DISCONTINUATION OF DISEASE-MODIFYING THERAPIES IN PATIENTS WITH LONG-TERM STABLE DISEASE IS SAFE AND APPROPRIATE: YES

Cris Constantinescu
UK

When considering the debate about the discontinuation of disease modifying therapies (DMT) in patients with long-term stable disease, first of all one must bear in mind that there is absolutely no high-level evidence base for arguing for or against such approach. Our argumentation on either side of the controversy by necessity has to be based on opinion, anecdotal, personal experiences, and extrapolation from studies that have not been designed to address this question. This is a concept of great importance but so far no randomised controlled trial (RCT), to my knowledge, has addressed this as a primary objective.

In such debates it is always very important to look very carefully at the title of the debate, and dissect its contents systematically.

First, we look at the word: "discontinuation". It implies an interruption, a break in continuity, stopping something that has been ongoing on a regular basis. However, it does not imply a permanent cessation. In terms of our debate, it leaves open the possibility that DMTs be reinstated if necessary. If one bears in mind this possibility, then once can be more confident in the safety of such discontinuation.

I will now review the current DMT scene. These treatments are becoming increasingly complex. In large part this is due to the emergence of new, increasingly more potent, and at the same time riskier, DMT. Related to this, and adding complexity, is the monitoring of DMT for safety and efficacy. For safety, blood tests and imaging procedures must be tailored to the particular DMT (e.g. JCV, blood counts, liver function tests and MRI for natalizumab). For efficacy, simple assessment of relapse rate is no longer sufficient. The lack of relapses should be doubled by lack of new/enlarging lesions on MRI, lack of sustained progression, no worsening of atrophy more than expected for the general population. We are now striving, in judging the efficacy of DMT, to achieve NEDA (no evidence of disease activity), a term borrowed from cancer treatments. Relapses and often MRI disease activity trigger escalation of treatment to more potent options to achieve NEDA.

When discussing discontinuation of DMT, we must consider which DMT from this increasing list we are talking about. As we borrow NEDA from cancer treatment, we have to acknowledge that treatment discontinuation in cancer patients with long term stable disease occurs routinely in those who achieve NEDA. The same holds true for strong "induction" DMT in MS. Alemtuzumab is given for 5 consecutive days, followed by another course 12 months later, and then its discontinuation is considered safe and appropriate. The treatment typically leads to long term stable disease.

This brings me to the next portion of the debate's title: long-term stable disease. This is again a matter of dispute. How long is long term? The natural history of MS is changing, possibly through earlier initiation or escalation of DMT. Given that relapse rate in the placebo arms of trials has reduced considerably and that some DMT reduce relapse rate to less than one in 5 years, I propose that "long-term" should at least exceed this duration in order to consider discontinuation of therapy, unless we talk about alemtuzumab (see above). We should also take into account the mode of action of the DMT. Drugs that reduce the pool or switch the phenotype of inflammatory cells may have achieved their function and induce long-term stability in responders. Drugs acting primarily on migration like natalizumab may not have sustained effects after discontinuation and despite long term active disease their discontinuation may pose risks.

How stable is stable? I support a high-standard, equivalent to NEDA, definition of of long-term stability for discontinuation. These patients do exist; if identified they could safely be discontinued.

What can lead to long-term stable disease on DMT? One mechanism is reduction to the mean, in which a chance increase relapse activity has led to institution of DMT and then there has been stabilization of otherwise more benign disease. In fact, due to the criteria for starting DMT (for example in the UK Risk Sharing Scheme the requirement has been 2 relapses in the last 2 years) there would have been many patients with long term stable disease who were not on DMT because they did not fulfil the criteria. Some of them had been in DMT trials for MS or CIS and stopped DMT at the end of the trial. Many remained stable long-term, without DMT. We need to think about a small but substantial number of CIS patients (London cohort) who acquired MRI lesions without clinical conversion to clinically definite MS for 20 years. Had they been on DMT, one would have attributed the stability of their condition to the DMT. The second mechanism of long-term stability is an "induction effect", an immunological effect in which initiation of treatment reduces pathogenic mechanisms leading to stability. The term "induction" is usually employed for strong drugs (alemtuzumab), but for a substantial number of patients glatiramer acetate, interferons have the same effect. Once this is achieved further treatment may no longer be necessary. This is done in some developing economies where DMT use is rationed and based on the evidence for benefits of early treatment, DMT are restricted to the first 5 years.

Finally, a discussion of what is safe and appropriate. In terms of safety, one concern is resumption of disease activity. However, discontinuation does not have to be a permanent cessation, and the DMT can be restarted. In fact DMT discontinuation may have safety benefits in terms of unwanted complications and side effects. Many of us I am sure have anecdotal evidence of such beneficial and safe discontinuations.

Discontinuation of DMT in patients with long-term stable disease is safe and appropriate. Such patients exist everywhere. Appropriateness of discontinuation depends on the type and mode of action of the DMT, the criteria for long-term stable disease and the ability to reintroduce DMT if necessary.