COMMENTARY

Discontinuing Disease-Modifying Therapies in Nonactive Secondary Progressive MS: Review of the Evidence

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Background: There are currently no disease-modifying therapies (DMTs) on the market approved for nonactive secondary progressive multiple sclerosis (SPMS), and lifelong DMTs are neither indicated nor supported by evidence. Nevertheless, the discontinuation of DMTs has been a long-debated topic with varied opinions on how and when to discontinue.
Observations: This article reviews the current literature regarding the discontinuation of DMTs in nonactive SPMS. Discontinuing DMTs does not seem to have deleterious effects on the nonactive SPMS disease course and may improve quality of life.
Conclusions: The growing evidence in this area may make discontinuation of DMTs in nonactive SPMS a less debatable topic, but it is still a major treatment decision that clinicians must thoroughly discuss with the patient to provide high-quality, patient-centered care.

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Multiple sclerosis (MS) is an immune-mediated demyelinating disorder. There are 2 broad categories of MS: relapsing, also called active MS; and progressive MS. Unfortunately, there is no cure for MS, but disease-modifying therapies (DMTs) can help prevent relapses and new central nervous system lesions in people living with active MS. For patients with the most common type of MS, relapsing-remitting MS (RRMS), DMTs are typically continued for decades while the patient has active disease. RRMS will usually transition to secondary progressive MS (SPMS), which can present as active SPMS or nonactive SPMS. The latter is the type of MS most people with RRMS eventually experience.

A 2019 study estimated that nearly 1 million people in the United States were living with MS.[1] This population estimate indicated the peak age-specific prevalence of MS was 55 to 64 years. Population data demonstrate improved mortality rates for people diagnosed with MS from 1997 to 2012 compared with prior years.[2] Therefore, the management of nonactive SPMS is an increasingly significant area of need. There are currently no DMTs on the market approved for nonactive SPMS, and lifelong DMTs in these patients are neither indicated nor supported by evidence. Nevertheless, the discontinuation of DMTs in nonactive SPMS has been a long-debated topic with varied opinions on how and when to discontinue.

The 2018 American Academy of Neurology (AAN) guideline recommends that clinicians advise patients with SPMS to discontinue DMT use if they do not have ongoing relapses (or gadolinium-enhanced lesions on magnetic resonance imaging activity) or have not been ambulatory (Expanded Disability Status Scale [EDSS] ≥ 7) for ≥ 2 years.[3] In recent years, there has been increased research on nonactive SPMS, specifically on discontinuation of DMTs. This clinical review assesses the recent evidence from a variety of standpoints, including the effect of discontinuing DMTs on the MS disease course and quality of life (QOL) and the perspectives of patients living with MS. Based on this evidence, a conversation guide will be presented as a framework to aid with the clinician-patient discussion on discontinuing MS DMTs.

DISEASE MODIFYING THERAPIES

Roos and colleagues used data from 2 large MS cohorts: MSBase and Observatoire Français de la Sclérose en Plaques (OFSEP) to compare high-efficacy vs low-efficacy DMT in both active and nonactive SPMS.[4] In the active SPMS group, the strength of DMTs did not change disability progression, but high-efficacy DMTs reduced relapses better than the low-efficacy DMTs. On the other hand, the nonactive SPMS group saw no difference between DMTs in both relapse risk and disability progression. Another observational study of 221 patients with RRMS who discontinued DMTs noted

that there were 2 independent predictors for the absence of relapse following DMT discontinuation: being aged > 45 years and the lack of relapse for ≥ 4 years prior to DMT discontinuation.[5] Though these patients still may have been classified as RRMS, both these independent predictors for stability postdiscontinuation of DMTs are the typical characteristics of a nonactive SPMS patient.

Pathophysiology may help explain why DMT discontinuation seems to produce no adverse clinical outcomes in people with nonactive SPMS. Nonactive SPMS, which follows after RRMS, is largely correlated with age. In nonactive SPMS, there is less B and T lymphocyte migration across the blood-brain barrier. Furthermore, a lifetime of low-grade inflammation during the RRMS phase results in axonal damage and declined repair capacity, which produces the predominance of neurodegeneration in the nonactive SPMS disease process.[6] This pathophysiologic difference between active and nonactive disease not only explains the different symptomatology of these MS subtypes, but also could explain why drugs that target the inflammatory processes more characteristic of active disease are not effective in nonactive SPMS.

Other recent studies explored the impact of age on DMT efficacy for patients with nonactive SPMS. A meta-analysis by Weidman and colleagues pooled trial data across multiple DMT classes in > 28,000 patients.[7] The resulting regression model predicted zero efficacy of any DMT in patients who are aged > 53 years. High-efficacy DMTs only outperformed low-efficacy DMTs in people aged < 40.5 years. Another observational study by Hua and colleagues saw a similar result.[8] This study included patients who discontinued DMT who were aged ≥ 60 years. The median follow-up time was 5.3 years. Of the 178 patients who discontinued DMTs, only 1 patient had a relapse. In this study, the age for participation provided a higher likelihood that patients included were in nonactive SPMS. Furthermore, the outcome reflects the typical presentation of nonactive SPMS where, despite the continuation or discontinuation of DMT, there was a lack of relapses. When comparing patients who discontinued DMTs with those who continued use, there was no significant difference in their 25-foot walk times, which is an objective marker for a more progressive symptom seen in nonactive MS.

