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Editorial

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

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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]. Rotstein 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 INFBeta-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 cross-over 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

[16]. 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 British 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- 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 IFNBeat -1b, 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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REFERENCES

1. Castrop F, Haslinger B, Hemmer B, Buck D. Review of the pharmacoeconomics of early treatment of multiple sclerosis using interferon beta. Neuropsychiatr Dis Treat. 2013; 9: 1339-1349.
2. Gustavsson A, Svensson M, Jacobi F, Allgulander C, Alonso J, Beghi E, et al. Cost of disorders of the brain in Europe 2010. Eur Neuropsychopharmacol. 2011; 21: 718-779.
3. Rice CM, Mallam EA, Whone AL, Walsh P, Brooks DJ, Kane N, et al. Safety and feasibility of autologous bone marrow cellular therapy in relapsing-progressive multiple sclerosis. Clin Pharmacol Ther. 2010; 87: 679-685.
4. Kobelt G, Berg J, Atherly D, Hadjimichael O. Costs and quality of life in multiple sclerosis: a cross-sectional study in the United States. Neurology. 2006; 66: 1696-1702.
5. Rotstein DL, Mamdani M, O'Connor PW. Increasing use of disease modifying drugs for MS in Canada. Can J Neurol Sci. 2010; 37: 383-388.
6. Pachner AR. A Primer of Neuroimmunological Disease. New York: USA: Springer. 2012.
7. Edan G, Kappos L, Montalbán X, Polman CH, Freedman MS, Hartung HP, et al. Long-term impact of interferon beta-1b in patients with CIS: 8-year follow-up of BENEFIT. J Neurol Neurosurg Psychiatry. 2013;.
8. Kappos L, Polman CH, Freedman MS, Edan G, Hartung HP, Miller DH, et al. Treatment with interferon beta-1b delays conversion to clinically definite and McDonald MS in patients with clinically isolated syndromes. Neurology. 2006; 67: 1242-1249.
9. Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. I. Clinical results of a multicenter, randomized, double-blind, placebo-controlled trial. The IFNB Multiple Sclerosis Study Group. Neurology. 1993; 43: 655-661.
10. Oger J, Francis G, Chang P. PRISMS Study Group. Prospective assessment of changing from placebo to IFN beta-1a in relapsing MS: the PRISMS study. J Neurol Sci. 2005; 237: 45-52.
11. Carter NJ, Keating GM. Glatiramer acetate: a review of its use in relapsing-remitting multiple sclerosis and in delaying the onset of clinically definite multiple sclerosis. Drugs. 2010; 70: 1545-1577.
12. O'Connor P, Filippi M, Arnason B, Comi G, Cook S, Goodin D, et al. 250 microg or 500 microg interferon beta-1b versus 20 mg glatiramer acetate in relapsing-remitting multiple sclerosis: a prospective, randomised, multicentre study. Lancet neurology. 2009; 8: 889-897.
13. Cadavid D, Wolansky LJ, Skurnick J, Lincoln J, Cheriyan J, Szczepanowski K, et al. Efficacy of treatment of MS with IFNbeta-1b or glatiramer acetate by monthly brain MRI in the BECOME study. Neurology. 2009; 72: 1976-1983.
14. Fillipi M, Rocca MA, Camesasca F. IFNB-1b com- pared with GA therapy for reducing evolution of permanent T1 hypo intensities (''black holes'') on brain MRI in treatment-naive RRMS patients 62nd Annual Meeting of the American Academy of Neurology; April 10-17 Toronto: Neurology.
15. La Mantia L, Munari LM, Lovati R. Glatiramer acetate for multiple sclerosis. The Cochrane database of systematic reviews. 2010; CD004678.
16. Fazekas F, Baumhackl U, Berger T, Deisenhammer F, Fuchs S, Kristoferitsch W, et al. Decision-making for and impact of early immunomodulatory treatment: the Austrian Clinically Isolated Syndrome Study (ACISS). European journal of neurology: the official

journal of the European Federation of Neurological Societies. 2010;17: 852-860.

17. Placebo-controlled multicentre randomised trial of interferon beta-1b in treatment of secondary progressive multiple sclerosis. European Study Group on interferon beta-1b in secondary progressive MS. Lancet. 1998; 352: 1491-1497.

18. Panitch H, Miller A, Paty D, Weinshenker B. North American Study Group on Interferon beta-1b in Secondary Progressive MS. Interferon beta-1b in secondary progressive MS: results from a 3-year controlled study. Neurology. 2004; 63: 1788-1795.

19. Shirani A, Zhao Y, Karim ME, Evans C, Kingwell E, van der Kop ML, et al. Association between use of interferon beta and progression of disability in patients with relapsing-remitting multiple sclerosis. JAMA. 2012; 308: 247-256.

20. Penner IK, Stemper B, Calabrese P, Freedman MS, Polman CH, Edan G, et al. Effects of interferon beta-1b on cognitive performance in patients with a first event suggestive of multiple sclerosis. Mult Scler. 2012; 18: 1466-1471.

21. Weinstein A, Schwid SR, Schiffer RB, McDermott MP, Giang DW, Goodman AD. Neuropsychologic status in multiple sclerosis after treatment with glatiramer. Arch Neurol. 1999; 56: 319-324.

22. Schwid SR, Goodman AD, Weinstein A, McDermott MP, Johnson KP. Copaxone Study Group. Cognitive function in relapsing multiple sclerosis: minimal changes in a 10-year clinical trial. J Neurol Sci. 2007; 255: 57-63.

23. Confavreux C, Vukusic S, Moreau T, Adeleine P. Relapses and progression of disability in multiple sclerosis. N Engl J Med. 2000; 343: 1430-1438.

24. Leray E, Yaouanq J, Le Page E, Coustans M, Laplaud D, Oger J, et al. Evidence for a two-stage disability progression in multiple sclerosis. Brain. 2010; 133: 1900-1913.

25. Scalfari A, Neuhaus A, Degenhardt A, Rice GP, Muraro PA, Daumer M, et al. The natural history of multiple sclerosis: a geographically based study 10: relapses and long-term disability. Brain. 2010; 133: 1914-1929.

26. Alkhawajah M, Oger J. When to initiate disease-modifying drugs for relapsing remitting multiple sclerosis in adults? Mult Scler Int. 2011; 2011: 724871.

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