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MS treatment: Postmarketing studies

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Abstract

Multiple sclerosis (MS) is an inflammatory chronic demyelinating disease. Nowadays, there are several registered drugs aimed to control the disease activity. Because these drugs are given parenterally for years, it is of utmost importance to attain maximum adherence to treatment through close and permanent care of patients.

The efficacy of the different registered drugs has been compared against placebo. Observational and head-to-head studies have shown controverted results in the degree of efficacy between the products. Despite the efficacy reported, a high proportion of patients will have a lack of response to treatment. Early identification of these patients is therefore essential in order to attempt other therapeutic approaches.

Keywords: Multiple sclerosis; Interferon; Observational studies

1. Introduction

Treatment of multiple sclerosis (MS) has experienced a radical change in the last decade. Nowadays, we have several formulations of immunomodulatory drugs (IMD) approved and registered for the treatment of the disease. Clinical trials with IMD in the past few years have demonstrated to exert a reduction of the disease activity [1–6]. Nevertheless, in most cases these data of efficacy emerge from clinical trials with durations under 4 years. Due to their short-term follow-up, clinical trials in RRMS can render erroneous clinical results [7,8]. Moreover, such results can be only partially reproducible in the daily clinical practice, because of the varying demographic backgrounds and clinical factors of the populations studied. Observational cohort studies bear the benefit of relatively easy long-term monitoring and can supply data on the behaviour of cohorts during extended treatment periods [9]. Although randomized, controlled trials must be considered the "gold standard" for research design, agreement between their results and those from observational studies support the potential value of the latter. Several reviews approaching meta-analysis have shown that results from observational studies consistently match the data obtained in randomized, controlled trials [10–12]. Nevertheless, there are factors that may hinder the analysis of such observational studies, including the very lack of randomization, variation in duration of treatment, incomplete monitorization, dropouts and unaccounted drug switches [9].

2. Factors related with dropouts and drug switches

One of the problems that new IMD therapies pose is a relatively inconvenient administration procedure, side effects and the long periods on therapy. These factors can contribute to diminishing a patient's adherence to treatment. Bearing in mind that there is no efficacy in the event of IMD interruption and with the aim to obtain maximum benefit from the drug, it is paramount to help patients adhere to treatment. Awareness of the factors influencing discontinuation of IMD therapy in MS can help to find approaches to patient management with the aim to establish more specific indications and also to attain more optimal patient selection

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in future clinical trials. Besides, the patients included in clinical trials are probably different from those in the daily clinical practice who receive less intensive monitoring. Reasons for interruption reported in clinical trials can hence be different from those in the clinical practice. A recent study including a long follow-up period and with a very low drop-out rate, has demonstrated an overall discontinuation rate of 17%, one of the lowest reported in the literature [13]. Another recently published study shows that in a cohort of patients followed for at least 3 years, 61% stayed on treatment with IMD [14], although this proportion raises to about 80% in cohorts with thorough and careful follow-up. It has been suggested that the critical period for stopping IMD is set within the first 6 months of therapy and regular patient support during this time is paramount [14,15]. Other authors, however, found that a very small proportion of patients (1.7%) stopped IMD therapy during the first 6 months of follow-up [13], Nevertheless, half of the patients stop treatment within the first 2 years into therapy. Thus, care and support must be constantly available during the first few years of therapy.

Probably, as other studies have shown, the implementation of a treatment protocol through expert and trained professionals who can explain the real treatment expectations and also give personalized healthcare services centered on the patient, allows for easy and quick contact with their neurologist and MS nurse resulting in a lower rate of patients discontinuing IMD [17].

The proportion of patients stopping IMD is significantly higher in the SPMS patient group than in the RRMS group. In a similar way, clinical trials report higher dropout rates and reduced efficacy for patients with SPMS [18,19]. Hence, IMD treatment should be accurately prescribed in the case of SPMS patients and the real expectations of the pros and cons of treatment clearly explained in order to avoid undesired dropouts. Patients with greater disability at therapy entry will also have a high risk to stop IMD. This probably points to a higher likelihood of short-term disability progression and the fact that they can become non-responders as shown in the natural history studies [8,20].

Recently published papers show that dropout patients have a worse response to treatment than patients who stay on treatment, thus favoring selective retention of responders to treatment [21]. In the light of this, it is paramount to follow up patients that become study dropouts after inclusion in therapeutic trials. Because they probably represent the group with poorer clinical evolution, the information provided by dropout patients is a cornerstone to result interpretation in clinical trials.

Thus, quality care and thorough service given to patients initiating IMD is fundamental when aiming to attain low dropout rates. On the other hand, it needs to be pointed out that patients who stop IMD therapy are usually those who will develop higher disability in the short run. Thus, the early identification of this group of patients can aid clinicians when approaching other therapeutic strategies.

3. Post-marketing efficacy

Recently, a study describing the behaviour of a large cohort of RRMS patients treated with different formulations of interferon beta has been published [22]. This is the study with the longest follow-up time reported to date. In this independent, open-label, non-randomized, observational study conducted to assess the efficacy and safety of IFNβ in a large cohort of RRMS patients representative of the general population on IFNβ therapy, the authors studied 495 RRMS patients. All patients initiated therapy with interferon because they had an active disease with two or more relapses in the previous 2 years with an EDSS score between 0 and 5.5. Patients were given information regarding the available therapies in RRMS including efficacy data from pivotal phase III studies as well as information regarding the safety profile of each agent. After a detailed discussion with the neurologist, patients made a final decision of selecting treatment: IFNβ-1b (Betaferon), IFNβ-1a (Avonex) or IFNβ-1a (Rebif).

Clinical outcome measures of efficacy were the proportion of relapse-free patients at 2 and 4 years and those with confirmed and sustained disability progression at 2 and 4 years. Additionally, the changes in annualized relapse rate, proportion of decrease in relapse rate, proportion of patients reaching EDSS 6 at 4 years and number of patients who discontinued treatment due to inefficacy were also studied. The results of this study evaluating the effects of IFNβ-1b (Betaferon), IFNβ-1a (Avonex) and IFNβ-1a (Rebif) as used in the clinical practice, are in agreement with the efficacy and safety results of phase III trials of IFNβ in relapsing MS. The proportions of relapse-free patients during the first 2 and 4 years of follow-up were not statistically different among the three groups. Each treatment group showed a significant reduction in relapse rate after 24 and 48 months of treatment ($p<0.0001$). There were no differences in relapse rate within the first 2 years of treatment nor in the percentage change from baseline in relapse rate among the three IFN formulations. At 4 years of treatment, the three formulations were associated with significant reductions from baseline in relapse rates. The difference between groups in the percentage change in relapse rate induced by the three formulations at 4 years was not significant. The proportions of patients in the various groups with confirmed and sustained disability progression (increase of at least 1 EDSS point) after 2 years of follow-up were not different; all three products were safe and well tolerated, although skin reactions from subcutaneous IFNs were significantly more frequent. The adverse events profile for each IFNβ product in the present study is similar to that reported in each of the pivotal phase III trials [1–3]. No differences in the proportion of patients who dropped out because of adverse events were observed.

In recent years, several head-to-head comparative studies with direct comparisons on the efficacy of IFNβ products in the treatment of relapsing–remitting MS have been published