Ocrelizumab and the Next Phase in Multiple Sclerosis Therapy

Advances in immune therapy may change how scientists and clinicians understand neurodegenerative components of MS.

By Thomas Leist, MD, PhD

At the recent Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS), Genentech reported much anticipated top-line results from its phase 3 trials of ocrelizumab, a humanized monoclonal antibody directed against anti-CD20 expressed on B cells. OPERA I and OPERA II, both phase 3 trials that enrolled patients with relapsing MS (RMS), met key efficacy endpoints against an active comparator. The third phase 3 study, the ORATORIO trial, enrolled patients with primary progressive MS (PPMS) and is the first trial to meet its primary endpoint in this form of MS. These data indicate that ocrelizumab has the potential to become a valuable tool in the treatment of a wider range of MS patients.

POSITIONING THE DATA

The two OPERA trials shared a common protocol, enrolled closely matched patient groups, and both were performed in double-blind and controlled fashion, with interferon beta-1a ebif (EMD Serono/Pfizer) serving as comparator. The annualized relapse rate in the 96 week studies was reduced by 46 percent and 47 percent, respectively in the ocrelizumab groups compared to the active comparator. Additionally, 12- and 24-week confirmed disability progression assessed in the combined cohorts was reduced by 40 percent in ocrelizumab treated individuals compared to the active comparator. MRI outcomes also significantly favored ocrelizumab.

The ORATORIO trial was conducted against placebo, as there is no approved therapy for PPMS and with a 2:1 randomization. The primary outcome was confirmed progression of disability at 12 weeks and the trial was continued until a predetermined number of such events had occurred in the total trial cohort. There was a 24 percent reduction of 12 week confirmed disability progression in the cohort receiving ocrelizumab compared to the placebo. In addition, a lower proportion of patients on ocrelizumab experienced a worsening 25-foot compared to placebo, and MRI outcomes significantly favored ocrelizumab.

Adverse events in the ocrelizumab cohorts were comparable to those in the observed in the comparator cohorts (interferon-1a and placebo). In contrast to the ORATORIO trial, prior trials in PPMS did not meet their primary outcomes.

The results of the ORATORIO trial suggest that disease-modifying therapy can ameliorate the disease course. That said, it will be of interest to learn whether certain patient characteristics such as age, presence of enhancing lesions, disease duration, and disability at study entry are associated with a better or muted response to the ocreli-

PRACTICAL POINTER

New Phase 3 data suggest that the monoclonal antibody ocrelizumab may be effective for both relapsing-remitting and primary progressive MS. Ocrelizumab is directed against CD20 and binds to and depletes B cells that express this antigen on their surface along the maturation spectrum. Along with the already approved alemtuzumab and natalizumab, ocrelizumab suggests the possibility of a new spectrum of therapies that interfere with the disease process of MS in a completely different fashion. Moreover, continued innovations in the realm of biologic therapy will usher in new understandings of the neurodegenerative components of MS and other neurological conditions.
zumab. Subgroup analysis of the PPMS trial with rituximab (OLYMPUS trial), a recombinant antibody against CD20 therapy, showed that while the primary outcome was not met, younger patients with active disease appeared to benefit form the treatment.

**B CELLS IN MS**

The results from the phase 3 trials presented at ECTRIMS and the data from previously reported phase 2 studies with anti-CD20 therapy suggest a role for B cell-directed therapy in MS. This is also based in part on observations in animal models of MS. T cells, particularly helper T cells used to be viewed as the central factor in the MS pathology. We have since appreciated—in part also from the rituximab trials—that B cells occupy a central function in the disease process of MS.

Ocrelizumab is a monoclonal antibody directed against CD20 and binds to and depletes B cells that express this antigen on their surface along the maturation spectrum. Pre-B cells and plasma cells do not express anti-CD20. B cells play a central role in the regulation of immune responses including antigen presentation and thus also modulate T cell responses.

To date there have been no immunologic or imaging characteristics that unequivocally link to a clinical phenotype of MS. The observation in the recent phase 3 trials that ocrelizumab may have benefit in both RMS and PPMS suggests that immune-mediated pathology also contributes to ongoing injury in PPMS. Should it turn out that younger patients with PPMS have a somewhat greater response to ocrelizumab (as was observed in the PPMS trial with rituximab), this may indicate that timely treatment should be initiated not only in RMS but also in PPMS.

Another point worth considering is how the positive results in PPMS may affect patients with secondary progressive MS. The trials did not look at this population, but these patients nevertheless have progressive disability and some of them have ongoing inflammatory activity. Thus, ocrelizumab may potentially offer hope for these patients, as well.

**A DISTINCT MODE OF ACTION: QUESTIONS TO CONSIDER**

Arguably the most compelling aspect of ocrelizumab is the effect across a spectrum of clinical presentations of MS. Ocrelizumab reduces circulating B cells that express CD20 but does not eliminate them from the tissue. Following treatment with ocrelizumab, the biologic effect persists beyond presence of the antibody. Ocrelizumab was given every six months in the Phase 3 trials. Nevertheless, the mode of action of ocrelizumab raises the question of whether treatment intervals could be extended for at least some patients.

Another consideration is whether ocrelizumab could be used with even greater benefit in very early MS as an induction therapy/first-line agent to rebalance the immune system. If the favorable safety profile seen in the clinical trials is confirmed in the extensions studies and in clinical use in a wider spectrum of patients, the notion of ocrelizumab as an induction therapy is especially exciting since we do not have such a treatment that allows a “soft reset” of the autoreactive immune response. The relatively short time interval during which ocrelizumab is detectable in the body may also allow for sequential treatments using induction therapy followed by a maintenance agent. These scenarios haven’t been studied, but the unique mode of action of this B cell antibody allows us to envisage new ways sequencing therapeutic agents to augment clinical benefit.

