

## **Raising Awareness for Managing Disease-Modifying Therapies in Aging Persons With Multiple Sclerosis**

Bianca Weinstock-Guttman, MD

Multiple sclerosis (MS) is a chronic, inflammatory demyelinating and neurodegenerative disease that affects the central nervous system. While there is no cure for MS, significant progress has been made during the last 2 decades, with over 25 medications developed, including disease modifying therapies (DMTs) that have shown benefit in reducing the number of acute events (relapses), curbing the development of new lesions seen on magnetic resonance imaging (MRI), and slowing disease progression/worsening. However, the benefit of available DMTs is seen primarily during the inflammatory stage of the disease (relapsing remitting) and is less clear in the later stages (secondary-progressive disease). Age was shown to be one of the most consistent contributing factors linked to disease worsening, and most studies suggest limited benefit of available DMTs in patients older than 50 years.

Meanwhile, the aging MS population is increasing worldwide, with most patients being between ages 55 and 65 years—a trend considered related to a general extended life expectancy, better diagnosis, early initiation of efficient DMTs, and improved general medical care. As persons with MS (pwMS) age, there is a clear change in the clinical presentation, with reduced risk for relapses and/or development of new MRI lesions but increased risk for disease worsening, with physical and cognitive decline. Systematic analysis—gathered data from clinical trials suggest an inadequate benefit of available DMTs in patients over 50 years, although the data have limitations, as most studies in relapsing MS did not enroll patients over the age of 55 years. In progressive MS trials, the median age of participants is 47 years; therefore, available data on aging populations are currently limited and cannot fully justify whether the medication is actually beneficial.

Another challenge in treating aging pwMS besides the limited benefit of DMTs is concern regarding safety and tolerability, especially as the most potent medications, which are now considered the most efficacious interventions for MS, are immunosuppressive agents. Aging populations with known weaker immune systems (immunosenescence) that are exposed to immunosuppressive interventions can be more susceptible to infections, have a decreased response to vaccinations, and face an increased risk of cancer.

The aging population is also known to have other health issues (comorbidities) and, therefore, may become more vulnerable to side effects from DMTs, making it necessary to consider a different management approach. Until more effective and safe therapeutic interventions become available for aging pwMS, discontinuation or de-escalation are the most frequently used approaches. Choosing between continuing, discontinuing, or de-escalating DMTs when treating aging MS patients is a complex process that requires careful consideration as well as active patient and patient family engagement in the final management decision.

The 2022 DISCO-MS trial was the first randomized discontinuation trial of MS drugs in older pwMS. The trial was designed to investigate the effect of discontinuing DMTs in patients aged 55 years and older who had not had recent relapses for at least 5 years and had no recent or new MRI lesions for at least 3 years. This multicenter study was conducted by the University of Colorado (supported/funded by a Patient-Centered Outcomes Research Institute grant) and included 259 participants with a median age of 63 years. Participants were randomly assigned to either continue or discontinue treatment and were followed for up to 22 months. The results of the DISCO-MS trial showed that 1 of 128 participants who stayed on medication had a relapse, and 3 of 131 people who discontinued medication had a relapse. There were no significant differences between the groups in progression of disability, cognition, quality of life, or adverse events. However, more participants who discontinued DMTs had new MRI lesions (16 vs 6), although there was no relationship to relapses or disability progression. Based on a noninferiority study design, the primary outcome (combined relapses and/or new MRI lesions) was not reached in this study. Other retrospective studies, such as a large study conducted in

2018, showed that most patients over age 60 years who discontinued DMTs remained off DMTs. These studies provide preliminary data that may guide clinicians who are considering discontinuing DMTs in their aging patients.

The second approach is de-escalation, which aims primarily to minimize the risk of side effects and complications while maintaining efficacy. Therefore, de-escalating MS medication in aging pwMS should always be done with great care. Some factors that should be considered when de-escalating treatment include the patient's age, their overall health, and the severity of their MS symptoms. Some approaches to de-escalating MS medication include gradually reducing the dosage of the medication over time or increasing the interval between the administration of infusible medications. This can help minimize the risk of side effects and complications, while still monitoring for maintained efficacy. These changes require shared decision-making between practitioners and patients after discussing the potential risks of MS relapse, new MRI lesions, or disease progression, along with the potential benefits of reducing medication-related side effects. Another approach is to switch to a different type of medication that is less immunosuppressive (ie, immunomodulatory) and that may be better suited to the patient's needs; these medications are less likely to cause side effects in older patients or may be better tolerated by patients with certain health conditions.

DMTs may cause side effects in patients of any age, but aging patients may be more susceptible to certain side effects due to changes in their physiology and increased vulnerability due to other health issues. Some side effects of DMTs in aging pwMS that should be considered include:

- Cardiovascular issues: some DMTs may increase the risk of cardiovascular complications such as hypertension, hyperlipidemia, and heart failure, which may be more concerning in aging patients who may already have cardiovascular risk factors.
- Infections: aging patients may be more vulnerable to more severe infections, which often require hospitalization. Such patients are also at higher risk for opportunistic infections, such as zoster infections, or progressive multifocal leukoencephalopathy due

to changes in the weakening of their immune system function and higher prevalence of other health issues.

- Skin reactions/change to skin pathology: sphingosine-1-phosphate receptor modulators are oral DMTs for MS that were associated with cases of basal cell carcinoma in clinical trials.

Ultimately, the decision to continue, discontinue, or de-escalate DMTs in aging pwMS should be based on the individual patient's needs and circumstances. It is important for clinicians to work closely with their patients to develop a personalized treatment plan that considers all the relevant benefits and risks. In the meantime, more research is needed on this topic to provide better outcomes for our growing population of aging patients who are living with MS.