Filling the Gaps in the Multiple Sclerosis Treatment Landscape

The addition of a potential breakthrough agent may change the treatment arena, but wellness and early treatment remain the foundation of effective care.

With Patricia K. Coyle, MD

With last month's FDA approval, the long-awaited arrival of ocrelizumab (Ocrevus, Genentech) is likely to have a significant and immediate impact on the treatment of both relapsing and primary progressive multiple sclerosis (MS). Though it is not a proverbial magic bullet, a robust efficacy profile in relapsing MS coupled with its status as the first approved treatment for primary progressive MS together make ocrelizumab a singular agent and a potential breakthrough that may shape new approaches to care. Still, many gaps remain in the therapeutic landscape. According to Patricia K. Coyle, MD, Professor of Neurology and Vice Chair of Clinical Affairs at Stony Brook University, selecting an optimal treatment regimen is no less a challenge. Ahead, Dr. Coyle reflects on the implications of the changing treatment market and assesses current approaches to care.

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How would you characterize the current therapeutic landscape for MS and what are some of the barriers to optimal care?

There are many gaps in the treatment spectrum for MS, according to Dr. Coyle, but two main domains in particular stand out as target points in current and future development to improve therapy. "The first is in the area of true neuroprotective treatments that are acting on mechanisms within the central nervous system," says Dr. Coyle. This would include treatment of the neurodegenerative phase of MS, which, she notes, underlies progressive MS. "The second domain is meaningful CNS repair strategies, which are currently lacking," observes Dr. Coyle. While little is established in either of these two domains, Dr. Coyle is nonetheless hopeful that ongoing and future research will produce meaningful treatment solutions. "It's very promising that we're actually engaged in preliminary trials that are evaluating potential therapies in both areas in MS patients."

Despite pronounced gaps, the therapeutic tool box for relapsing MS boasts a number of molecules and unique mechanisms of action. With such a robust treatment armamentarium, selecting an optimal disease modifying therapy can be a dilemma. "We have major issues with regards to how we optimally choose what might be best for the individual patient," Dr. Coyle observes. "Since we currently lack meaningful biomarkers, when selecting a treatment regimen we generally talk about broad patient factors, disease factors, and drug factors, in addition to more practical concerns such as insurance." (*Editor's Note: For more insight on weighing patient, disease, and drug factors, see Dr. Coyle's article in the March 2016 edition of Practical Neurology® magazine, available at PracticalNeurology.com.*)

Regarding financial aspects of treatment, specifically, Dr. Coyle notes that third-party payers often limit access to disease modifying therapy, either not funding certain therapies or requiring patients to fail other costly therapies first. In addition to insurance-related challenges, Dr. Coyle observes that the high cost of MS medications places great restric-

tions on the ability to deliver the therapy that patients need. "In the United States, we pay more than anyone else in the world for disease modifying therapy," Dr. Coyle notes. "While the expectation is that generic drugs are cheaper and drive prices down, we need to get control of the price of therapies." She adds that one solution to the unsustainable costs of therapy would be for the government to get involved and negotiate prices.

Can you talk about the recent approval ocrelizumab and the role it may play in both relapsing and primary progressive MS therapy?

The approval of ocrelizumab (Ocrevus, Genentech) is significant for a number of reasons, not least among which is the psychological impact of the first approved drug for primary progressive MS, according to Dr. Coyle. "We have not yet had a DMT for a pure progressive form of MS approved, which makes the approval of any agent a huge psychological boost for patients and physicians alike," Dr. Coyle notes.

Regarding the benefits of ocrelizumab in primary progressive MS, the data do not suggest it will be a home run therapy, says Dr. Coyle. "While this agent appears to slow progression in a modest fashion, ideally you want to prevent progression," she says. "Based on the data, the benefits are predominantly upfront, demonstrating an anti-inflammatory impact as opposed to documenting a true effect on neurodegeneration." Dr. Coyle notes further that future studies will likely elucidate whether ocrelizumab proves to be a truly effective agent that offers neuroprotection for primary progressive MS. Nevertheless, she points out, the psychological benefit of the approval cannot be overstated. "To be able to say to optimized, younger primary progressive patients early in their course that we have an agent that we can try is a huge psychological boost," she says, while further noting that those who have a superimposed inflammatory component as marked by contrast enhancing lesions seem to be the optimal treatment response group.

Ocrelizumab's efficacy in relapsing forms of MS, however, appears to be much stronger, as data from the OPERA trials suggest. In addition to its excellent efficacy profile, Dr. Coyle notes that ocrelizumab is very well tolerated and comes with a favorable delivery and dosing schedule. "The patient is going to an infusion center for a couple of hours, two days out of the year, which is both convenient and ensures adherence." While ocrelizumab will likely be very appealing for many patients, the critical issue regarding its use will be cost. Given the already burdensome financial limitations of many disease-modifying therapies, it's very likely that the high cost of treatment (roughly $65,000 per year, according to *The New York Times*) may limit its use. Genentech has indicated that it will be offering comprehensive services for individuals who are prescribe Ocrevus to help minimize barriers to access and reimbursement.

