Are DMDs a Good Choice in the Early Treatment of CIS and MS?

Saeed Shahbeigi*

Department of Medicine, UBC Division of Neurology, Canada

About 2.5 million individuals worldwide are currently being affected by MS [1]. In Europe, mean annual cost per person with MS is estimated to be around €27,000 [2]. In the European Union, the estimated costs of MS are calculated to be at €9 billion per year [3]. In a survey among patients receiving Disease Modifying Drugs (DMD) in the United States in 2004, total average costs per patient were estimated as high as US$47,000 per year. Of these costs, 63% were direct costs, including 34% of total costs (US$16,000) for DMD [4]. Rosstein et al describe that prescriptions of the 4 DMDs used in MS (3 Beta Interferons and Glatiramer Acetate (GA)) increased by 50% over five years. Their cost jumped from 15 to 28 million dollars per year from 2001 to 2007 in Canada [5]. Therefore, the answer to the question posed here is probably worth a few Billion dollars.

Up to now, the DMDs have been generally approved for treatment of Relapsing Remitting MS (RRMS) on the basis of trials demonstrating a reduction in Annual Relapse Rate (ARR), a delay in conversion of Clinical Isolated Syndrome (CIS) to Clinical Definite MS (CDMS) and a decrease in the occurrence of gadolinium-enhancing lesions [6]. We will see here that, unfortunately the DMDs seem not to alter the course of the disease once it becomes progressive. We will stress that there is no accepted rules for stopping a treatment that has become useless even though it had been started at a time in the disease process when it was demonstrated to be useful.

CHAMPS was the first study that demonstrated that in patients with CIS patients conversion to CDMS was reduced from 50% in placebo to 35% in Beta-1a treated patients. In addition, the gadolinium enhancing lesions were significantly reduced. Subsequent studies with Beta-1a IFNBeta-1b and GA have confirmed these results [7]. The BENEFIT [8] and INF Beta MS study group [9] which conducted a study at the same time in the US and Canada, showed that the risk of developing CDMS was reduced significantly in the IFNBeta-1b group compared to the placebo. In parallel, the number and volume of gadolinium-enhancing lesions were decreased, as well as the cumulative number of new T2 lesions. However, in the 8-year follow-up of BENEFIT, the long-term impact of INFBeta-1b in patients with CIS the median EDSS in both early and late treatment group remained 1.5 from baseline to 8 years. The mean EDSS after 8 years in the early treatment group was 1.87; however, in the late group it was 1.56 [7]. In fact, BENEFIT has demonstrated that patients who started off in the treatment arm did better than those who were crossed over to the treatment arm. That was also demonstrated for RRMS patients included in PRISMS crossover study [10] and in the GA US-based study [11] creating the consensus that to get the most benefit with those drugs patients should be treated early.

The INFBeta MS study group demonstrated that despite the fact that ARR was consistently about one-third lower in patients treated with INFBeta-1b 250 mg than in those who received placebo, there were no statistically significant differences between INFBeta-1b treated and placebo groups for the mean change in EDSS from baseline to 2 years [9].

The BEYOND [12] and BECOME [13] studies evaluated the efficacy of INFBeta-1b and GA in patients with RRMS. No statistically significant differences between treatment groups for ARR were seen. Brain MRI outcome measures, including mean change in T1-hypointense lesion volume from MRI screening and the median number of active lesions per patient per MRI were also not significantly different between treatment groups [14].

Subsequently, for evaluation of efficacy of GA, a meta-analysis among 409 retrieved references was published in Cochran review. In RR MS, a decrease in the mean EDSS score (-0.33 and -0.45) was found respectively at 2 years and 35 months without any significant effect on sustained disease progression. The authors concluded that GA did show a partial efficacy in RR MS in term of ARR, without any significant effect on clinical progression of disease measured as sustained disability. It should be further stressed that the drug has not been shown to be effective in progressive MS [15].

In order to find when to start DMD in patients with CIS, a study was conducted in 29 multiple sclerosis (MS) centers in Austria. Interestingly, those patients who were not given GA during the 2-year follow-up had a significantly lower rate of conversion to CDMS and a better quality of life (using a visual analogue scale - VAS), than patients belonging to other groups. In a comparison of patients with and without immediate treatment, they saw no significant differences, neither in EDSS nor in QOL.
In another study, the European group showed that INFbeta-1b significantly delayed neurological deterioration in patients with SPMS. Compared with placebo, treatment with INFbeta-1b for up to 3 years significantly increased the time to confirmed disease progression as assessed by EDSS scores. There were also statistically significant advantages for INFbeta-1b over placebo to delay the time to become wheelchair-bound and was associated with significantly lower rates of hospital admission [17]. Nevertheless, the North American study that even compared two different dosage regimens of INFbeta-1b (250 mg and 160 mg/m²) with matching placebo demonstrated that there were no statistically significant differences between INFbeta-1b groups and placebo for confirmed disease progression or for changes in mean EDSS score from baseline to end-point treatment groups [18]. And in a large Retrospective cohort study based on prospectively collected data (1985-2008) that was done in Britain Columbia, Canada the exposure to interferon beta was not associated with a statistically significant difference in the of reaching an EDSS score of 6. The author concluded that among patients with RRMS, INF-1b was not associated with a reduction in progression of disability [19].

In terms of the efficacy of INFs on cognition one study has shown that initiation of treatment with IFNbeta1-b, at the time of the first event of CIS has a beneficial effect on cognition as measured by PASAT-3 [20]. However, in another randomized, placebo-controlled, multicenter, phase III trial, no difference in therapeutic effect on cognition was assessed when GA was compared with placebo [21]. Similar finding was also seen in a long-term study after 10 years among patients receiving early versus delayed treatment with GA [22].

Therefore, it seems obvious that it is not demonstrated that a medication that will lower relapse rate, will also control disease progression. Confavreux et al. showed that once EDSS has reached to 3 to 4, progression of disability is not affected by relapses anymore [23]. Similar conclusion came from the group in Rennes [24].

This also suggests that drugs that have a short-term effect on relapses in patients with MS may not necessarily delay the development of disability in the long term. In addition, neither total number of attacks nor attacks experienced after the second year of the disease can be correlated with disability progression [25,26].

The absence of a relationship between relapses and disability suggests that there is a dissociation at the biologic level between recurrent acute focal inflammation and progressive degeneration of the central nervous system [6]. This makes us believe that DMDs including INF Beta and GA which are the only first line treatment candidates in RRMS, should be discontinued when patients reach the progressive phase and will lose their market dominating position in the near future. We suggest that other treatment options such as monoclonal antibodies (Natalizumab, Alemtuzumab and Ocrelizumab) as well as cell-based therapy could become better treatment options for MS in the future perhaps even from onset of the disease.

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