experimental questions are rarely black or white.

Clinical experience remains the most important guide to treatment decision-making, given the inherent heterogeneity of the condition, combined with the absence of predictive biomarkers to inform treatment selection. In terms of safety, a possible increase in cancer risk is the most salient issue that was identified during clinical trials of Ocrevus. The drug is contra-indicated in patients with hepatitis B infection—experience with other anti-CD20 antibodies indicates that the virus can become dangerously reactivated in patients who take such a drug. Progressive multifocal leukoencephalopathy, a devastating demyelinating condition caused by activation of the JC virus, has not been observed in any patient on Ocrevus, but previous cases with Rituxan suggest a risk. "I think it is likely to happen," says Lassmann. "The incidence is going to be much lower in comparison with what you see with natalizumab [Biogen's Tysabri]," he adds. In relapsing MS, that may well represent a key competitive differentiator for the drug.

Cost could be another. Genentech's pricing strategy counters a long-standing trend of steep price increases for MS drugs. According to data published this year by the National Multiple Sclerosis Society in collaboration with Dennis Bourdette and Daniel Hartung, of Oregon Health & Science University, in Portland, the average wholesale price for disease-modifying therapies has climbed from $16,000 in 2004 to $61,000 in 2013, and to $83,688 in 2017 Whether the Ocrevus headline price will translate into actual cost benefits to patients and payers after its rivals apply discounts and rebates is an open question for now, given the complexity of and lack of transparency in the drug pricing system. The company has made clear its commitment to stable pricing: "Genentech is committed to fair, reasonable pricing at launch and over the life cycle of Ocrevus, and we do not intend to follow the pattern of current MS [drug] manufacturers with regard to price increases," a spokesperson who wishes to remain anonymous states. Ocrevus will face direct competition from off-label use of Rituxan, as well as its biosimilar successors. It could face a further challenge from another anti-CD20 antibody, ofatumumab, which Novartis already markets in B-cell leukemia as Arzerra. But if it delivers on its undoubted promise, it should allow Genentech to build a substantial position in a completely new disease area.

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