The DISCOMS trial (NCT03073603) has been completed, but full results are not yet published. In this noninferiority trial, > 250 patients aged ≥ 55 years were assessed on a variety of outcomes, including relapses, EDSS score, and QOL. MS subtypes were considered at baseline, and subgroup analysis looking particularly at the SPMS population could provide further insight into its effect on MS course.

QUALITY OF LIFE

Whether discontinuation of DMTs is worth considering in nonactive SPMS, it is also important to consider the risks and burdens associated with continuation. Medication administration burdens come with all MS DMTs whether there is the need to inject oneself, increased pill burden, or travel to an infusion clinic. The ever-rising costs of DMTs also can be a financial burden to the patient.[9] All MS DMTs carry risks of adverse effects (AEs). These can range from a mild injection site reaction to severe infection, depending on the DMT used. Many of these severe AEs, such as opportunistic infections and cancer, have been associated with either an increased risk of occurrence and/or worsened outcomes in older adults who remain on DMTs, particularly moderate- to high-efficacy DMTs, such as sphingosine-1-phosphate receptor modulators, fumarates, natalizumab, alemtuzumab, cladribine, and anti-CD20 antibodies.[10] In a 2019 survey of 377 patients with MS, 63.8% of respondents ranked safety as the most important reason they would consider discontinuing their DMTs.[11] In addition, a real-world study comparing people with nonactive SPMS who continued DMTs vs those who discontinued found that discontinuers reported better QOL.[8]

CONVERSATION GUIDE FOR DISCONTINUING THERAPIES

The 2019 survey that assessed reasons for discontinuation also asked people with nonactive SPMS whether they thought they were in a nonactive disease stage, and what was their likelihood they would stop DMTs.[11] Interestingly, only 59.4% of

respondents self-assessed their MS as nonactive, and just 11.9% of respondents were willing to discontinue DMTs.[11] These results suggest that there may be a need for patient education about nonactive SPMS and the rationale to continue or discontinue DMTs. Thus, before broaching the topic of discontinuation, explaining the nonactive SPMS subtype is important.

Even with a good understanding of nonactive SPMS, patients may be hesitant to stop using DMTs that they previously relied on to keep their MS stable. The 2019 survey ranked physician recommendation as the third highest reason to discontinue DMTs.[11] Taking the time to explain the clinical evidence for DMT discontinuation may help patients better understand a clinician's recommendation and inspire more confidence.

Another important aspect of DMT discontinuation decision making is creating a plan for how the patient will be monitored to provide assurance if they experience a relapse. The 2019 survey asked patients what would be most important to them for their management plan after discontinuing DMT; magnetic resonance imaging and neurologic examination monitoring ranked the highest.[11] The plan should include timing for follow-up appointments and imaging, providing the patient comfort in knowing their MS will be monitored and verified for the relapse stability that is expected from nonactive SPMS. In the rare case a relapse does occur, having a contingency plan and noting the possibility of restarting DMTs is an integral part of reassuring the patient that their decision to discontinue DMTs will be treated with the utmost caution and individualized to their needs.

Lastly, highlighting which aspects of MS treatment will continue to be a priority in nonactive SPMS, such as symptomatic medication management and nonpharmacologic therapy, is important for the patient to recognize that there are still opportunities to manage this phase of MS. There are many lifestyle modifications that can be considered complementary to medical management of MS at any stage of the disease. Vascular comorbidities, such as hypertension, hyperlipidemia, and diabetes, have been associated with more rapid disability progression in MS.[12] Optimized management of these diseases may slow disability progression, in addition to the benefit of improved outcomes of the vascular comorbidity. Various formats of exercise have been studied in the MS population. A meta-analysis of aerobic, resistance, and combined exercise found benefits in these formats on health-related QOL.[13]

Many dietary strategies have been studied in MS. A recent network meta-analysis reviewed some of the more commonly studied diets, including low-fat, modified Mediterranean, ketogenic, anti-inflammatory, Paleolithic, intermittent fasting, and calorie restriction vs a usual diet.[14] Although the overall quality of evidence was low, the Paleolithic and modified Mediterranean showed greater reductions in fatigue, as well as increased physical and mental QOL compared with a usual diet. The low-fat diet was associated with a reduction in fatigue. Many of these lifestyle modifications may complement optimized vascular comorbidity treatment; however, any exercise regimen or dietary change should be considered with the whole health of the patient in mind.

As with any health care decision, it is important to involve the patient in a joint decision regarding their care. This may mean giving the patient time to think about the information presented, do their own research, talk to family members or other clinicians, etc. The decision to discontinue DMT may not happen at the same appointment it is initially brought up at. It may even be reasonable to revisit the conversation later if discontinuation is not something the patient is amenable to at the time.

CONCLUSIONS

There is high-quality evidence that discontinuing DMTs in nonactive SPMS is not a major detriment to the MS disease course. Current literature also suggests that there may be benefits to discontinuation in this MS subtype in terms of QOL and meeting patient values. Additional research particularly in the nonactive SPMS population will continue to improve the knowledge and awareness of this aspect of MS DMT management. The growing evidence in this area may make discontinuation of DMT in nonactive SPMS a less-debatable topic, but it is still a major treatment decision

that clinicians must thoroughly discuss with the patient to provide high-quality, patient-centered care.

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