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Treatment Optimization for Multiple Sclerosis: An Expert Interview With Mark Freedman, MD

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Editor's Note:

Multiple sclerosis (MS) is a debilitating, incurable disease, and characterizing patient response to various treatments for MS continues to challenge clinicians and researchers. A poster presentation at the recent European Committees for Treatment and Research in Multiple Sclerosis (ECTRIMS) conference in Vienna, Austria, applied published treatment-optimization recommendations[1] to data collected from the Prevention of Relapses and Disability by Interferon beta-1a Subcutaneously in Multiple Sclerosis (PRISMS) study of 560 MS patients.[2] Medical Editor Penelope Gray-Allan, on behalf of Medscape, discusses the results of this study and its clinical implications with Mark S. Freedman, MD, Professor of Medicine (Neurology) at the University of Ottawa in Ottawa, Ontario, Canada.

Medscape: The results of your study to measure the effectiveness of the Treatment Optimization Recommendations (TOR) model with data from the PRISMS study were presented in a poster at ECTRIMS.[3] What were the highlights of the results?

Dr. Freedman Rather than validating the TOR (recently published in *The Canadian Journal of Neurological Sciences*[1]), it was an attempt to see whether, when applied to actual, prospective trial data, the TOR had the sensitivity to be a useful outcome measure in prospective studies. In addition to the number or rate of relapses, we hypothesized that we could improve sensitivity by focusing on relapse quality and severity. Similarly, we focused not only on the amount of disease progression measured by Expanded Disability Status Scale scores, but also the quality of the progression.

We applied these TOR to the 560 patients who were followed as part of the PRISMS study. We evaluated patients with substantial changes in year 1 or 2 (during the placebo-controlled phase) vs year 3 (at which time all patients on placebo were switched to active treatment). Our results were remarkably sensitive in determining activity that was of significantly "higher concern" in the placebo vs active-treatment patients. Once the placebo patients switched to active treatments, the level of concern dropped dramatically.

Medscape: What do you see as the main clinical implications of your results?

Dr. Freedman: The key questions addressed in the TOR are: How much activity is "acceptable," and when should treatment be switched due to disease progression? We based our recommendations on the most solid data we could find. The only thing that we didn't have, and still don't have, are prospectively collected data showing that these recommendations help differentiate serious vs less serious disease activity. Your first thought might be that any activity is bad, but the reality is that none of our current treatments are able to fully stop disease activity. We must therefore accept a certain amount of disease activity as the "best we can do."

Other groups have produced similar recommendations in their respective countries. For example, the Germans reduced our tables into a checklist to facilitate decision making about individual patients. The French neurologists sent it around to hundreds of their colleagues and asked them to use it. They hope to determine how clinically useful these recommendations are in helping neurologists to optimize treatment decision making.

Medscape: Why are these treatment-optimization recommendations important?

Dr. Freedman: Because no one could define what a treatment failure was. Everybody with MS worsens; it's just a question of how much worse and how soon. So how can clinicians evaluate the success or failure of the current therapies? We couldn't define it by failure, but we could define it by an optimal response, which means a lack of disease progression. We defined degrees of suboptimal response, and that's what the TOR reflect: a low, medium, or high level of concern about whether a patient is getting the most out of his/her medications.

The TOR were based on data obtained from natural history studies and clinical trials. The type or quality of relapse, disease progression, or even MRI change could be of low-level concern, which means that there is little chance of progression in the near term. If a medium-to-high level of concern is met, it means that there is a strong likelihood that this activity will translate into an earlier progression. In that case, it is important to consider changing to a therapy that may more effectively control this "concerning" activity.

Medscape: MRI use for determining an MS patient's disease status has become fairly widespread in some countries. Do you use MRIs in your practice?

Dr. Freedman: I would never act solely on the results of an MRI. It is nothing more than a snapshot of a moving picture. We know that brain activity can change day by day, if not week by week, and you take 1 snapshot every 6 months. How is that going to provide any information about what has transpired over the entire period? If you take a picture of a patient's brain 6 months into treatment, and it's lit up with all these enhancing lesions, it might have been just a bad day. Two months later, all those lesions might have normalized and the patient might actually be doing quite well. The presence of lesions, however, still represents ongoing disease "activity," which we all agree is not good. But should having an MRI with enhancing lesions carry a greater level of concern than having an attack that affects motor capabilities that don't recover? Most believe not.

