Reverse engineering continues to advance the field.

Much has changed in multiple sclerosis (MS) in the past 3 decades. MRI has clarified that disease activity occurs even in periods of clinical stability without new neurologic symptoms, providing a rationale for continuing disease-modifying treatment (DMT) when clinical relapses do not occur. MRI has become indispensable for diagnosis and monitoring and is included in clinical guidelines, although without technical requirements including for quantitative longitudinal scans. Although presence of gray matter lesions has been recognized as a part of MS since Charcot’s initial observations, for many years MS was viewed as primarily a white matter disease. MRI has also led us to reappraise this view. Gray matter lesions correlate with disability progression and develop largely independently of white matter disease rather than being secondary to it. The central vein sign (CVS) on MRI has shown potential to help differentiate MS from its mimickers.\(^2\) As discussed by Dr. Bernitsas in *The Central Vein Sign*, detection of gray matter lesions, the CVS, and more complete assessment of white matter lesions require higher-field MRI, although high-field scanners are not readily available in most communities.

Prognostic and disease-activity biomarkers for MS have long been desired. The new ability to measure minute serum levels of neurofilament light (NFL) provides a potential candidate. Shed into the extracellular fluid when nerve cells are injured or degenerating, increased NFL is a nonspecific marker of neuronal injury that could, perhaps, be likened to erythrocyte sedimentation rate (ESR) in inflammatory conditions. Drs. Adil Javed and James Stankiewicz present the pros, cons, and limitations in *Point-Counterpoint: Neurofilament Light*.

In 2019, 2 DMTs were approved by the Food and Drug Administration (FDA), and it is likely that 2020 will bring more approvals. The increasing number of DMTs with different modes of action holds promise for more effective management of MS. This will only become reality if there is access to the most appropriate therapy at diagnosis and effectiveness is monitored and reevaluated in an ongoing manner at the individual level. Dr. Soneji, and Amezcua, which is especially important given the underrepresentation of these groups in clinical trials.

In 2019 by the FDA for relapsing MS and given in short treatment cycles. Although approved DMTs are directed toward immune processes, there is strong interest in neuroprotective and remyelinating agents. In *Drugs in Development*, Dr. Balashov highlights agents in this category with positive clinical data, several of which are approved for other conditions and may have a “second career” in MS.

In 2019, the FDA approved indications for specific MS subcategories, which previously were subsumed within the term *relapsing forms*. Indications for clinically isolated syndrome (CIS), relapsing remitting MS (RRMS), and active secondary progressive MS (aSPMS) are now specifically granted. Ocrelizumab is the only agent for adults with approved indications for CIS, RRMS, aSPMS, and primary progressive MS (PPMS). Although no agents are approved for inactive SPMS, the lack of discernable inflammatory activity on MRI and absence of relapses does not equate with stable neurologic function. For agents to claim efficacy for neuroprotection or remyelination, new clinically relevant measures going beyond relapses and disability progression are needed. Drs. Eckert, Weinstock-Guttman, and Krieger present *Point-Counterpoint: Food and Drug Administration Multiple Sclerosis Categorization Changes*, bringing forward arguments that are passionately discussed in the field.

Questioning long-held beliefs about MS in the context of new data also extends to risk and incidence. Several groups report a higher risk of MS for black women rather than white women as previously believed. This leads to the question of *Treatment in Racial and Ethnic Minorities* by Drs. Robers, Soneji, and Amezcua, which is especially important given the underrepresentation of these groups in clinical trials.

It seems appropriate to close with some disclaimers. Authors were asked to succinctly review assigned topics rather than provide in-depth reviews in the hope of encouraging readers to further explore areas of interest. Authors were also asked to express opinions with the goal of providing insight to what we know or still need to learn. Other topics could well have been included and will be addressed in future issues. If there if there is a specific MS-related topic you would like to see discussed, please let the editor know.

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