The landscape of disease-modifying therapies (DMTs) in multiple sclerosis (MS) has rapidly evolved over the past 20 years, leading to many different treatment options, earlier initiation of highly effective immunotherapies, and a growing number of patients receiving continuous treatment for many years. Despite the increasing number of available DMTs for MS, however, there remains a major lingering question surrounding MS DMT management: when is an appropriate and safe time to consider discontinuation of DMTs?

As with other medical therapies, the general principle of MS DMT use is that the potential benefits should exceed the potential risks. For most people with MS, the earlier period of the disease is characterized by both clinical and radiographic relapses. New inflammatory activity caused by disturbances in the adaptive immune system tends to decrease with disease duration and age, considered likely contributions of immunosenescence.1 In a long-term study in 2,477 participants with MS, the relapse rate decreased by 17% every 5 years with accelerated rates of decline in relapse frequency as age increased.2 As persons with MS age, the frequency of clinical and radiographic relapses diminish and are replaced by apparent clinical quiescence in some and by slow progressive disability accumulation and brain atrophy in others. This likely reflects ongoing neurodegeneration but is also pathologically characterized by microglial activation and accumulation of B lymphocytes and plasma cells in the meninges.

MS DMTs and Aging

Considering that MS changes with aging, it is reasonable to theorize DMTs might perform differently as people age and disease pathogenesis changes. It would be optimal to have randomized, controlled trials in all age groups and all MS phenotypes. In most, but not all, phase 3 clinical trials, however, the maximum age at time of randomization has been 55. Thus, although 46% of adults with MS in the US are 55 or older,3 safety and efficacy data for many of the approved MS DMTs does not exist for this population. Subgroup analysis in several large seminal drug trials has typically used binary discriminators such as age above or below 38, with relapse and disability outcomes both more favorable in the younger subgroup in most comparisons.4,5 Similarly, those with active, enhancing MRI lesions at baseline typically benefit to a greater degree than those without these lesion types. This is true in studies of both relapsing and progressive MS, and benefits for progressive MS are modest in general. In a meta-analysis of several DMT effects on disability, it was noted that there was no discernible effect above median age 53 in the studies evaluated.6 As benefits of presently available DMTs wane with age, disease duration, and the change from a relapsing to progressive phenotype, side effects and risks associated with those DMTs may become more pronounced. Rates of infection increase with age, especially for those with significant disability. Persons with MS using immunosuppressive medications are at higher risk of infections compared with the general population, including progressive multifocal leukoencephalopathy (PML) and infections with herpes family viruses, fungal infections, and SARS-CoV-2 infections (See COVID-19, Vaccinations & MS in this issue). Such infections can lead to substantially poorer outcomes. Other long-term side effects of DMTs, including hypogammaglobulinemia with long-term use of B-cell depleting agents or prolonged lymphopenia with sphingosine-1-phosphate receptor (S1PR) modula-

Discontinuing Disease-Modifying Therapies in Multiple Sclerosis

Over the course of multiple sclerosis, there may come a point where the risks of disease-modifying therapies outweigh the benefits.

By Anna A. Shah, MD and John R. Corboy, MD
De-escalation or Discontinuation of MS DMTs

When considering DMTs in people with MS over age 55 who have been without clear recent clinical or radiographic relapse, options include continuing the presently used DMT, de-escalating therapy, or discontinuing DMTs. De-escalation refers to use of DMTs when they are most needed and beneficial, with acceptable risks, and subsequent changes to less potent DMTs as MS disease activity declines and risks of DMT use increase. It is also possible to use reduced doses or extended interval dosing of certain DMTs as a means of de-escalation. Although there are significant differences among individuals with MS, this strategy allows DMT use to be tailored specifically to levels of disease activity and risk. A noteworthy limitation with this strategy is the inability to predict the appropriate time to deescalate as well as the appropriate de-escalation strategy considering the very limited data on de-escalation strategies in MS.10

Discontinuation, in contrast, means a complete, prolonged cessation of DMTs. To date, studies on discontinuation have been observational and retrospective, some with propensity matching in larger databases11,12 and others simply evaluating factors associated with return of disease activity if DMT is halted for any of a variety of reasons.13,14 Some discontinuation studies do not include information on disease stability or age, whereas others have explicitly considered discontinuation in individuals who were stable for defined periods of time with particular age cutoffs.15,16 With some exceptions, almost all have evaluated primarily discontinuation of first-generation medications (eg, glatiramer acetate or interferons). In most studies, discontinuation has occurred for many reasons, especially intolerance or perceived lack of efficacy, with substantial or unknown numbers restarting DMT, such that these may more appropriately be termed DMT interruption studies.