It's very easy to misinterpret a single MRI result, and the way the MRI was used in PRISMS and other clinical trials was very different from day-to-day practice. These were sequential scans done every 4-6 weeks that used the same scanner; the patient was positioned in such a way that the brain lined up exactly in 3 dimensions. This enabled investigators to remap every lesion within 1 mm from scan to scan. Only then can one really confirm that it is the same lesion and determine whether a lesion has gotten bigger or smaller, disappeared, or re-enhanced. That's not how MRIs are used today in our regular practice. We do not yet have a scanning protocol for MS that is followed by all

clinicians and researchers in Vancouver, Ottawa, and elsewhere. If we do someday, perhaps we will be able to better follow patients with sequential MRI results.

Medscape: The PRISMS study focused on the treatment of MS with interferon (IFN)-beta-1a, and study results indicate that early treatment with IFN-beta-1a was important to a positive outcome. Why do you think that is?

Dr. Freedman: There is a narrow window of opportunity for this group of drugs known as immunomodulators. The exact width of that window is determined by the individual patient's status early in the course of disease. The more disease that accumulates, the greater the chance that progression has begun and the window of opportunity has closed. Therefore, a patient probably warrants immunomodulatory treatment if he/she is either at high risk of developing MS, even after 1 episode, or clearly has MS by virtue of the new McDonald criteria.[4] Rather than waiting for further events in an individual that meet one of these criteria, treatment should be started once a definitive diagnosis is established.

In the PRISMS study, investigators actually looked at a group of patients who were receiving a placebo and a group who had received low-dose (22 mcg) or high-dose (44 mcg) IFN-beta-1a 3 times weekly. Later in that study, the patients in the placebo group were crossed over onto the active medication, and long-term follow-up showed that those patients with delayed full-dose treatment were worse off. They had more attacks, more MRI lesions, and were progressing faster than the group who was receiving IFN-beta-1a right from the start. What was lost by delaying therapy was never regained -- and that's an important message.

Medscape: Is high-dose, high-frequency IFN-beta-1a effective in reducing the long-term accumulation of brain-lesion volume in patients with relapsing, remitting MS?

Dr. Freedman: It's very effective. If we start this treatment early, we can knock down the development of new lesions 80% to 90% and improve on whatever lesion load was there. At the end of 4 years,[5] those patients who received IFN-beta-1a from the beginning of the study had a net reduction in lesion load, which means that they had less than they did at baseline. In contrast, any patient who received placebo (and was subsequently switched to high-dose therapy) had more lesion load than they did at baseline. Another perfect example of why it's important to institute early treatment.

Medscape: Also at ECTRIMS, data from poster presentations suggested some therapy-adherence strategies. Is patient compliance an issue with these treatments?

Dr. Freedman: It's very much an issue in many countries. Our nurses have done extraordinarily well in Canada, however, in getting our patients to adhere to the medication. I think the adherence rate in our clinic is about 95%.

Medscape: What solutions have been suggested to improve adherence and patient outcome?

Dr. Freedman: We think that one of the most important reasons for our success in Canada is that our patients have been well educated in terms of what they are to expect from the drugs, and they have had regular follow-up visits.

In the early period of the disease, all MS patients feel normal most of the time. They'll get maybe 1 attack every 1-2 years. So as the months go by and their thighs and their arms and their bellies are all looking red from the injections, and they're feeling a bit like a pin cushion, they will often wonder why they need to endure the injections. There might be no evidence that the treatment is doing anything. It is then that they might start slacking off. That's why patients need to be seen on a regular basis, and not just to put out fires when they're in trouble. A clinician should regularly follow efficacy, side effects, and the adherence rate, and it doesn't hurt to review proper injection techniques and why they are taking these treatments.

Medscape: On the basis of available therapeutic agents, what do you consider to be the optimal treatment regimen for MS?

Dr. Freedman: In patients with early, mild disease, we tend to use all 4 therapies, and we try to choose according to what the patient will most likely be able to tolerate. Once patients have more advanced and clinically detectable disease, most physicians will move right away to the high-dose IFNs, because you really want to quiet down the disease as quickly as possible. When I'm using IFNs for established MS, I will almost always use a high-dose, high-frequency regimen from the start.

For patients who have definite relapsing, remitting MS with at least 2 attacks of MS, we know that the high-dose, high-frequency IFN is effective.[5] We don't know how that directly compares with the other therapies, such as glatiramer acetate, because the "head-to-head" trials are only going on now, but clinically from the original studies, the relapse rates were somewhat similar.[6,7]

It is important to remind patients that these treatments are not a cure. We're aiming for disease control. Some of us have actually put together a treatment algorithm, which was one of the other posters at this conference.[8] An algorithm, together with the treatment-optimization recommendations, turns out to be one of the most helpful tools to guide MS treatment decision making.

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