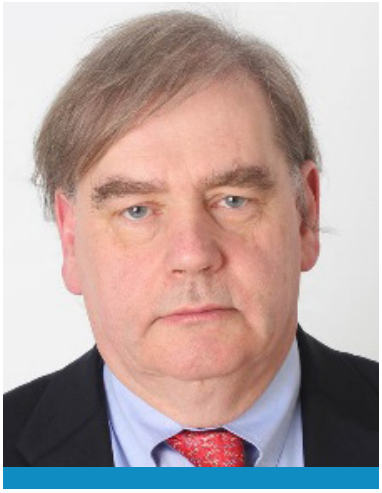
PERSPECTIVES IN MS

Preserving the Brain: How Advances in Pathogenesis Are Fueling New Approaches to Treatment and Highlighting the Need for Biomarkers

A Q&A With Thomas P. Leist, MD, PhD



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***AJMC®*: What are your impressions of the expanding multiple sclerosis (MS) therapeutic landscape and the implications for management?**

LEIST: Over the last 8 years we have had several oral disease-modifying therapies added to the treatment arena for relapsing MS. These medications are attractive choices for patients because they do not have to be self-injected and do not require an infusion. Dimethyl fumarate was added to the market in 2013 and was preceded by fingolimod (2010) and teriflunomide (2012). All 3 [agents] are small molecular entities that allow oral dosing. In 2017, the FDA approved ocrelizumab, a depleting monoclonal antibody. This product was introduced not only for relapsing MS but also primary progressive MS, for which it was the first drug approval. Ocrelizumab was evaluated in 2 sister trials against an existing approved therapy. The prespecified analyses of the individual and combined trial cohorts allowed a hierarchical analysis of a greater number of outcomes and demonstration of superiority in many of these against the active comparator medication.

As we move forward, several agents are being considered, such as a number of S1P receptor modulators following in the footsteps of fingolimod, such as siponimod and ozanimod. This new generation of S1P modulators [have] a shorter half-life than fingolimod and are being tested with a starting initial dose titration in the hope that this may obviate the need for first-dose monitoring. Additional anti–B-cell antibodies are also being studied. Oral cladribine has been approved in many jurisdictions outside the United States and is currently under review by the FDA. Also among these are agents [that target] CD-20, as well as another oral formulation.

These agents add significantly to the treatment armamentarium. They offer hope that effective treatment [will be] accessible to patients in a timely fashion, [and] will lead to more effective management of MS, going beyond the prevention of relapses and motor disability and [toward] preserving brain function in its broadest measure from declining in patients with MS.

***AJMC®*: Can you discuss the concept of brain preservation and why it is important in MS?**

LEIST: Currently, the main disability outcome measure is the Expanded Disability Status Scale [EDSS], so when we refer to the fact that a product reduces disability progression, we are generally referring to EDSS outcomes. The EDSS significantly assesses ambulation and motor function but does not include measures of cognition or memory.

In recent years, it has become clear that disease burden in gray and white matter correlates with outcomes related to brain function and preservation, such as cognition and employability in individuals with MS. Brain and central nervous system preservation is a concept that aims to minimize loss of function and preservation of premorbid functioning in all domains of central nervous system functioning.

As I said, the EDSS, while a valuable tool for many years, does not cover cognitive aspects of neurologic functioning in a meaningful way. The need for new outcome measures in MS is, thus, very great. Our current medications aim to restore immunologic

balance and control autoimmunity. The next generation of medications may exert neuroprotective effects, stimulate remyelination, or help recovery through enhancement of neuronal plasticity. For such efforts to lead to medications with an efficacy claim, recognized novel meaningful outcome measures are needed through which such claims can be established. It has been a long-term effort from all the key stakeholders, including the regulatory agencies, manufacturers, and patient organizations, to come up with a new outcome measure that overcomes the shortcomings of the EDSS. This is an area of active research and a new measures will need to build on the success and intuitiveness of the EDSS while expanding the reach into vision and cognition, because of their importance with respect to functioning in the community.

***AJMC®*: What is the role of gray matter and white matter in the pathogenesis of MS?**

LEIST: Gray matter injury drives a significant component of cognitive decline and motor disability in patients. The appreciation that gray matter pathology is a driver of motor and cognitive disability has raised the need to monitor such pathology during routine care. In everyday practice, we have a hard time assessing injury to gray matter. Routine MRIs obtained as part of regular care can, with adequate technical characteristics, do an adequate job monitoring disease burden in the white matter. Routine MRIs are far less sensitive in detecting gray matter injury and overall the current generation of routine MRIs underestimate the total disease burden. Better MRI tools are needed to assess the disease impact and monitor the effectiveness of interventions.

