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Importance of Patient-Centered Outcomes When Evaluating Treatments for Secondary Progressive Multiple Sclerosis

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COMMENTARY

“As my MS specialist said, I have now moved out of the heavily funded relapsing-remitting research category to the little known, least explored category of SPMS [secondary progressive multiple sclerosis]... I may have a rough road ahead.” These are powerful words from a multiple sclerosis (MS) patient obtained as a comment through the MS Coalition Patient Survey.¹

In March 2019, the U.S. Food and Drug Administration (FDA) approved the use of siponimod in patients with relapsing-remitting multiple sclerosis (RRMS) and active SPMS. The manufacturer sought to receive approval for use of siponimod in nonactive SPMS, but the FDA did not agree with the subset analysis of the clinical trial data submitted. The FDA also clarified that active SPMS is a subset of RRMS and all currently approved medications for use in RRMS is also indicated to treat active SPMS.^{2,3}

One of the major determinants by the FDA to grant approval only for the active SPMS indication was due to the subgroup analyses performed regarding patients who had the presence or absence of relapses in the 2 years before the study began. The FDA determined that, while efficacy was demonstrated against placebo in the blended SPMS patient population, this effect was

driven by active SPMS patients due to the effect on the inflammatory aspects of MS (e.g., relapses, MRI activity) versus those with nonactive SPMS.³

In May 2019, the Institute for Clinical and Economic Review (ICER) published its final evidence report on the clinical and economic review of the use of siponimod in active and nonactive SPMS.⁴ ICER determined that there is a small net benefit in patients with active SPMS when compared with the best supportive care. For patients with nonactive disease compared with best supportive care,

or when looking at all patients with SPMS compared with other disease-modifying therapies, there is insufficient evidence for ICER to determine an evidence rating. The economic analysis portion of the ICER report determined that siponimod exceeds commonly accepted willingness-to-pay thresholds of \$50,000-\$150,000 per quality-adjusted life-years gained, when compared with best supportive care in active, nonactive, and overall SPMS populations.

The ICER report listed many sources of uncertainty, most importantly the challenge in clinically differentiating between RRMS and SPMS. In addition, it listed lack of evidence, both in long-term safety and effectiveness of the data, along with lack of patient-reported and patient-centered outcomes. The clinical trials for siponimod did not evaluate outcomes of interest to patients, such as improvement in MS symptoms, caregiver burden, mental health, and overall quality of life.

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MS is a chronic and complicated disease that requires a multifactorial treatment approach to achieve the best clinical outcomes. Patients have symptoms that range from relatively benign to entirely devastating. Patients with MS experience a variety of side effects including bladder, bowel, and/or sexual dysfunction; cognitive impairment; depression; fatigue; gait impairment; heat intolerance; pain; seizures; vertigo; and tremor. As the disease progresses, these symptoms tend to worsen and begin to affect the patient's quality of life.

Many patients with RRMS will transition to SPMS because of gradual worsening of relapses, more frequent relapses, and less recovery of functioning between relapses. It is estimated that approximately 85% of patients are initially diagnosed with RRMS, with a portion of these patients who transition to SPMS. In general, about 25%-40% of patients with RRMS progress to SPMS after about 6-10 years, with a median time to transition anywhere from 10-23 years.⁵

Even the term "transition" is not quite right. It is thought that while some patients may move from RRMS, the predominantly inflammatory type of MS, to SPMS, the predominantly neurodegenerative type, some patients may actually experience both in parallel, rather than consecutively, and both contribute to the pathophysiology of the disease. It is also unclear if SPMS is a result of the chronic inflammation caused by RRMS, or if it is its own separate neurodegenerative process. Studies thus far demonstrate that effective prevention of relapses do not prevent disability in patients with progressive MS.³

Providers also have a difficult time identifying patients with SPMS and/or those in transition from RRMS to SPMS. The 2 types of SPMS, active and nonactive, are determined by whether a patient has experienced either a relapse or there is MRI imaging consistent with MS.⁶ The inconsistency in diagnosing patients with SPMS is a factor, as evidenced in the unclear estimates on prevalence of SPMS, which range from 10.9 per 100,000 to 57.8 per 100,000 across the United States and Europe.⁷ Some providers may not definitively diagnose patients with SPMS, despite suspicions, due to fear of lack of payer coverage for disease-modifying therapies. Unfortunately, there are no biomarkers to test for either active or nonactive SPMS.

It is evident that there is a significant need for high-quality evidence, not only for patients with SPMS, but for outcomes that MS patients deem important. MS patients report that disability progression is one of the most important outcomes, followed by outcomes related to quality of life; MS symptoms (e.g., fatigue, urinary urgency, and pain); and preservation of cognition. Most trials that report on disability use the Expanded Disability Status Scale, which does not account for other elements of disability not associated with mobility, such as cognition and vision. In addition, clinical trials and other studies in the literature are inconsistent in incorporating patient-reported outcomes as either primary or secondary outcomes measures.⁸

The current MS guidelines by the American Academy of Neurology reported that of 58 Class I or Class II clinical trials of disease-modifying therapies, very few trials reported patient-reported outcomes such as improved quality of life, preserved cognition, and improved symptoms, despite patients being overwhelmingly concerned about these drug therapy results.⁸

Most literature today focuses on the somatic effect of therapies on MS but not on how patients' lives are being improved by the therapy. While clinical efficacy is important, creating studies to only show effects on pathology, but not how patients' lives are being improved, will never yield information to clinicians on how best to manage patients with SPMS, a disease mainly of disability. As managed care professionals, our goal should be to promote researchers and manufacturers to design studies that include evaluation of patient-reported outcomes in addition to meeting clinical efficacy.

ICER's report on the use of siponimod is an important step towards adding to the literature for patients suffering from SPMS. It demonstrates that there is still much work to be done to find effective therapies to improve outcomes for patients with this disease. We must listen to patient comments, such as the one at the beginning of this article, to remember the reason we are all here—to help patients live longer, healthier, and more fulfilling lives.

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