ONCE STARTED, MS THERAPIES SHOULD BE CONTINUED

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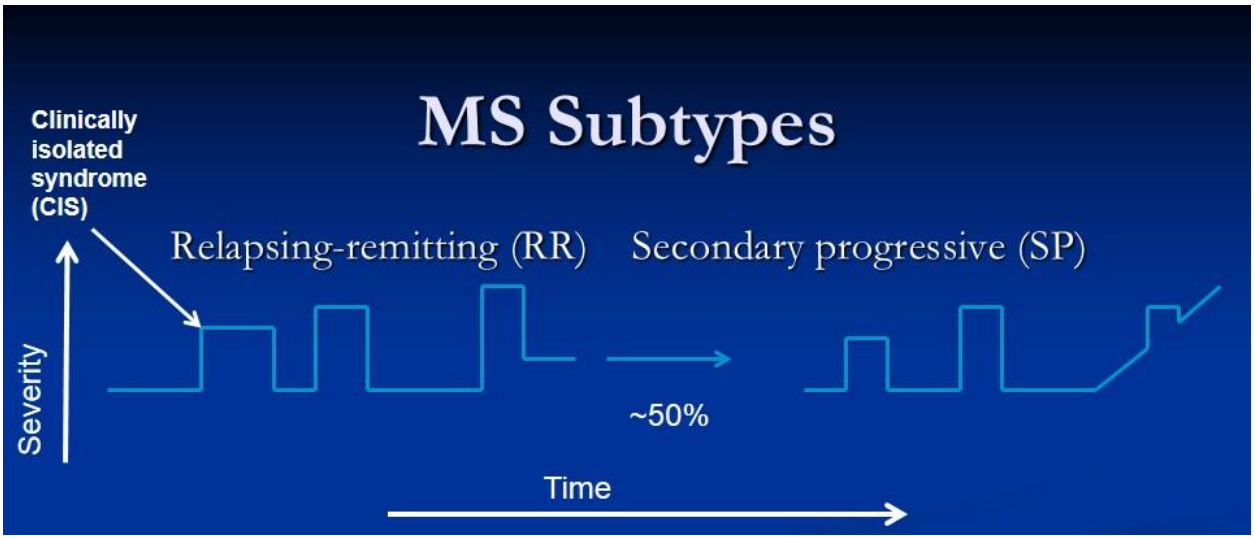
Overview: Multiple sclerosis (MS) is a disease that, for most individuals, is characterized in the early phase by episodes of neurologic symptoms (called “relapses,” “exacerbations,” or “flares,”) that are thought to be caused by an autoimmune attack on the myelin sheath surrounding nerve axons in the central nervous system (see diagram below). Subclinically, such activity also appears to occur, as noted by brain (or spinal cord) magnetic resonance imaging (MRI) evidence of the accumulation of FLAIR/T2-weighted hyperintense lesions in a characteristic pattern. This phase of MS is known as relapsing-remitting MS (RRMS). There are more than a dozen FDA-approved disease-modifying therapies (DMTs) that treat RRMS, and the success of those treatments is measured by the subsequent reduction (or absence) of new MS relapses or the subclinical accumulation of new lesions on imaging. However, even without MS therapies, the development of relapses and new lesions lessens with time in a person diagnosed with the disease. In some individuals, the course changes and is characterized by slowly worsening disability (with or without relapses), traditionally known as secondary progressive (SP) MS, which is thought to be caused by cumulative damage to underlying axons themselves rather than due to autoimmune attacks.(1) Unfortunately, DMTs do not definitively reduce the slow accumulation of such neurodegeneration among those with secondary progression of MS symptoms.



The Dilemma

While there is often reasonable consensus about the importance of starting DMTs, even in clinically isolated syndrome (CIS; the first relapse of RRMS, as per the diagram above), there is less consensus about whether such therapies should be continued indefinitely. While an American Academy of Neurology “Choosing Wisely” recommendation in 2013 suggested that patients with SPMS not be treated with injectable therapies based on the available literature, many neurologists were concerned that patients with longer-duration and even secondary progressive MS who had been stable with respect to new inflammatory activity (relapses and new subclinical FLAIR/T2-weighted hyperintense lesions on MRI) may still be at risk for those relapses and thus may still benefit from DMTs.

