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## **Does it Make a Difference Which Interferon- $\beta$ to use for Relapse and Remitting Multiple Sclerosis (RRMS)?**

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Commentary on:

Nikfar *et al.* (2010a-c). A systematic review on the efficacy of interferon beta in relapsing remitting multiple sclerosis; Comparison of different formulations. *Int. J. Pharmacol.*, 6: 638-644.

Central Nervous System (CNS) myelin related disorders could be broadly categorized into demyelinating (loss of myelin) and dysmyelinating (abnormal myelin formation) disorders. Among demyelinating disease of the central nervous system, Multiple Sclerosis (MS) is the most common one, especially among the younger population. Inflammation, demyelination and axonal degeneration, could end to MS resulting from various defects in tissue repair mechanisms, injury and demyelination (Weiner, 2004). Although autoimmune model is not a perfect model to explain all aspects of MS, it is difficult to disregard the considerable evidence that points us toward the important role of immunity in disease progression and development.

The most commonly accepted picture of MS pathogenesis, involves activation of autoreactive lymphocytes and later, in the course of the disease, microglial activation and neuronal degeneration (Weiner, 2004; Compston and Coles, 2008). This could be the crucial mechanism underlying the therapeutic benefits observed from certain immunomodulatory agents and disease modifying drugs such as interferon  $\beta$ -1a (Avonex and Rebif), interferon  $\beta$ -1b (Betaseron), glatiramer acetate and natalizumab (Nikfar *et al.*, 2010a). This group of medications has been shown to be most effective in relapse and remitting type of MS (RRMS).

The unblinded randomized INCOMIN study compared interferon  $\beta$ -1b (Betaseron) with intramuscular interferon  $\beta$ -1a (Avonex) found the results in favor of Betaseron in both clinical and imaging measures (Durelli *et al.*, 2002). For over two years of follow-up, significantly more number of patients who received interferon  $\beta$ -1b remained relapse-free than those assigned to interferon  $\beta$ -1a. In contrast to the INCOMIN study, an open-label randomized multicenter trial showed similar efficacy for subcutaneous interferon  $\beta$ -1a (Rebif) and Betaseron in relapse rates after treatment between the two group (Koch-Henriksen *et al.*, 2006). The result of a meta-analysis by Nikfar and coauthors (Nikfar *et al.*, 2010c) also confirms these findings by showing similar efficacy for Betaseron and Rebif, which is slightly but not significantly superior to intramuscular interferon  $\beta$ -1a (Avonex). In this, meta-analysis authors looked at three different interferon  $\beta$  preparation; showing no significant difference among Avonex, Rebif and Betaseron in term of their relapse rate and disability scores (Nikfar *et al.*, 2010c). Lack of finding significant difference, in this study could be well explained by (1) type II error due to low statistical power or (2) poor quality of included studies, since 5 out of 6 included studies had score of three or lower on Jadad scale, indicating a poor study quality. Another important issue considering the clinical efficacy of these drugs is the slow natural progression course of MS, with the median time to reach disability of around 14 years since diagnosis (Confavreux and Vukusic, 2002) as a result short-term clinical trials become less informative and methodologically hard to conduct and interpret. These methodological and practical issues well reduce the reliability of meta-analysis as a technique to combine and use the pooled data.

Another important issue to consider is the ethnicity related differences in efficacy of interferon- $\beta$ . It has been shown for example that in Japanese population optic-spinal variant of MS is more frequent and Betaseron has particularly shown to have good outcomes for this subtype of MS. The lack of data for other population groups and formulations makes it difficult to draw any further conclusion at this point (Saida *et al.*, 2005).

The three drugs that are compared in this study have different safety profiles. Interferons in general have several common mild to moderate side effects such as "flu-like" symptoms and injections site pain and necrosis.

However, one systematic review comparing these three medications concluded that Rebif and Betaseron have similar side effects, which were slightly higher than Avonex when they considered liver enzymes as a marker of hepatotoxicity (Tremlett *et al.*, 2004). These side effects have been shown to be dose-related (Francis *et al.*, 2003). It has also been shown that history of alcohol use, obesity, or combined use of other medications or male gender raises the risk of hepatotoxicity and should be checked and considered during treatment (Tremlett *et al.*, 2004).

The efficacy of Interferon- $\beta$  has been well established for treatment of RRMS (Nikfar *et al.*, 2010b); However as it has been shown in this meta-analysis by Nikfar and colleagues (Nikfar *et al.*, 2010c) that the difference between various preparations is subtle and quite often indistinguishable. Therefore, availability, costs and individualized responses to particular formula remain to be the main determining factors when it comes to decision making for each patient. Immunopathology of MS is complex and long term effects of treatment is unknown and the current amount of evidence on safety and efficacy is not enough; therefore investigation for new drugs and long-term efficacy assessment is necessary before any change in current management of MS to take place.

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