Review of interferon beta-1b in the treatment of early and relapsing multiple sclerosis

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Abstract: Multiple sclerosis (MS) is the most common autoimmune illness of the central nervous system. For many years the inflammatory manifestations of MS were treated using only corticosteroids. Since the 1990s the results of several clinical trials with immunomodulatory agents have changed the therapeutic approach to this disease. Interferon beta (IFNβ)-1b represents the pioneer of those therapies. There is growing evidence from clinical trials on relapsing-remitting MS and clinically isolated syndromes suggestive of MS that IFNβ-1b reduces the frequency and severity of relapses and the development of new and active brain lesions as assessed by magnetic resonance imaging. Long-term data suggest a persistent efficacy of IFNβ-1b on disease activity and a positive effect in slowing disability worsening. Furthermore a reduction of relapse rate and a slight positive effect on the progression were demonstrated when IFNβ-1b was administered to still-active secondary progressive MS. IFNβ-1b therapy is well tolerated and relatively free of long-term side effects. In spite of the emergence of new agents for the treatment of MS, IFNβ-1b still remains a first-line therapy with a fundamental role in all stages of the disease.

Keywords: interferon beta-1b, relapsing-remitting multiple sclerosis, clinically isolated syndromes, efficacy, safety, neutralizing antibodies

Introduction
Interferon beta (IFNβ)-1b was the first immunomodulatory therapy approved for the treatment of relapsing-remitting (RR) multiple sclerosis (MS) and currently is the only IFNβ licensed for use in secondary progressive (SP) MS. Moreover, recent studies have defined IFNβ-1b efficacy in treating patients with clinically isolated syndrome (CIS).

In this review we focus on biologic activity, clinical and magnetic resonance imaging (MRI) evidence of efficacy, and safety of IFNβ-1b in RRMS and patients with CIS.

Pharmacokinetics and pharmacodynamics of IFNβ-1b
Human IFNβ-1b (Betaferon®, Betaseron®; Bayer HealthCare) is a lyophilized protein produced by DNA recombinant technology by E. coli. As bacteria lack the ability to glycosylate proteins, the recombinant protein was not glycosylated. The cysteine residue at position 17 was replaced with a serine residue to ensure the stability of the molecule and the N-terminal methionine residue was deleted. It is combined with mannitol and human albumin to reach a neutral pH of 7.2.
Assessment of serum IFNβ concentrations is technically difficult and, thus, the pharmacokinetic characteristics of IFNβ-1b are not well described. Lower serum concentrations of IFNβ-1b were detected after subcutaneous (SC) compared with intravenous administration, with a relative bioavailability of 51%.8 The liver is probably the predominant site of metabolism.9

The mechanisms of action of IFNβ are not yet finally understood, but there is agreement that the major effects are:

- inhibition of T lymphocyte proliferation and decrease of IFN-γ production;10
- inhibition of major histocompatibility complex class II (MHC II) expression, with reduced antigen presentation within central nervous system (CNS);11
- inhibition of matrix metalloproteinase (MMP) production and cell-associated adhesion molecule expression;12-14
- induction of anti-inflammatory and inhibition of pro-inflammatory cytokines;15-17
- induction of CD8 regulatory cell function and inhibition of monocyte activation.18

**Pilot dose-finding trials of IFNβ-1b**

A pilot study9 demonstrated that a dose of 250 µg of SC IFNβ-1b increased CD8 cell-mediated suppressor activity in MS patients to levels approaching those in patients without MS. Lower doses showed a lesser effect on CD8 suppressor cell function, suggesting an adequate dosing is important for IFNβ-1b treatment. In a pilot dose-finding trial of SC IFNβ-1b,20 5 groups of RRMS, each including 6 patients, were treated with 25, 125, 250 or 500 µg of IFNβ-1b or placebo, respectively, 3 times weekly. The dose-finding results (after 24 weeks) showed a dose-related reduction of relapse frequency. However, patients receiving the highest dose of IFNβ-1b experienced side effects that led to a dose reduction or dropout within a short time-frame. Four of these patients subsequently received the 250 µg dose. The 10 patients receiving the 250 µg dose of IFNβ-1b, at the end of the study, had a reduced attack frequency compared to the 6 patients receiving placebo. Based on these results, a dose of 250 µg of IFNβ-1b every other day (EOD) was selected for further investigation.