Another intriguing possibility is that the approval of ocrelizumab might draw more attention to rituximab and possibly liberalize its use, according to Dr. Coyle. "Rituximab was the basis for the expectation that ocrelizumab would work in treating relapsing MS," says Dr. Coyle. She also points out that a previously published phase 2 trial in relapsing MS was very positive and that it has been used off label in MS a fair amount with good results. "From a financial point of view, if ocrelizumab come with a steep price, the possibility that third-party payers making rituximab available at a lower price would represent a reasonable alternative for patients."

Beyond pharmacologic therapies, what other developments or trends may impact future care?

In addition to new therapies and ongoing inquiry into neuroprotective treatments, Dr. Coyle observes that strides are being made elsewhere in the realm of MS research. "We're starting to see non-conventional imaging techniques being put into the clinical marketplace, with the big one being brain atrophy, volume loss," she says. "The dogma has been that you really can't use volume loss as helpful biomarker on an individual basis, but we now have two commercial programs that offer brain volume readouts and we're also beginning to see studies that are making this available to individuals on one-to-one patient basis," she says. This will allow physicians to see exactly how the data may be used in addition to conventional clinical and conventional MRI data.

Another area of increasing emphasis is controlling vascular risk factors and aiding CNS reserve through wellness programs. Wellness programs encompass appropriate diet and exercise regimens, which Dr. Coyle believes can have a powerful impact on the disease. "We should really consider these distinct treatments for all patients with MS, and I personally believe these programs can enhance response to a disease modifying therapy," she explains.

The concept of early treatment of MS is also gaining more traction, says Dr. Coyle. "Increasingly we're going to be wrestling with the concept of escalation versus induction therapy, which prompts us to weigh the importance of efficacy in the initial selection of a disease modifying therapy," she says. "Are there some patients that should be put on an

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Wellness regimens can enhance response to a disease modifying therapy and can also be considered distinct treatment for all patients with MS.

efficacious treatment early even if they may be at somewhat greater risk?" Whether patients ultimately do better under this paradigm remains to be seen, but Dr. Coyle notes that studies are being funded to address these questions.

How important are pain and symptom management in MS care?

"Pain is a symptom that is increased in MS, reflecting sensory tract involvement," explains Dr. Coyle. While pain can be considered a positive sensory symptom of MS, Dr. Coyle emphasizes the importance of understanding and addressing it. "Regarding optimized symptom management of MS, the better we understand the symptom, its classification, and what works with regard to effective therapies or what should be offered, then the better care we are delivering to the patient." Education in symptom management can have a keen impact on quality of life, she notes, and is essential for those treating patients with MS. In addition, understanding and treating pain can also offer insights into the individual patient's disease. "Your treatment will likely differ based on the type of pain a patient is feeling, whether it's a paroxysmal pain or a secondary musculoskeletal arthritic type pain, for example," she explains. "All of that influences how you optimize approaches to treatment."

Pain is classically a later symptom of MS (with the exception of paroxysmal neuralgia). Therefore, according to Dr. Coyle, early and aggressive treatment may have an impact on the patient's pain spectrum later in the disease. "To my way of thinking, in part, if you get patients on effective treatment early, that's going to minimize the damage to their central nervous system and potentially avoid future significant pain symptoms." This, she notes, represents another justification for early treatment. "The concept of minimizing injury to the CNS tissue should be a guiding one in MS treatment, as such injuries may ultimately manifest as cognitive loss, or as pain or bladder bowel dysfunction."

The broader importance of symptom management in the treatment of MS is magnified by the fact that virtually every patient is going to have one or more symptoms of their disease, Dr. Coyle emphasizes. "Optimized management of MS includes optimized management of their symptoms in addition to optimizing disease modifying therapies and a wellness health maintenance vascular risk factor control program."

How do you expect treatment protocols and guidelines to change if more of those gaps in the therapeutic landscape are filled?

"We may begin to establish some meaningful neuroprotective strategies and ultimately neurorepair strategies, some of which may perhaps come to the marketplace in the next couple of years," says Dr. Coyle. She also expects more progress in the realm of biomarkers that would help to judge treatment response to disease modifying therapies. And finally, she is hopeful that with these continued advances, the concept of early treatment and wellness control will gain more prominence and help improve outcomes in MS patients. "As more research continues to elucidate the mechanisms of the disease and its symptoms, I think that we'll be able to show the concept of early treatment—following patients closely and changing treatment if they're not doing well—and wellness regimens actually help to improve long-term outcomes of our MS patients." ■

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