Potential Risks of De-escalation and Discontinuation

Taking these limitations into account, regarding risk of recent relapses or active MRI scans have a significantly greater risk. Risk of increased disability accrual may also be greater amongst this group, but this is less studied.11,12 A recent study devised a 6-point scoring system for risk of disease activity recurrence (Table) that gives a maximum of 2 points each for categories of age (2 for <45, 1 for 45-55, and 0 for ≥55), number of lesions at discontinuation, and years of stable disease without relapse. This score was tested in the developers’ cohort in Innsbruck, Austria and validated in another cohort in Vienna, Austria.17 Mean age at discontinuation was 38, and there was an average follow-up of 5 years. In both cohorts, disease reactivation over 5 years (ie, relapse, change in disability, or restarting DMT), was approximately 10% in those scoring 0 to 1, 40% in those with scores of 2 to 3, and 90% with scores of 4 to 5.

Whether there is an association between disability progression and DMT discontinuation is an area of ambiguity. In the 2 propensity-matched database studies comparing those remaining on DMT (stayers) vs those who discontinued (stoppers), 1 study demonstrated a slightly increased risk of worsened EDSS after discontinuation,11 whereas the other study did not show increased risk of disability worsening with discontinuation.12 Notably, mean ages in these studies were 45 and 53, respectively. In the New York State MS Consortium registry, 32.9% of previously stable patients experienced disability worsening and/or progression.18 There were higher rates of progression in those with higher

### TABLE. VIENNA INNSBRUCK DMT DISCONTINUATION SCORE BASED ON AGE, MRI ACTIVITY & DURATION IN STABLE COURSE

<table>
<thead>
<tr>
<th>Age</th>
<th>Value</th>
<th>Points</th>
<th>Subtotal</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;45</td>
<td></td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>45-55</td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>≥55</td>
<td></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>MRI activity at discontinuation</td>
<td>≥3 new/enlarging T2 lesions</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>OR 1 Gd+ lesion</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;3 new/enlarging T2 lesions</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>AND no Gd+ lesions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of stable disease</td>
<td>&lt;4 years</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>4-8 years</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>≥8 years</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>TOTAL SCORE</td>
<td></td>
<td></td>
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</tbody>
</table>

Abbreviations: DMT, disease-modifying therapy; Gd+, gadolinium-enhancing. *In the score development and validation study, disease reactivation occurred in 10% of those who scored 0 to 1, 40% with scores of 2 to 3, and 90% with scores of 4 to 5.
levels of disability without clear notation of age of those that were progressing. In a separate analysis, those under age 55 and those 55 or more had similar rates of disability progression; however, there was not a distinction made between those that were previously stable vs those with recent disease activity. Finally, in the Rennes database analysis of 100 people with secondary progressive MS (SPMS) patients with an average age 47 at the time of discontinuation there was no greater likelihood of disability progression after discontinuation.

A major caveat is the nominal data from individuals discontinuing more highly effective therapies, especially those that block immune cell trafficking (ie, S1PR modulators and natalizumab). Individuals discontinuing DMTs within this category are at risk for potential rebound disease activity. A recent study, however, demonstrated that the risk of rebound after fingolimod (an S1PR modulator) decreased with increasing age. Approximately 36.5% of those less than 50 had rebound vs 19% of those age 50 to 60 and 0% of those over age 60. Clinical stability before discontinuation did affect the proportion of each age group that had rebound disease activity in this study.

A study in people age 40 to 55, with at least 1 year without relapse while taking natalizumab, compared natalizumab continuation vs de-escalation to interferon, glatiramer acetate, or intermittent steroids vs placebo for 24 weeks. More relapses occurred among those whose treatment was de-escalated or stopped (15%-29%), vs continuation of natalizumab (4%). MRI lesions were higher with de-escalated DMT or placebo (7%-53%) compared with natalizumab continuation (0%) as well. In another small study, 15 participants who were stable for 5 years with mean age 50 (range 32-72) discontinued natalizumab; two-thirds experienced an early relapse, and one-third experienced increased disease activity (rebound disease activity). Age of those with recurrent activity was not explicitly stated in this study. These few reports suggest de-escalation may be a better alternative than complete cessation after discontinuation of S1P modulators or natalizumab, especially in those at higher risk of disease activity recurrence.

