Care of persons with MS in clinical practice

Management by majority

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The mid-1990s saw the advent of a new therapeutic era for multiple sclerosis (MS) with the approval of injectable disease-modifying therapies for relapsing-remitting MS. Despite some differences in routes of injection, frequency of administration, and adverse effects, the 4 initial therapies (interferon- β -1b, interferon- β -1a IM, interferon- β -1a subcutaneous, and glatiramer acetate) were remarkably similar in efficacy and generally safe. In the last 10 years, the landscape has changed dramatically. In addition to the initial 4 injectable therapies and new formulations of 2 of those therapies, 3 oral therapies and 3 infusion therapies are approved for use in relapsing forms of MS, excluding generics. In addition to differences in their routes of administration, these therapies differ importantly in their mechanisms of action, efficacy, and safety.

In this issue of *Neurology® Clinical Practice*, Tornatore et al.¹ surveyed US neurologists identified through the Consortium of MS Centers regarding their approaches to the diagnosis and management of radiologically isolated syndrome, clinically isolated syndrome, and relapsing-remitting MS. The authors defined consensus opinion as $\geq 75\%$ agreement and aimed to identify areas of consensus in the studied areas. A consensus statement typically involves a synthesis of available evidence by a group of experts for the purpose of improving the understanding of an issue or identifying priority areas for future research. Tornatore et al. have taken the approach of identifying consensus in clinical practice, which may or may not reflect the best available evidence.

Multiple points of consensus were identified, largely emphasizing changes in practice that reflect emerging evidence. For example, the diagnostic criteria for MS changed in 2001 to more heavily emphasize MRI as a tool to accelerate diagnosis,² as have all subsequent iterations of the criteria; therefore, US neurologists appropriately use MRI when evaluating individuals presenting with a first clinical attack, or clinically isolated syndrome, which may represent MS onset, using guidelines promoted by the American Academy of Neurology.³ They closely monitor individuals with radiologically isolated syndromes, as up to 30% of these individuals will ultimately develop clinical symptoms and be diagnosed with MS, and would include spinal cord imaging in their evaluations, reflecting the substantially higher risk of MS in those with spinal cord lesions than without such lesions.⁴ As such, these consensus practice patterns provide some guidance for the general neurologist as to how new information about the diagnosis of MS and natural history of demyelinating syndromes can be incorporated into clinical care.

However, limitations of the study must be recognized. The sample was drawn from neurologists identified through a single organization, and the response rate was only 44.8%, potentially limiting the generalizability of the findings. A relatively limited number of scenarios were presented. Drugs were grouped by route of administration (injectable, oral, IV) rather than by

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level of efficacy, although the latter would be more clinically relevant when considering scenarios such as treatment switches for suboptimal response or the management of highly active MS. More generally, however, consensus summaries such as this one tell us what experts think they do in clinical practice, not necessarily what should be done. For example, most neurologists surveyed indicated that they still treat at least some relapses with IV corticosteroids, despite evidence that high-dose oral corticosteroids achieve comparable efficacy and tolerability at much lower cost and greater convenience to the patient.⁵

Nonetheless, the areas in which consensus was not achieved are illuminating. Surveyed neurologists did not agree on the need to treat individuals with radiologically isolated syndrome, the choice of initial therapy in individuals with clinically isolated syndrome or relapsing-remitting MS, when therapies should be switched because of suboptimal response to current therapy and what alternative therapy should be chosen, or how long washout periods needed to be between therapies. Variation in clinical practice tends to arise when adequate evidence is lacking to support such decisions. Indeed, phase III clinical trials have not addressed these clinical scenarios, and findings from observational studies related to some of these scenarios have important limitations. Furthermore, most clinical trials restrict their study populations regarding age, comorbidities, and other clinical and demographic characteristics, which may not be representative of the populations seen in clinical practice.⁶

Variation also arises when several choices may be appropriate. The choice of a particular disease-modifying therapy ideally involves shared decision-making between the person with MS and their health care team,⁷ and considerations may include perceived disease severity, patient preferences regarding route of administration, and tolerance of risks related to therapy.^{8,9} This decision-making process offers the opportunity to individualize therapy to meet the needs of the individual patient while considering the best available evidence and practice guidelines.

Unfortunately, the sharply rising costs of these therapies and consequent responses of insurers are likely to have an increasing role in these decisions, interfering with the shared decision-making process.¹⁰ Although costs of the first-generation injectable therapies ranged from \$8,000 to \$11,000 annually when they were first released into the market, their costs have risen 21% to 36% annually, reaching more than \$60,000 annually.¹¹ More recently approved therapies are even more expensive. Such costs place disease-modifying therapies completely out of reach of some individuals and require others to rely on drug-support programs. Other individuals are limited in their choice of therapies by prescription drug plans that limit their costs through the use of required step therapy, tiering, or increasing deductibles and copays.^{10,12}

In principle, the emergence of generic versions of these therapies should reduce costs and obviate some of these concerns, but this has not been the case in MS in the United States. To date, one generic therapy has been approved for MS in the United States, Glatopa, a generic form of glatiramer acetate. Also in this issue of *Neurology: Clinical Practice*, Hua and Cohen¹³ review the complex issues surrounding the development and approval of generic disease-modifying therapies, as illustrated by the case of generic glatiramer acetate (Glatopa). The Biologics Price Competition and Innovation Act of 2009 established an approval pathway for biosimilars, but because of unclear requirements for clinical data and the need for public disclosure of proprietary data, manufacturers of generic biologics may not take advantage of such an approval process. Such generics must be comparable to the reference product in safety and effectiveness. Moderately large clinical trials may be needed to demonstrate whether generics that are not bioidentical are comparable to the brand name preparation.¹⁴ EXTAVIA (interferon- β -1b) is identical to BETASERON (interferon- β -1b), therefore it did not need to demonstrate comparability, but it is not widely used in the United States because of high costs, unlike Europe where the costs are lower. These complexities may, in part, account for the relatively limited cost savings observed to date.

Neurologists treating MS in an increasingly complex therapeutic environment need additional evidence to support clinical decision-making around such issues as therapeutic switches because of suboptimal treatment response, including how suboptimal response should be

defined. There is also an urgent need to make disease-modifying therapies, including generics, more accessible regarding cost so that clinical decisions can be made on the best available evidence and patient preferences, rather than on affordability of therapy.

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