Previous Literature Regarding Patterns of Discontinuation of MS DMTs Historical publications have evaluated the patterns of stopping MS DMTs, including predictors of which patients are more likely to stop:

- Stopping interferon therapy was more common in secondary progressive than relapsing-remitting MS (p=0.0003); the reason for stopping was more commonly due to ineffectiveness in SPMS patients than in RRMS patients p=0.037.(2)
- Predictors of self-discontinuation of [injectable] medication in Australia included *lower* education level and recent relapse (not disability or disease duration). (3)

- In Norway, on the other hand, *greater* education level was associated with higher risk of stopping therapy, as was perceived lack of effect/adverse effects.(4)
- In a Swedish cohort, MS patients discontinued fingolimod more often than they did natalizumab; fingolimod was more often stopped due to adverse events, while natalizumab was stopped due to conversion of JC virus serostatus.(5)
- An additional review noted that misperception of treatment goals is a common reason that patients stop therapy (1)

Considerations: Stopping DMTs

Gajofatto and Benedetti provided a review that included a section focusing on treatment discontinuation.(6) There are some cases in which, they note, discontinuing a DMT is advisable:

- Serious adverse event
- Pregnancy (?)
- Non-adherence

In other cases, decisions to discontinue DMT may be more challenging:

- Stable on DMT without adverse effects
- Transitioned to secondary progressive MS without new inflammatory activity

The decision to discontinue DMT in a person with MS from a DMT may depend on which DMT the person was on, particularly as stopping some medications may lead to a rebound of disease activity. Age may also play a role, since advancing age is associated with a reduced frequency of inflammatory activity.(1)

Towards Reducing Bias in Assessing the Effect of Stopping Treatment: An Evaluation of DMT Discontinuation Using Propensity Matching

Kister and colleagues performed a study within MSBase, an international collaborative research database in which patient data are collected, including details about MS course, relapses, disease-modifying therapy (DMT) use, and disability (Expanded Disability Status Scale).(7) They evaluated people who stopped DMT versus those who stayed on DMT as follows:

- Stoppers: Adults with MS who were previously treated with injectable DMTs (n=426), who at "baseline" (defined as time DMT stopped):
  - ✓ stopped DMT after 5+ years of relapse freedom
  - ✓ were on DMT for at least 3 years prior to baseline
  - ✓ didn't restart a DMT within 3 months of stopping
  - ✓ had at least 3 years of follow-up after stopping DMT
- Stayers: initially included 1,133 "DMT stayers" who:
  - ✓ Demonstrated 5+ years of relapse freedom
  - ✓ were on injectable DMT for at least 3 years prior to and for 3 years after "baseline"

To conduct the statistical analyses, predictors of stopping DMT were identified in logistic regression models; these were used to generate a propensity score among stoppers. Each DMT stopper was then matched to 2 DMT stayers based on the score. Stoppers were more likely to be on interferon than glatiramer acetate. Of note, 46% of those who stopped DMT restarted within an average of less than a year.

155 (36%) of those who stopped DMT had a relapse during the follow-up period, while 322 (38%) of those who stayed on DMT had a relapse during follow-up. There was no clinically meaningful difference in multivariate Cox proportional hazards models in risk of relapse between the two groups. Among those who had previously had no progression of disability for at least 5 years, those who stopped DMT were 1.5 times more likely to develop disability progression in follow-up than were those who stayed on DMT.

Limitations of the study include that the study includes evaluating those treated with injectable therapies, whereas many patients now are using non-injectable MS therapies. It's not clear if the analyses for risk of disability progression took into account the relapses that patients experienced, which is perhaps particularly of note because disability progression could be confirmed after a change in disability status after only 3 months. Excluding those who restarted DMT quickly, which was presumed to indicate the patients were simply switching DMTs, could have led to bias (towards the null) if in fact those patients had planned to stop but experienced breakthrough disease and thus restarted therapy early. Similarly, excluding those without 3 years of follow-up may have led to bias, potentially away from the null, as presumably those who were doing well having stopped therapy would be less likely to continue to follow up.

Can We Evaluate Treatment Discontinuation in a Randomized Trial?

Tobin and Weinshenker suggested that a randomized trial of treatment discontinuation in appropriate patients may help to clarify the impact of treatment discontinuation.(1) They proposed choosing patients for inclusion who meet the following criteria:

-secondary progression for at least 5 years
-Age > 55 years
-No clinical relapse or increase in MRI lesion burden for ≥ 5 years

They proposed starting with a pilot trial, using as an outcome the development of new brain lesions on MRI, and that patients would restart DMT if they developed a certain accumulation thereof after stopping DMT. If in the pilot study, there seemed to be reasonable equipoise between arms, then a clinical trial with relapse as an endpoint may be considered.

In addition to what Tobin and Weinshenker discussed, additional challenges in considering such a trial exist, including that lack of evidence of inflammatory disease activity while treated with a DMT may not mean the same thing for first-line versus higher-efficacy therapy. Furthermore, whether a relapse in a person with progressive disease has the same short-term or long-term impact on the well-being of a person with MS is not clear and deserves consideration.

Conclusions

Much interest remains in evaluating if there are some patients with MS who would benefit from stopping DMTs, particularly among those who may not have had any inflammatory activity in a long time or who seem to have transitioned to a progressive phenotype. A randomized trial, particularly given the suggestion in a propensity analysis that stopping DMTs may lead to worsening of disability, is likely needed to address these questions.

References

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