**Efficacy of IFNβ-1b in RRMS**

In 1993 a double-blind, placebo-controlled phase III trial1 led to approval of IFNβ-1b as the first therapeutic agent for RRMS. It included 372 patients with RRMS who had scores on the Expanded Disability Status Scale (EDSS) <5.5 and who had experienced at least two attacks in the previous 2 years. Patients were randomized to receive placebo, low dosage (50 µg) or high dosage (250 µg) of SC IFNβ-1b EOD for 2 years. Exacerbation rates (primary endpoint of the study) were significantly lower in both treatment groups compared with the placebo group (high dosage vs placebo P = 0.0001; low dosage vs placebo P = 0.01) and in high dosage vs low dosage group (P = 0.0086), suggesting a dosage effect. The MRI results2 supported the clinical results showing a significant reduction of T2 active scans (high dosage vs placebo P = 0.0089; low dosage vs placebo P = 0.04), appearance of new T2 lesions (high dosage vs placebo P = 0.0026; low dosage vs placebo P = 0.03) and MRI burden of disease (high dosage vs placebo P < 0.001; low dosage vs placebo P = 0.04) in the treatment groups as compared with placebo group. An extension study, lasting up to 5 years, showed that IFNβ-1b at dose of SC 250 µg EOD continued to have a persistent effect on exacerbation rate reduction (~33%) and MRI burden of disease, and was relatively free of long-term side effects.21 Moreover a post-hoc analysis showed that the beneficial effect of IFNβ-1b on relapse frequency had rapid onset, an effect being observed as early as the second month of treatment.22 The increase in MRI lesion burden in the placebo arm was approximately 5-fold higher than that seen in the higher dose IFNβ-1b group, and even the lower dose reduced MRI lesion burden substantially.

A more recent study23 on 30 RRMS patients, followed monthly for a 6-month baseline period and then for a period up to 36 months from the start of treatment with IFNβ-1b (SC 250 µg EOD), demonstrated a significant effect of the drug in slowing the progression of cerebral atrophy during years 2 and 3.

To evaluate long-term safety and efficacy of IFNβ-1b in RRMS patients, a multicenter, open-label, observational study was conducted up to 16 years of follow-up using cross-sectional data collection from patients having participated in the original pivotal trial.24 Survival, disease status, relapse rate, EDSS score, adverse events, MRI data were collected. The results were analysed by stratification according to the original assignment of the pivotal trial (placebo, 50 µg, 250 µg of IFNβ-1b) and according to the duration of treatment exposition during 16 years of follow-up (<20% of exposition; 20% to 80%; >80%). Eighty-eight percent of the patients from the original trial participated in the long-term follow-up. High adherence to the treatment was evidenced by the median treatment duration of the whole cohort (almost 10 years). The final results of this longer follow-up study suggested that early and continuous long-term treatment with IFNβ-1b was favorable for the patients, since relapse...
frequency reduction was similar to the pivotal study (>40%), and progression of disability, evaluated at the EDSS score of 6 (unable to walk without assistance), was even slower in patients exposed for a longer period compared to other groups with a shorter period of treatment.

These reported results were confirmed by a more recently published long-term observational study showing that IFN-β treated patients have a significant reduction in the incidence of secondary progression, EDSS 4.0 and 6.0, compared with untreated patients, during a follow-up lasting up to 7 years.

**Efficacy of IFNβ-1b in patients with CIS**

MRI and histological findings demonstrate that irreversible axonal damage begins early in the course of MS. Furthermore, neuropathological findings suggest the potential for immunomodulatory treatment of MS to have a greater effect early in the disease course. Three multicenter, placebo-controlled studies have shown that IFNβ treatment delays conversion to clinically definite MS (CDMS) when administered to patients with CIS (Table 1). However the Betaferon/Betaseron in Newly Emerging Multiple Sclerosis For Initial Treatment (BENEFIT) study was also designed to assess if early initiation of treatment with IFNβ-1b is more efficacious than a delayed treatment for preventing the development of long-term confirmed disability.

