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Multiple Sclerosis on behalf SFSEP

First-line therapy in relapsing remitting multiple sclerosis

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INFO ARTICLE

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ABSTRACT

Today, first-line treatments for multiple sclerosis include injectable immunomodulators – some of which have been on the market for nearly 25 years – as well as teriflunomide and dimethyl fumarate, which are more recent, but have opened the way for oral treatments. These drugs are considered similar in effectiveness, and their safety and side-effect profiles are generally reassuring. These treatments have been associated with a reduction in radiological and clinical disease activity, and a positive effect on patient quality of life, especially when introduced early in the disease process. This article will discuss data on first-line treatments currently available in France, their effectiveness and safety, and their place in pediatric patients and in woman who plan to become pregnant.

In 2018, in France, patients with relapsing-remitting MS have many treatments available to control clinical and radiological inflammatory activity in the short term that are also potentially effective against mid- and long-term disability accumulation. Treatments considered to have the best balance between effectiveness and safety (and often price) are called first-line treatments. The first of these were the injectable immunomodulators, i.e., beta interferons and glatiramer acetate (GA). But in the last few years, the oral treatments teriflunomide and dimethyl fumarate (DMF) have been added to the arsenal of first-line treatments. Second-line treatments, mainly fingolimod and natalizumab, can be used as first-line therapy in certain particularly aggressive cases of MS, but these treatments will not be discussed in depth in this article.

First-line treatments have, overall, reduced the annualized rate of attacks by about 30% in studies, reduced the radiological inflammatory activity by two-thirds, and have the potential to reduce disability, generally evaluated using the EDSS. In recent years, the analysis of results from pivotal studies, extension studies, and real-life cohort studies, and a better understanding of the pathophysiology and natural history of MS, have demonstrated the benefit of these treatments when prescribed as early as possible in the clinically defined disease, or even at the clinically isolated syndrome stage (a single attack with the MS diagnostic criteria met).

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1. Injectable immunomodulatory treatments

1.1. Beta interferons (IFNβ)

1.1.1. Mechanisms of action

Beta interferons consist of the IFNβ1a group (Avonex®, IM, once a week, Rebif®, SC, 3 times a week, Plegridy®, SC, every other week) and IFNβ1b group (Betaferon® and Extavia®, SC, every other day). The first, Betaferon®, was approved in the United States in 1993. US approval was obtained for Avonex® in 1996, Rebif® in 2002, and Plegridy® in 2014.

The mechanism of action of these interferons is still not fully understood. Their immunomodulatory effect is the result of several mechanisms combined. These mechanisms include: Th17-cell inhibition [1], regulatory [2] and suppressor T-cell restoration [3,4], autoreactive T-cell apoptosis induction [2], reduced proinflammatory cytokine production [5,6] and antigen presentation [2], a shift in the Th1/Th2 balance toward Th2, or even decreased passage of inflammatory cells through the blood-brain barrier [7,8].

The latest member of this drug family – the PEGylated form of IFNβ1a – is obtained by combining IFNβ1a and methoxy polyethylene glycol, which increases the bioavailability of the resulting compound by reducing renal clearance [9].

1.1.2. Pivotal studies

The Pivotal studies are:

- IFNβ1b: IFNb Multiple sclerosis study group [10]. Two-year placebo-controlled study of IFNβ1b, SC, 50 μg or 250 μg every 48 hours;
- IFNβ1a IM: Multiple sclerosis collaborative research group [11]. Two-year placebo-controlled study of IFNβ1a, IM, 30 μg per week;
- IFNβ1a SC: PRISMS (Prevention of Relapses and Disability by Interferon beta-1a Subcutaneously in Multiple Sclerosis). two-year placebo-controlled study of IFNβ1a, SC, 22 μg or 44 μg, three times a week [12];
- PEGylated IFNβ1a: ADVANCE [13]: two-year placebo controlled study of PEGylated IFNβ1a, SC, 125 μg every 2 or 4 weeks.