Regular monitoring of MS patients with MRI is now part of the recommendations of the recommendations of the American Academy of Neurology. The Consortium of Multiple Sclerosis Centers has proposed minimal standards for such MRIs. Unfortunately, many MRIs obtained for MS patients fail to meet these standards. Also, qualitative assessments alone of such scans may not be adequate to fully ascertain disease progression. Solutions to improve the technology are being explored, including the development of automated techniques that allow comparison of MRIs. It is important that there is a standardization of analysis of MRIs and report of findings to improve disease monitoring. We need to move forward toward quantitative measures that are integrated into long-term assessment of patients.

We all know that many patients with MS progress, and some do so in a more overt fashion while others experience less visible changes. It has to be the goal to allow a person with MS to lead a life that is as little encumbered by MS as possible. To achieve this, we need better understanding of the effect of interventions on prevention of progression. This does not just include prevention of inflammatory activity but also neuroprotection and repair. There are several challenges on the path to answering such questions that [need] to be overcome. For instance, we do not have a biomarker that allows us to forecast how a given patient will respond to a specific medication or to prognosticate which patient should be started on which mode of action to garner the greatest therapeutic benefit at [the] lowest safety risk and cost. How do we monitor patients on whether [or not] they are doing well? This information is needed to arrive at the best treatment decisions together with patients. Right now, it is very difficult to assess cognition, and full testing is not feasible in community practice.

A new potential biomarker in development, known as neurofilament light [NFL], has shown promise. NFL may represent a measure to also assess silent neurological injury in patients. If patients have low NFL levels and have stable white matter findings on brain MRI, the combined information may also be reflective of stability in the grey matter. Of course, there are some well-recognized challenges, [namely that] NFL is not MS-specific and may be affected by comorbid conditions, age, and other factors.

***AJMC®*: Can you discuss some of the challenges associated with treatment of MS?**

LEIST: Ideally, we would like to attain a state of no detectable neurologic disease activity within a very short period after diagnosis. I do think that in MS there is a window of opportunity early in the disease during which MS is more amenable to treatment and possible remission. At this point, more often a model of treatment escalation is employed, and patients need to fail treatments in order to gain access to "high-efficacy intervention." Neurologic function lost on this path will not be regained. There is an illusion in MS that one may intervene at different points of disease with the same effect. The reality is that MS is best controlled early on. What is lost cannot be regained, and the disease process may also change in character and be less amenable to disease modification.

Depending on initial presentation of patients and disease severity, there may be a shifting of consideration of both the risk of the disease and [treatments] with proven high efficacy but higher risk cost. My hope is that patients are afforded the opportunity to profit from such efficacy-guided treatment considerations, rather than a step approach affected by extraneous factors, because the window of opportunity is best harnessed early. Additionally, any patient who demonstrates disease activity should be offered alternative treatments, and patients should not be forced through policies to go back to [the] mode of action that [they] have previously used. Patients should always have [the] opportunity to move forward to a mode of disease modification that is distinct from what they have had before.

Because of the maturing MS treatment market, we are finding ourselves at a point [at which] treatment cost and efficacy considerations can be in conflict with each other. The only way to end this is unsatisfactory situation is to work toward treatment and monitoring standards.

***AJMC*®: What are the implications for managed care regarding new advances in the pathogenesis and treatment of MS?**

LEIST: The managed care provider perspective has changed in recent years. It used to be that commercial products were significantly managed by payers, and Medicare and Medicaid coverage were separate. In a certain way, there was a likelihood that an MS patient was going to move on to a government-administered program. This is no longer the case. Very often the same insurance companies may provide coverage to an MS patient across product lines and along the disease path. In certain situations, such coverage may extend to the nursing home products, as in the Commonwealth of Pennsylvania, where dual-eligible patients are enrolled in Health Choice that provides such extended coverage. This potentially affords a rethinking of the approach of carriers to chronic diseases such as MS and may make early stabilization an important goal.

If payers can affect population health, particularly the health of individuals at high risk for the utilization of additional resources, then that consideration may also potentially affect the total profit line of the company. Insurances are changing. The direction in which we are moving is not just [to insure] individual lives but populations. This may potentially offer a new focus on treating diseases, such as MS, across [the] course of these costly disease states, particularly if best management is not introduced in a timely fashion.

***AJMC*®: Given the new directions we are seeing in pathogenesis and treatment, how do you see the MS spectrum taking shape over the next several years?**

LEIST: We are in an era in which we have a number of treatments in our armamentarium. With that, we really need to work hard to prevent disability progression in a given patient. What this also requires is regular monitoring and standardized methods of assessing patients. This will allow more timely recognition when someone is not doing well. This will include integration of wearable technologies.

We have many treatments that have proven efficacy. If one thing is clear, it is that early and effective treatment very often affords patients greater treatment success with the possibility of disease remission in some. When patients have disease activity, they need to be able to switch to other medications that afford the possibility of a better response. Recycling previously experienced modes of action is not in the interest of the patient.

Looking forward, we would like to prevent progression of disease. This will require agents that go above and beyond immunomodulation, and it will require a new set of outcome measures. Without measures, it will be very different to establish an efficacy claim. We need agents that can claim neuroprotection and cognitive preservation for the overall preservation of the brain.