Between February 2002 and June 2003, patients with CIS from 18 European countries, Israel, and Canada were randomized in 98 centers. The inclusion criteria were: age between 18 and 45 years, a first clinical neurological event suggestive of MS, at least two clinically silent lesions on their T2-weighted brain MRI scan (at least one of which being ovoid, periventricular, or infratentorial), and EDSS score of 0 to 5. Study treatment had to be started within 60 days after onset of the first clinical event. Patients were centrally randomized (in a 5:3 ratio) to IFNβ-1b 250 µg (8 MIU) or placebo SC EOD and scheduled to receive double-blinded injections for up to 2 years or until CDMS was reached. This first phase ended in 2005 and assessed the efficacy, safety and tolerability of IFNβ-1b 250 µg. After 2 years, 45% of placebo patients had converted to CDMS (primary outcome measure) and 85% fulfilled the McDonald criteria (co-primary outcome measure). Overall IFNβ-1b delayed the time to diagnosis of CDMS (P < 0.0001) and McDonald MS (P < 0.00001). The risk for CDMS in the IFNβ-1b group was reduced by 50% and for Mc Donald MS by 46%. Based on Kaplan-Meier estimates, the probability of the development of CDMS over

<table>
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<tr>
<th>Drug</th>
<th>Study</th>
<th>Study design</th>
<th>Follow-up years</th>
<th>No. of patients</th>
<th>Probability of conversion to CDMS (%)</th>
<th>No. of new or enlarging lesions</th>
<th>No. Gd+ lesions</th>
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<tbody>
<tr>
<td>IFNβ-1a 30 µg IM OW</td>
<td>CHAMPS®(2000)</td>
<td>treated vs placebo</td>
<td>3 years</td>
<td>383</td>
<td>35 vs 50%</td>
<td>2.1 ± 3.2 (M ± SD) vs 5.0 ± 7.7 (M ± SD)</td>
<td>0.4 ± 1.5 (M ± SD) vs 1.4 ± 3.6 (M ± SD)</td>
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<td></td>
<td>CHAMPIONS®(2006)</td>
<td>early vs delayed treatment</td>
<td>5 years</td>
<td>203</td>
<td>36 vs 49%</td>
<td>3.5 (0.5–8.5) vs 6.0 (2.0–13.0)</td>
<td>&gt;1 lesions</td>
</tr>
<tr>
<td>IFNβ-1a 22 µg SC OW</td>
<td>ETOMS®(2001)</td>
<td>treated vs placebo</td>
<td>2 years</td>
<td>309</td>
<td>34 vs 45%</td>
<td>2.0 (0.5–4.5) (median) vs 3.0 (1.5–6.25) (median)</td>
<td>0.5 (0–1) (median) vs 0 (0–1) (median)</td>
</tr>
<tr>
<td>IFNβ-1b 250 µg SC EOD</td>
<td>BENEFIT®(2006)</td>
<td>treated vs placebo</td>
<td>2 years</td>
<td>468</td>
<td>25 vs 44%</td>
<td>2.9 ± 4.9 (M ± SD) vs 4.4 ± 5.7 (M ± SD)</td>
<td>1.9 ± 5.2 (M ± SD) vs 4.3 ± 7.1 (M ± SD)</td>
</tr>
<tr>
<td></td>
<td>BENEFIT®(2007)</td>
<td>early vs delayed treatment</td>
<td>3 years</td>
<td>418</td>
<td>37 vs 51%</td>
<td>18 (7.0–39.0) (Median) vs 17 (8.0–37) (median)</td>
<td>0 (0.0–1.0) (median) vs 0 (0.0–1.0) (median)</td>
</tr>
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*Controlled high risk subjects Avonex® Multiple Sclerosis Prevention Study.
*Controlled high risk subjects Avonex® Multiple Sclerosis Prevention Study in Ongoing Neurologic Surveillance.
*Early Treatment of Multiple Sclerosis Study.
*Betaferon®/Betaseron® in Newly Emerging Multiple Sclerosis for Initial Treatment.
*Based on Kaplan-Meier life tables.

