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Multiple sclerosis should be treated using a step-down strategy rather than a step-up strategy–Commentary

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In this issue of *Multiple Sclerosis Journal*, Prof. Gavin Giovannoni and Dr Robert Naismith have argued, respectively, that initiation of disease-modifying therapy (DMT) for multiple sclerosis (MS) should utilize a step-down approach (i.e. beginning with a high-efficacy induction strategy)[1] versus a step-up or escalation approach.[2] This is a critically important issue as we all would like to be able to provide people with multiple sclerosis (PwMS) the most effective, safe, and well-tolerated DMT possible. Both authors have provided cogent, but flawed, arguments in support of their positions.

Prof. Giovannoni has eloquently emphasized the importance of "hidden" disabilities in MS, particularly the high prevalence of cognitive impairment, which occurs even very early in the disease process.[3,4] Cognitive abnormality has been demonstrated for people with clinically isolated syndrome (CIS) and even for asymptomatic patients with the so-called radiologically isolated syndrome. Giovannoni notes, for example, the very high rates of unemployment among PwMS, even at times when their physical disability is modest as indicated by Expanded Disability Status Scale (EDSS) in the range of 3.0–3.5 (or even less). He also points out the evidence for axonal loss early in the course of the illness. Indeed, this destruction of axons, often regarded as part of a neurodegenerative process, may be even greater in the early stages of MS.[5] In making his argument for a step-down approach, Giovannoni focuses on an induction therapy with what he regards as high-efficacy DMT, including treatments such as alemtuzumab, cladribine (an agent which has heretofore been denied approval by both American and European regulatory agencies), or hematopoietic stem cell therapy (a treatment that as yet has not been subjected to any definitive randomized controlled trial). Induction therapy in his description is "given as a short course and has the ability to induce long-term remission and the possibility of a cure." In his discussion, he neglects the possibility of high-efficacy therapies that do require continued administration, such as natalizumab or ocrelizumab. The latter is a humanized anti-CD20 monoclonal antibody, which has recently had two highly successful phase III trials against interferon beta-1a (IFNB-1a) thrice weekly as an active comparator[6] and will likely achieve approval from regulatory agencies in late 2016 or early 2017.

In advocating for his step-down approach, Giovannoni has essentially borrowed the "time is brain" concept from the stroke field, albeit on a longer time spectrum. His argument that this strategy might preserve cognitive function may well be true, but, unfortunately, currently very little evidence exists to support its validity. This is certainly a hypothesis that is amenable to testing with the use of an adequate neuropsychological evaluation, rather than a single modality such as the Paced Auditory Serial Addition Test (PASAT) or the Symbol Digit Modality Test (SDMT).

Most importantly, Giovannoni has neglected to consider safety issues in the choice of the initial DMT. While efficacy is very important, it must be balanced by acceptable risk. The high-efficacy strategies he advocates carry the risk of potentially very serious or even fatal adverse events. Alemtuzumab is associated with serious autoimmune disorders;[7,8] cladribine raised safety concerns, particularly related to malignancies,[9] for regulators; and hematopoietic stem cell transplantation (HSCT) continues to be associated

with serious morbidity and mortality (albeit to a lesser extent in more recent studies) because of the profound immunosuppression or immunoablation involved.[10–12]

In stark contrast, Naismith emphasizes the safety and long experience with the injectable drugs. Both glatiramer acetate (GA) and IFNB preparations have been used extensively for more than 20 years. Serious adverse events have been extremely unusual and, as Naismith points out, they "do not cause cancers, opportunistic infections, or secondary autoimmune diseases, nor … teratogenicity."

Does this edge in safety, justify the use of these less effective agents as initial therapy for relapsing multiple sclerosis (RMS)? Naismith emphasizes the efficacy of interferon and GA when used very early in the course of MS, specifically in patients with CIS and in those with favorable clinical and magnetic resonance imaging (MRI) prognostic features. Yet, these prognostic features are fallible and many patients initiate DMT when they already have a diagnosis of definite MS. In a recent trial comparing alemtuzumab to thrice weekly IFNB-1a, the annualized relapse rate with the former (0.18) was less than half that of the latter (0.39).[7] In the CombiRx trial[13] cited by Naismith, 23%–25% of patients treated with IFNB, GA, or the combination experienced confirmed disability progression over the 3-year period of the trial. And this is a measure only of physical neurological disability without consideration of cognitive change.

At this time, then, the controversy posed about the correct strategy for initiation of DMT in RMS patients cannot be resolved. A clinical trial could be designed to address this question by assigning one group of patients initially to high-efficacy therapy and another to other drugs, allowing for step escalation. However, the answer would require a long trial that should properly include a multi-dimensional cognitive battery.

In the meantime, how should clinicians advise PwMS about the wisest course of action when initiating a DMT? The physician should have a very frank discussion about the risks of the respective agents, as well as about the efficacy data. Consideration should be given to the prognostic factors in the individual's situation and this information should be utilized to help the patient select the initial therapy in a process of shared decision making. In all cases, the importance of close follow-up and regular monitoring, both clinically and by MRI, should be emphasized in order to determine the need for alternate therapy in a timely manner.

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