# ASSESSMENT OF NEED

**Clinical Gap 1: Differentiating and Evaluating:** *It is important that clinicians are equipped to accurately differentiate and evaluate PPMS (as compared with RRMS or secondary progressive MS [SPMS]), which affects a smaller percentage of patients but is also potentially much more disabling.*[1] *In addition, acquiring foundational knowledge regarding pathophysiology can help to frame mechanisms of action for potentially effective treatments.*

Increasing understanding of PPMS has helped to inform research approaches, and in the clinical arena related foundational knowledge can ultimately affect determination of prognosis and treatment decisions, as well as information relayed to patients. Just as a more precise understanding of MS progression has been called for in the research realm, it is important that clinicians managing patients with PPMS are familiar with the latest scientific findings on the pathophysiology, hallmarks, and course of this type of MS, with an eye toward practical applications of this knowledge.

Progressive forms of MS are characterized by widespread demyelination as well as diffuse degenerative changes in both white and gray matter (in RRMS, active focal lesions occur mainly in white matter).[2] The exact mechanisms of PPMS progression are still being elucidated, but a pathogenic role of B lymphocytes has been suggested, and a widespread demyelinating pathology has been shown to be associated with inflammation in the overlying meninges, suggesting a potential role for immunotherapy to target this inflammatory aspect. The role of oxidative stress and mitochondrial dysfunction are also hypothesized to have a role in PPMS' pathology.[3] Importantly, recent clinical trial results are challenging the widely held belief that progressive forms of PMS are more degenerative than inflammatory.[4]

Clinicians can be challenged by changes in disease course over time as well as the variable presentation of PPMS, both clinically and on MRI. Because of the criterion of gradual progression without remission over at least a year, a longer time trajectory is required for definitive identification.[5] While patients with PPMS present most commonly with spastic paraparesis, others can exhibit cerebellar ataxia; or brainstem, cognitive, or visual signs/symptoms.[1,6] The use of objective measures whenever feasible to evaluate disease activity and disability progression are crucial, since patients often have trouble determining if they are worsening over time and can also have symptoms that are typical of RRMS, such as fatigue and memory problems.[7]

Overall, PPMS is associated with smaller and fewer lesions on MRI, although the general pattern of PPMS vs RRMS findings on MRI is not objectively distinguishable.[1,6] PPMS is also associated with greater and earlier spinal cord atrophy than RRMS, and cervical cord volume

decreases significantly over 2 years in PPMS.[3] Recent evidence from MRI research has connected the extent and topography of diffuse damage seen in normal-appearing brain white matter, gray matter, and the spinal cord with the severity of PPMS disability. Quantifying this damage with MRI, especially with advanced techniques, can help to predict subsequent MS evolution.[8] However, while MRI findings can shed light on some aspects of progression, at the same time clinicians must be aware of the potential *lack* of correlation between the visualized pathology and actual clinical symptoms, especially early on in progressive cases. And, adding further complexity, there are cases in which patients with progressive disease that manifest with an inflammatory component (as evidenced by relapses and/or MRI changes) and might respond to drugs traditionally used for RRMS.[Error! Bookmark not defined.,9]

Taken together, an evaluation for signs of relapse, MRI lesions, and the speed of disability progression (eg, progression to more advanced disability on the Expanded Disability Status Scale) can help to differentiate PPMS from other types, as well as inform prognosis and related treatment plans.[10,11,12,13,14]

**Clinical Gap 2: Developments in Treatment:** *Due to the lack of approved effective treatments for PPMS thus far, clinicians must be informed about emerging agents that may offer some modification of the disease course.*

To date, most drugs approved for RRMS have demonstrated little efficacy with progressive forms of MS. Adding to the aforementioned sense of shared clinician and patient frustration with the lack of treatment options, trials for progressive forms of MS can be especially lengthy, since progression itself takes place over a prolonged period of time.[Error! Bookmark not defined.] In the past, studies of US neurologists' practice patterns have shown a lack of consensus on treatment initiation and the best treatment approaches for PPMS, and authors noted that these findings have highlighted the need for effective therapies.[15]

Fortunately, several agents intended for PPMS have progressed into phase 2 or 3 study, including monoclonal antibodies targeting CD-20, a tyrosine kinase inhibitor, and a PDE4/10 inhibitor.[16,17,18,19] In June 2016, the FDA granted priority review status to an application for approval of one of the anti-CD-20 monoclonal antibodies, ocrelizuamb, to treat PPMS as well as RRMS. The results of the review are pending.[20] Phase 3 data showed a significant risk reduction by 24% (compared with placebo) in reaching the primary endpoint of time to onset of 12-week confirmed disability progression.[3,21]

According to the extensive needs assessment associated with a recent ACTRIMS/ECTRIMS meeting, "the lack of therapeutic options for progressive disease represents a great unmet need. All the currently available therapies primarily target inflammatory mechanisms reflected most directly by MRI lesion activity and clinical relapses. As a result, none is effective in

progressive forms of the disease...Neurologic clinician learners need up-to-date information on…emerging therapies to assess their benefit-risk profile, consider them for appropriate patients, and to effectively educate their patients.[22]"In addition to these factors, should an agent or agents be approved for PPMS treatment, clinicians must also be apprised of dosing and administration recommendations, contraindications, etc, that can affect the use of these therapies.

## Summary

In summary, clinicians managing patients with PPMS are challenged by several aspects of this responsibility. Assessment can be confounded by patient perceptions and variable presentations and course, so effective evaluation must consider objective data such as MRI and assessment scale findings as well as the individual patient's presentation and history. Treatment options have been limited to date and there is a lack of consensus on approach to treatment, so it is important that clinicians are able to analyze new data/treatment options expected to emerge, as a means of informing the selection of the safest and most effective options for care.

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