**Abbreviations:** EOW, every other week; IM, intramuscular; SC, subcutaneous; OW, once weekly.
2 years was reduced by treatment from 45% in the placebo group to 28% in the IFNβ-1b group corresponding to an absolute risk reduction by 17%. IFNβ-1b prolonged the time to CDMS by 363 days (255 days in the placebo group, 618 days in the IFNβ-1b group). The patient number needed to be treated (NNT) in order to prevent one case of CDMS within the study period of 2 years was estimated to be 5.9. Within the first 6 months, the probability to reach MS diagnosis according to the McDonald criteria was 51% for placebo and 28% for IFNβ-1b-treated patients. Within 2 years this probability was reduced by treatment from 85% in the placebo group to 69% in the IFNβ-1b group, corresponding to an absolute risk reduction of 16%. There was also a significant treatment effect of IFNβ-1b on time to CDMS in all subgroups defined by different baseline characteristics (monofocal or multifocal manifestation, number of T2 lesions <9 or >9 and absence or presence of at least one gadolinium positive [Gd+] lesion in the screening MRI). The treatment effect was more pronounced in patient subgroups with less inflammatory disease activity as documented by Gd enhancement or T2 lesions count and less dissemination in space at the time of the first event. The MRI results from patients completing 2 years of follow-up demonstrated that IFNβ-1b had a robust effect on MRI measures: the cumulative number of new T2 lesions and new Gd+ lesions was 60% lower in patients receiving IFNβ-1b vs placebo. A robust treatment effect was found throughout all subgroups defined by clinical and MRI measures of disease activity or dissemination in space at onset. The subgroups analysis reveals a consistently stronger treatment effect in patients with monofocal clinical presentation, fewer T2 lesions, or not contrast enhancement at baseline, confirming that treatment was particularly beneficial in patients with less active or disseminated disease.

Patients who completed the placebo-controlled phase were eligible to participate to a single-arm (IFNβ-1b) follow-up phase lasting at least 5 years from the period of randomization. This was prospectively designed to explore the long-term impact of early vs delayed treatment on progression of neurological disability and on brain MRI measures, including outcomes of neurodegeneration such as brain atrophy. Primary outcomes were time to diagnosis of CDMS and time to confirmed EDSS progression. Of the 468 patients originally randomized, 418 (89%) entered the follow-up phase; 392 (84%) completed 3 years post-randomization follow-up. After 3 years 99 (37%) patients in the early group developed CDMS compared with 85 (51%) patients in the delayed treatment group. Early treatment reduced the risk of CDMS by 41% compared with delayed treatment. Over 3 years, 42 (16%) patients in the early group and 40 (24%) in the delayed group had confirmed EDSS progression; early treatment reduced the risk for progression of disability by 40% compared with delayed treatment.

Polman et al evaluated the impact of the demographic, clinical and MRI parameters on the ‘natural’ risk of MS in placebo-treated patients, and the IFNβ-1b treatment effect in subgroups of the study population. Four hundred and sixty-eight out of 483 patients from the BENEFIT (IFNβ-1b: n = 292; placebo: n = 176) were grouped according to demographic, clinical, cerebrospinal fluid (CSF), and MRI findings at disease onset. The ‘natural’ risk of CDMS over 2 years was estimated by Kaplan-Meier statistics in placebo-treated patients; the IFNβ-1b treatment effect was analysed by Cox proportional hazards regression. In the placebo-treated group a higher risk to develop CDMS was found in younger (<30 vs >30 years: 60% vs 33%), CSF-positive patients (49% vs 36%), in those who had received steroid treatment (48% vs 38%) and had ≥9 T2 (48% vs 39%) or ≥1 Gd+ T1 (52% vs 41%) MRI lesions. The CDMS risk was higher (75%) in placebo-treated patients with monofocal disease onset displaying higher MRI disease activity (≥1 Gd+ lesion) and dissemination (≥9 T2– lesions).