Potential Benefits of De-escalation or Discontinuation

There are several potential benefits to DMT discontinuation in appropriate individuals, especially the reduction in DMT-associated adverse effects. Additionally, the overall costs of DMTs have been rising rapidly over the past 2 decades, including out-of-pocket costs for patients and healthcare system costs. This may be the costs of the drug itself and drug administration (for infusions), as well as costs of side-effect monitoring, adverse events, and other health care use. Awareness of these costs is increasingly important in the US for elders and those with increased disability because their income sources and health insurance coverage may be more limited. There may also be a psychologic benefit to discontinuation, with less frequent reminders of the fact that an individual has MS.

Clinical Practice

Guidelines have not been developed when to consider or recommend DMT discontinuation in MS. We start to have that discussion with people with relapsing MS who are age 50 or more if there has been a period of at least 5 years of both clinical (no relapses) and radiographic stability. This conversation should also be considered for individuals age 50 or more who have had several years of disability progression, independent of relapses and in spite of treatment with highly effective immunotherapy. The decision to deescalate vs discontinue DMT should be through shared decision-making with the patient and their family. Most patients report being unlikely to willingly stop DMT use, even in the setting of stable disease. It is exceedingly important that this is recognized as a change in the MS care plan and by no means a discontinuation of care for the person with MS. There may be a psychologic sense of failure or despair in individuals with disability progression as this indicates transition to a phase in which there are currently no or very limited effective interventions. This may pose a substantial risk of patient disengagement from the treatment team. In this context, it is important to encourage continued interaction with the treating team, focusing on wellness, exercise, control of symptoms, aggressive treatment of comorbidities, and a hope for the future with ongoing research.

Monitoring should not stop once there is discontinuation of a DMT. Examinations and MRI imaging should continue, although the rate and intensity may diminish over time if stability continues in a person with relapsing but quiescent MS. General practice guidelines that should be considered include a new baseline brain MRI around the time of DMT discontinuation with regular annual brain MRI scans at the end of years 1 and 2 without use of a DMT. This is in conjunction with biannual clinic visits during years 1 and 2 for clinical monitoring. If MS activity remains stable, a transition to annual clinical visits could be considered with intermittent MRIs. For those with progressive disease, assessing whether ongoing progression off DMT is similar to that while on therapy should be attempted, although this is quite challenging and often vague. Overall there is a need for better biomarkers to assess and track progressive MS.

Future Directions

It is important to understand that there are notable limitations in our knowledge regarding discontinuation of
MS DMTs. There are multiple, relatively less visible parameters that are not always evaluated in these studies (eg, cognitive impairment, fatigue, and upper limb and fine motor function). These outcomes are critical to quality of life and may be indicative of ongoing neurodegenerative processes. Biomarkers such as neurofilament light (NFL) may help define subtle changes in axon damage that may be pathologic, although these are not yet routinely used in clinical practice.

Several upcoming trials likely will provide the field with more robust data surrounding DMT discontinuation. The DISCOMS study9 is assessing DMT discontinuation in participants, age 55 or more, who have been clinically stable (no relapses) for at least 5 years and radiographically stable for 3 or more years. The DOT-MS trial10 is investigating discontinuation of DMTs in participants, age 18 or more, who have had clinical and radiographic stability for 5 years. A third study, STOP-I-SEP,11 will evaluate discontinuation in participants with SPMS who are age 50 or more and have had clinical and radiographic stability for 3 or more years. Taken together, these studies should add significant data regarding outcomes of MS DMT discontinuation to our body of knowledge.

Conclusion

Potential discontinuation of MS DMTs is an important topic with a great need for more data. As patients with MS age, clinicians should consider changes in DMT, including de-escalation and possible permanent discontinuation. There are observational data suggesting DMT may be safely discontinued in some people over 55 with stable disease. There are 3 ongoing randomized clinical trials that will provide us with more data in the upcoming years. There remains a tremendous unmet need for DMT, including those focused on repair or regeneration, in those with significant, progressing disability.

References


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