Expert Perspective on Evolving Diagnostic and Therapeutic Strategies in Multiple Sclerosis, With Ben Thrower, MD

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***AJMC®*: When evaluating patients, do you perform diagnostic tests other than magnetic resonance imaging (MRI) scans?**

THROWER: MRI scans are the primary tests that are performed to diagnose and evaluate patients with multiple sclerosis (MS). Yes, there are circumstances in which additional testing is needed. Those include, but are not limited to:

1. Lumbar puncture (LP) procedures with cerebrospinal fluid (CSF) analysis to evaluate for elevated immunoglobulin G antibodies, oligoclonal bands, and proteins that breakdown myelin.
2. Blood tests to help rule out diseases with symptoms similar to MS (such as antinuclear antibody and neuromyelitis optica) can also be useful. Additionally, blood tests associated with MS are currently under development that may aid in diagnosing MS.
3. Optical coherence tomography scans to visualize and quantify layers of the retina are also sometimes used.

***AJMC®*: Clinical trials are now routinely measuring brain atrophy as a secondary endpoint. Do you measure brain atrophy in your clinic? If so, do standards exist, or is brain atrophy measured differently depending on the clinical trial or institution?**

THROWER: There is software available which most clinics have access to that includes normative data based on large population analyses. It is important to note that this software is not specific to any particular clinical trial or institution.

In addition, the amount of atrophy can be monitored within the same patient by using serial MRI data. Over time, information obtained from these serial MRI scans can provide patient-specific useful data. In many cases, serial monitoring of MRI data is more useful to clinicians than the software because serial MRI data are patient-specific.

***AJMC®*: Can you discuss the clinical implications related to whole brain atrophy, white matter atrophy, and gray matter atrophy, as well as how each is measured?**

THROWER: Whole brain atrophy, white matter atrophy, and gray matter atrophy can result in cognitive deficits and motor impairment. Determining the contributions of each remains an active area of research. It is currently thought that gray matter atrophy may be more responsible for the cognitive impairments seen in MS. They are all measured the same regardless of system or technique. Different structures and/or spaces, however, are measured to determine the amount of atrophy in that specific area.

***AJMC®*: How does brain atrophy correlate with disease progression as well as with expanded disability status?**

THROWER: A correlation between atrophy, disease progression, and Expanded Disability Status Score (EDSS) does exist. This correlation appears to be most pronounced in patients with primary progressive MS compared with those having relapsing-remitting MS. Overall, there is a lot of variation in clinical

trials and MS clinics in how to correlate brain atrophy with disease progression and EDSS.

AJMC®: How important is neuroprotection?
THROWER: The concept of neuroprotection and the prevention of neurodegeneration is extremely important to clinicians and patients alike. Since the goal of treatment, specifically with regard to the disease-modifying therapies (DMTs), is to prevent disability progression, products that have neuroprotective properties, in theory, can delay disease progression. Data show that preventing disability progression should occur as early in the disease process as possible. This includes patients having clinically isolated syndrome, radiologically isolated syndrome, or relapsing-remitting disease. Likewise, preventing disease progression is also important in patients having active disease defined by clinical relapses and/or new MRI lesions. Defining what parameters constitute neuroprotection is somewhat controversial, however, because no standard definition or criteria exist.

AJMC®: How has first-dose monitoring of fingolimod impacted clinical practice?
THROWER: It is occasionally difficult to gain approval of the first-dose monitoring from managed care organizations. This is frustrating to patients and can delay treatment. On occasion, use of fingolimod has been impacted because of these issues. However, this is not typical.

AJMC®: There are several sphingosine-1-phosphate products in clinical development. In addition to binding to receptor-1, some of these products also bind to receptor-5. What are the clinical implications of binding to both S1P1R and S1P5R? Do you anticipate improved efficacy and safety?
THROWER: More selective binding may translate into a more favorable adverse-effect profile. It will be interesting to see if there are differences in the risk of cardiac adverse reactions and the degree/length of lymphopenia following discontinuation with the products that have more selective binding.

AJMC®: What are the current unmet needs regarding DMTs?
THROWER: Current unmet needs include:

1. Effective treatment for patients with secondary progressive MS.
2. More and improved treatment options for patients with primary progressive MS.
3. Biomarkers to help predict optimal DMT selection for individual patients.