Treatment effects on time to CDMS conversion were significant in all subgroups, with a greater impact on patients with less disease dissemination/activity at onset (monofocal vs multifocal: 55% vs 37%; <9 vs >9 MRI T2– lesions: 60% vs 43%; absence vs presence of MRI Gd+ lesions: 57% vs 38%). Moreover monofocal patients had further greater treatment effects if they had ≥9 T2– lesions or presence of Gd+ lesions, or both.

**Efficacy of IFNβ-1b in SPMS**

Two large placebo-controlled studies of IFNβ-1b in SPMS have been conducted: the European study and the North-American study. In both studies, IFNβ-1b 250 µg recipients had fewer relapses and less MRI-assessed disease activity than placebo recipients. Only the European trial provided evidence that the treatment delays the progression of the disease. The conflicting result on the primary endpoint might be explained by differences in the inclusion criteria and baseline characteristics of the study populations. In the European SPMS trial, the patients appeared to be younger, with a shorter duration of disease, faster disease progression and disease characteristics thought to reflect the inflammatory component of the illness, such as higher relapse rates and a greater number of contrast enhancing lesions. These results were supported by a post-hoc analysis of the European SP
MS trial36 in which patients with higher pre-study disease activity (>2 relapses, EDSS progression >1 point over the 2 years before study) seemed to have a more favorable treatment effect.

**Head-to-head comparative studies of IFNβ-1b**

Low dose IFNβ-1a intramuscular (IM) was compared with high dose IFNB-1b SC in 188 patients of the Independent Comparison of Interferon (INCOMIN) study.37 After 2 years the percentage of patients free from relapses and from new T2 or Gd+ lesions was higher in IFNβ-1b than in IFNβ-1a group. Patients in high-dose IFNβ-1b had a lower risk for confirmed disability progression (EDSS increase of at least one point sustained for at least 6 months and confirmed at the end of follow-up) than those in low-dose IFNβ-1a.

The Betaseron®/Betaseron® Efficacy Yielding Outcomes of a New Dose (BEYOND) study38 investigated the effect of two high doses of IFNβ-1b regimens (500 µg and 250 µg SC EOD) or glatiramer acetate (GA) in RRMS treatment-naïve patients (N = 2244).

Patients with age between 18 and 55 and EDSS in 0 to 5 range were enrolled. There were no significant differences between the two IFNβ-1b regimen groups for the primary and secondary clinical (relapse-related measures, progression as assessed by EDSS score) and MRI (new T2 lesions, and volume of T2 and Gd+ lesions) outcomes. The comparison between IFNβ-1b arms and GA arm showed similar treatment effects on clinical endpoints,38-39 but a significant superior effect of both IFNβ-1b arms on the cumulative number of T2 lesions up to the last scan and on the relative increase in T2 lesion volume.40

A Danish head-to-head, controlled, open-label, randomized study aimed to compare the effects of IFNβ-1b 250 µg EOD with IFNβ-1a 22 µg once weekly (OW) in RRMS did not prove significant differences on clinical and MRI measures during a period of a follow-up of 2 years.41

**Clinical relevance of neutralizing antibodies against IFNβ**

During IFNβ therapy a significant percentage of patients develop neutralizing antibodies to IFNβ (NAbs).

In the pivotal phase III trial of IFNβ-1b,1 35% of treated patients developed NAbs to IFNβ-1b. In this study a sample was considered positive if the NAb titer was at least 20 NU/mL based on a viral cytopathic effect reduction assay (CPE). NAb positive (NAb+) patients were the ones with two consecutive positive samples, 3 months apart.

The results from an extensive study aimed to assess the therapeutic impact of Nabs32 suggested a lesser efficacy of IFNβ-1b in NAb+ patients with respect to relapse rate reduction, whereas the disease progression in NAb+ patients appeared less marked than in NAb negative (NAb–) patients. Similar results were reported by a number of other short-term trials,45-46 demonstrating that patients who develop NAbs to both IFNβ-1b and 1a were associated with higher relapse rates and lesion activity on MRI, but without relevant effect on disability progression.