These pivotal studies showed, in comparison with placebo:

- a significant reduction in the annualized rate of attacks: 32% for IFNβ1a, IM [8,11]; by 34% at 2 years for IFNβ1b ($P = 0.0001$) [10]; by 33.2% at 2 years for IFNβ1a, SC, ($P < 0.005$) [14]; by 36% at 48 weeks for PEGylated IFNβ1a ($P = 0.0007$) [13];
- a reduction in confirmed disability progression: a 37% reduction in time to disability progression confirmed at a minimum of 6 months ($P = 0.04$) for IFNβ1a IM [11]; −30% at 12 patient-weeks with confirmed progression ($P < 0.05$) for IFNβ1a SC [12]; a 38% reduction in relative risk of disability progression at 48 weeks (confirmed at 12 weeks) for PEGylated IFNβ1a ($P = 0.038$) [13], with no significant effect for IFNβ1b [10];
- a reduction in the number of new gadolinium-enhanced lesions and/or new T2-weighted lesions: for IFNβ1a SC, the median number of MRI-enhanced lesions went from 2.25 in the placebo group to 0.5 (IFNβ1a SC 44 μg, $P < 0.0001$) while changes in the T2-weighted lesion load at 2 years went from +11% in the placebo group to −3.8% in the treated group ($P < 0.0001$). For IFNβ1a IM, the mean number of lesions with gadolinium uptake at 2 years went from 1.65 in the placebo group to 0.8 ($P = 0.05$), while the T2-weighted load did not change significantly [11]. For IFNβ1b, the pivotal studies provided no data on gadolinium-enhanced lesions on MRI; however, the median lesion load appeared to be significantly lower in the treated group ($P < 0.0001$). Finally, with regard to the PEGylated form of IFNβ1a, the number of enhanced lesions decreased by 1.4 in the placebo group to 0.2 at 48 weeks ($P < 0.0001$) and the mean number of new or enlarging T2-weighted lesions decreased by 33%, from 10.9 to 3.6 ($P < 0.0001$) [13].

1.1.3. Extension studies

IFNβ1a SC: 15-year extension studies confirm the results of the pivotal studies, highlighting the benefit of early treatment [15]. On the other hand, in the 11-year extension study BENEFIT (Betaseron in Newly Emerging MS for Initial Treatment; IFNβ1b at the clinically isolated stage), the significant impact on the risk of conversion to clinically defined MS appeared to have a long-term effect in the group treated early, while the impact on disability progression did not differ between groups [16]. Finally, an analysis performed 21 years after the pivotal studies on IFNβ1b showed that early implementation of this treatment (versus the placebo group in the pivotal studies) was associated with an overall reduction in mortality [17].

PEGylated form of IFNβ1a (ATTAIN [18]): During the two additional follow-up years of the pivot study, a reduction of 39% in the risk of attacks and 41% in disability progression was observed in patients who continued treatment every 2 weeks compared with those who received the placebo the first year. Effectiveness was most significant in the group treated every 2 weeks, compared with the group receiving treatment every 4 weeks.

1.1.4. Current indications in France

IFNβ1a IM (Avonex®): Indicated for patients with remitting multiple sclerosis (MS). In clinical trials, this was characterized by two or more attacks in the past three years with no evidence of regular progression between attacks; patients who had a single demyelinating event, accompanied by an active inflammatory process, if severe enough to require intravenous corticosteroid treatment, if differential diagnoses have been ruled out, and if they are considered at high risk of developing clinically defined multiple sclerosis. Treatment with Avonex must be discontinued in patients who develop a progressive form of MS.

IFNβ1a SC (Rebif®): Indicated for patients who have had a single demyelinating event accompanied by an active inflammatory process, if differential diagnoses have been ruled out and if these patients are considered at high risk of developing clinically defined multiple sclerosis. Treatment of patients with relapsing multiple sclerosis. In clinical trials, these were characterized by two or more attacks in the past two years. Its effectiveness was not demonstrated in patients suffering from

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