EDITORIAL

Complexity of MS management in the current treatment era

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Prodigious progress in the treatment of multiple sclerosis (MS) has occurred over the last 20 years, with the licensing of more than 15 novel and highly effective disease-modifying therapies (DMTs) to treat the disease. In this new complex scenario, an update of the previous therapeutic guidelines published by the American Academy of Neurology (AAN) in 2002 is needed for an appropriate and effective use of the old and new agents in clinical practice.

In this issue of *Neurology*®, Rae-Grant and colleagues published 2 reports on MS therapeutics on behalf of the Guideline Development, Dissemination and Implementation Subcommittee of the AAN. The first report is a summary of practice guideline recommendations on DMTs for adults with MS.[1] The second report is a comprehensive systematic review on the same topic.[2] The practice guidelines were driven by clinical rationale, from which recommendation statements were developed based on the premise of meeting at least 1 of the 4 criteria: evidence-based conclusions from the systematic review, generally accepted principles of care, strong evidence from related conditions, and deductive inferences from other premises, followed by committee consensus.

The comprehensive systematic review summarizes over 50 clinical trials in MS that have taken place largely in the past 20 years. These include pivotal phase III industry-sponsored studies, as well as academic-led studies, and include both Food and Drug Administration–approved as well as drugs commonly used off-label for MS. The review starts by summarizing the reduction in annualized relapse rate using the raw mean difference for each drug compared to placebo or other DMTs. The authors grade the evidence based on study design and sample size, with low-high confidence in the results. This summary provides a useful scale that can inform clinical decisions. However, we note that some commonly used MS drugs, such as rituximab and cyclophosphamide, achieved only Class III or IV evidence. Additional clinical outcome measures that were evaluated included risk of relapse in secondary progressive MS (SPMS) and conversion to MS from clinically isolated syndromes (CIS). Again, not all drugs were evaluated for these outcomes, although many are in common clinical use in for these indications based on scientific principles and clinical acumen. Thus, absence of definitive proof does not necessarily constitute proof of absence.

Included are some extraneous reviews of the efficacy of combination drug therapies, such as natalizumab and interferon, which are combinations rarely used in clinical practice. There is the possibility that the inclusion of these combinations may confuse the casual reader.

The practice guideline[1] focuses on statements that seem to stem from common issues encountered in clinical practice, such as how and when to discuss DMT use with patients, when to initiate DMTs, and when to switch. Embedded are statements addressing adverse events, adherence, and patient preferences in relation to DMT choice, factors which likely drive much of the decision-making for MS DMT choice. The statements are qualified by grades A, B, and C, which translate into "must, should, and may" recommendations, respectively. The important musts of MS care include ascertainment and incorporation and review of preferences relative to

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administration, lifestyle, cost, efficacy, common adverse effects, and tolerability in the choice of DMT in people with MS; engagement in an ongoing dialogue regarding treatment decisions; and counseling patients to notify clinicians about new or worsening symptoms. Intrinsic to these recommendations is the need to offer DMT to patients with MS, and especially for the initial discussion of these complex issues to take place at a dedicated visit. The article discusses 17 statements pertaining to starting treatment, 10 statements regarding switching treatments that largely relate to informing patients of the side effects and adverse events of the various choices, and 3 statements regarding stopping DMTs. In the last category, there are level C statements regarding stopping DMTs in stable, nonambulatory SPMS without relapses or any evidence of new MRI activity. Relevant data do not exist, particularly on switching and stopping treatment; thus, some of these specific recommendations need particularly careful consideration, since they could create confusion about the use of DMTs in the real world.

Overall, these 2 AAN articles reflect the complexity of MS management in the current treatment era, and advocate for expertise in MS management for optimal care. These statements serve as guidelines for MS patient care; however, they do not replace the clinician–patient relationship in which the most informed decision rests.

There are many areas that require further research, including SPMS, an entity for which a clear definition is lacking.[3,4] Delayed risks and long-term benefits of many of the current DMTs have not been assessed. Good-quality real-world observational studies with a sufficiently long follow-up may address some of these issues.[5,6] Also needed is guidance to identify radiologically isolated syndromes or CIS cases at risk for developing, or declaring themselves, as MS.[7] Studies that provide guidance on when it is safe to stop MS treatments, and in which populations, are needed, particularly in the aging population, in whom long-term immunomodulation could have adverse effects. The MS field is sorely in need of validated predictive biomarkers and algorithms that will identify patients at high risk for more aggressive disease, and, therefore, who would be appropriate for more effective early treatments.[8–10] At present, these determinations are made by the experienced MS clinician, who is needed to help guide patients through this complex landscape. The revised AAN guidelines are a starting point for the use of the multiple treatments now available for MS; however, further work is needed to further refine the choices appropriate for the individual patient.

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