

DISCONTINUATION OF DISEASE-MODIFYING THERAPIES IN PATIENTS WITH LONG-TERM STABLE DISEASE IS SAFE AND APPROPRIATE: NO

Brian G. Weinschenker

Mayo Clinic, Rochester MN, USA

While the benefits of MS disease modifying treatments (DMTs) for MS are best proven and probably greatest in the early stages of MS when the frequency of relapses and gadolinium-enhancing or new T2 lesions) is greatest, inflammatory disease may persist over the course of the disease and safety of discontinuation of DMTs is never assured. There a number of instances, examples of which will be shown, where apparent stability of MS was presumed to indicate that it was safe to discontinue DMTs; discontinuation was followed in some instances by severe exacerbations of MS with permanent sequelae. Although this is not to say that DMTs may never be able to be stopped, solid evidence supporting safety of discontinuation are lacking. Data regarding discontinuation of treatment at present are largely confined to patients early in the course of their disease and of receiving DMTs; the predominant reason for discontinuation was adverse effects.

A recent prospective study analyzed 65 patients who developed progressive MS who stopped DMTs¹; of 59 who did so on the recommendation/with the approval of their neurologist, only 4/59 developed MRI evidence of relapse and only 1/4 with MRI evidence of relapse developed clinical symptoms; by contrast, 4/6 who discontinued treatment on their own without the knowledge/approval of their neurologist developed recurrent disease activity. Amongst those patients who discontinued with approval of their neurologist, patients without relapse were older than those who relapsed and had been off treatment longer. Considering all patients who relapsed in this study, the only difference from those who didn't relapse was their greater age.

There is some recent evidence that the risk of relapse persists after onset of secondary progressive phase, at least for the first 5 years, and may impact disability². There is additional evidence that this may be the case from prospective clinical trials³. Continuation of DMT into this phase might be appropriate even though starting DMTs at this phase has not been studied and is not approved by regulatory authorities.

Discontinuation of treatment is well known to be associated with rapid recurrence of inflammatory disease activity, particularly in patients who had aggressive MS prior to discontinuation. This has been especially well documented for natalizumab either in the context of a clinical trial⁴ or in clinical practice when switching from natalizumab to fingolimod⁵. These observations provide further warning about the dangers of discontinuation of DMTs.

Prospective studies addressing discontinuation with stratification of patients according to risk factors that may predict permanent remission from inflammatory disease activity (e.g. age, duration of treatment, duration of relapse-free or "evidence of disease activity"-free status) are welcome. However, until the safety or at least relative safety of discontinuation is proven, ad hoc withdrawal of DMTs by clinicians should be discouraged.

1. Birnbaum G. Stopping disease modifying therapy in progressive multiple sclerosis: A prospective study. In: American Academy of Neurology 2014 Annual Meeting. Philadelphia PA, 2014.

2. Paz Soldán MM, Martina N, Crusan DJ, Atkinson EJ, OH K. Pre- and post-progression relapses impact disability in progressive multiple sclerosis. *Mult Scler* 2013;19:65.

3. Fabian MT, Lublin F, J W, TPTS G. Evaluation of progressive relapsing MS patients in the PROMISE Trial. *Neurology* 2011;76:A613.

4. Vellinga MM, Castelijns JA, Barkhof F, Uitdehaag BM, Polman CH. Postwithdrawal rebound increase in T2 lesional activity in natalizumab-treated MS patients. *Neurology* 2008;70:1150-1151.

5. Killestein J, Vennegoor A, Strijbis EM, et al. Natalizumab drug holiday in multiple sclerosis: poorly tolerated. *Ann Neurol* 2010;68:392-395.