More recently, meningeal B cell follicles have been described particularly in patients with progressive MS. It has been proposed that in such follicles cyto- and chemokines are produced that may be neurotoxic for neurons in the adjacent cerebral gray matter. Based on these considerations and separate other immune functions and production of antibodies, B cells may contribute to neuronal injury in addition to immune effects. It will be interesting to explore whether anti-CD20 therapy could ameliorate the potential contribution of meningeal B cell follicles to injury of abudding gray matter.

**TOWARD A NEW MODEL OF TREATMENT**

Ocrelizumab appears to offer benefit in both RMS and PPMS. As with other high efficacy MS medications, there is also a suggestion with this agent that we have reached a limit of what can be achieved with immunomodulation alone in RMS. While we still have much to learn about ocrelizumab and other immune-targeting therapies, these data nevertheless suggest the possibility of a new spectrum of therapies that interfere with the disease process in a completely different fashion. In the very near future, we may no longer just be targeting immune cells but offering reparative and neuroprotective mechanisms. Agents such as ocrelizumab and the already approved alemtuzumab (Lemtrada, Genzyme) and natalizumab (Tysabri, Biogen) have pushed us to a point where we have potentially reached a ceiling effect of immune interventions, particularly as immune mechanisms outside the CNS are concerned.

However, despite these positive developments and the suggestion of new types of therapies, the road ahead is not...
necessarily smooth, for every advance into new territory is a reminder of how far we have yet to go. We now have medications that significantly reduce relapses, disability progression, and MRI measures beyond that achieved by first generation MS medications. However, the results of the ORATORIO trial also indicate that control of more established processes within the central nervous system (as are present in progressive MS) may pose additional challenges.

Also, when it comes to clinical trials for progressive forms of MS, new tools to quantitatively assess disability progression are urgently needed. Hopefully this will change, but at present this poses as a significant roadblock for clinical research in this area of great unmet needs.

Another question that remains is whether the effect of anti-CD20 therapy observed in PPMS in the ORATORIO trial and a younger more active subgroup in the OLYMPUS trial is conveyed solely by the anti-inflammatory effect, or whether the effect of anti-CD20 therapy also exerts an indirect effect on neurodegenerative processes mediated by cytokines and cells of the innate immune system.

NEW PATHWAYS IN UNDERSTANDING NEURODEGENERATIVE DISEASE

It has become abundantly clear that we urgently need new composite outcomes that allow us to assess other dimensions, such as cognition, vision, and other functions that are significantly affected in MS. After all, without meaningful outcomes, therapeutic modalities in development cannot establish an indication.

As we strive to answer questions at hand, new ones emerge. In the era of treatment, much has been learned about MS via the process of “reverse engineering.” While the first successful trial in PPMS answers certain questions, other agents directed to improve neuronal repair—e.g. anti-lingo (Biogen) and Anti-Repulsive Guidance Molecule A (AbbVie)—have entered clinical development. Therefore, if ocrelizumab secures approval, it would hopefully be the first of several biologic agents, each potentially addressing different aspects of progressive forms of multiple sclerosis.

In addition to potentially offering significant benefit for patients with MS, the addition of such agents may enable scientists and clinicians to better understand and address neurodegenerative components not only in MS, but also in Parkinson’s disease, ALS, Alzheimer’s disease, and other neurological conditions.

Thomas Leist, MD, PhD is a Professor of Neurology and Director of the Comprehensive Multiple Sclerosis Center at Thomas Jefferson Memorial Hospital in Philadelphia, PA.

NEW DEVELOPMENTS IN MULTIPLE SCLEROSIS

GLOBAL MULTIPLE SCLEROSIS THERAPEUTICS MARKET EXPECTED TO REACH $20 BILLION BY 2024

The global therapeutics market over the next decade for MS is expected to swell to $20 billion at a compound annual growth rate of 1.5 percent, according to a new report. The recently published “EpiCast Report: Multiple Sclerosis – Epidemiology Forecast to 2024” concluded that this growth mostly will be driven by the continued uptake of premium products and an increase in treatment rates as a result of the availability of novel alternatives. The report provides an overview of the risk factors, comorbidities, and global trends for MS in the 10 major multiple sclerosis markets (10MM: US, France, Germany, Italy, Spain, UK, Japan, Canada, China, and India). It includes a 10-year epidemiological forecast of the diagnosed prevalent and diagnosed incident cases of MS segmented by sex and age in these markets. For more information, visit http://www.rnrmarketresearch.com/

NEW FINDINGS SUGGEST THAT NEURAL STEM CELLS PROMOTE REMYELINATION

Endogenous neural stem cells might offer a new therapeutic avenue for the treatment of demyelinating disorders such as MS, according to a new study published in Nature (October 15). Specifically, the authors looked at a subset of adult neural stem cells, identified by their expression of Gli1, a transcriptional effector of the sonic hedgehog pathway. They showed that these cells are recruited from the subventricular zone to populate demyelinated lesions in the forebrain but never enter healthy, white matter tracts. The authors concluded that inhibition of Gli1 improves the functional outcome in a relapsing/remitting model of experimental autoimmune encephalomyelitis and is neuroprotective.