A longer-term follow-up47 of two cohorts from the original pivotal IFNβ-1b trial provided further data on the development of NAbs showing their transient nature. Moreover this study demonstrated that 91% of NAb+ patients reverted to NAb– status after 8 years of treatment. A longitudinal study48 confirmed that high titres of NAbs suppress the relapse-reducing efficacy of IFNβ. However since a gradual reduction in titres appeared and NAbs frequently became undetectable with the continuation of the therapy, extending the medication resulted in full return of efficacy for the 20% of patients for whom the appearance of NAbs was clinically significant. Sorensen et al49 evaluated the clinical relevance of NAbs in 541 RRMS who started treatment with IFNβ between 1996 and 1999 in Denmark. The results showed that relapse rates were significantly (P < 0.03) higher during NAb+ periods (0.64 to 0.70) than they were during NAb– periods (0.43 to 0.46). Time to first relapse was significantly increased by 244 days in patients who were NAB– at 12 months (log rank test 6.83, P = 0.009). During a follow-up period of 60 months, the presence of NAbs did not affect significantly the disability progression as measured by time to confirmed progression of 1 point on EDSS, sustained for at least 6 months.

The INCOMIN study50 showed a greater frequency of NAb+ patients in the group treated with high-dose IFNβ-1b SC in comparison to those treated with low-dose IFNβ-1a IM, in spite of better clinical and MRI outcome.

In a more recent prospective, multicenter, observational study by the same authors,50 MRI activity and NAb positivity (assessed by MxA protein assay) in the first 6 months of IFNβ treatment resulted predictors of long term clinical response (occurrence of one or more relapses or confirmed disease progression), particularly when combined. Patients with negative predictors showed less than 10% risk of developing clinical activity, while patients with positive predictors showed a 50% risk of further clinical activity. Similar conclusions were reached by another group in patients treated with IFNβ-1a or IFNβ-1b, measuring the IFNβ bioavailability marker mRNA MxA.51
In CIS patients included in the BENEFIT study the incidence of positive NAb titers ranged from 16.5% to 25.2% of the treated patients. Neutralizing activity was detected at least once in 75 out of 251 (29.9%) IFNβ-1b patients who provided samples during the treatment phase; of these, 17 (22.7%) converted to negative status later in the study. No significant effect of NAb status on time to CDMS in IFNβ-1b treated patients was found; in this analysis there was a trend toward a lower risk of progressing to CDMS in patients with at least one positive NAb titer. When analyses were performed at the end of the study (at least 180, 270 or 360 days after start of treatment) no differences were observed between NAb+ and NAb− patients.

The clinical impact of NAbs on treatment efficacy in 6698 MS patients receiving IFNβ-1b was investigated by Goodin et al suggesting that NAbs are not responsible for poor clinical responses and NAb status is of little clinical value.

In conclusion the results derived from existing studies are conflicting and have to be interpreted with caution. The differences might be due to the different duration of follow-up, assays and definitions of NAb positivity used. The impact of NAbs seems to be more frequently evident on proper inflammatory clinical events of MS (relapse rate) but the influence of NAbs on the progression of the disease remains uncertain. Therefore the decisions to discontinue IFNβ therapy are still based mainly on the patient’s clinical response to the treatment.

**IFNβ-1b and adverse events**

The administration of IFNβ is associated with the risk of a variety of adverse effects. The most common, compared with placebo, are flu-like symptoms and, in SC-treated patients, injection-site reactions. In the pivotal IFNβ-1b trial, flu-like symptoms in the high-dose group were initially observed in 52% of patients. However, by the end of the first year, these had decreased to 8%, only 3% to 8% of patients experiencing symptoms throughout the study. Injection-site reactions in the same pivotal trial were initially reported by 80% of those receiving 250 µg IFNβ-1b, a figure that declined to between 44% and 50% at years 4 and 5.

During the first year of the BEYOND study, flu-like symptoms were reported significantly more frequently in the IFNβ-1b 250 µg group compared to the GA group. Although initially high, the frequency of flu-like symptoms in IFNβ treated group declined very quickly over time. For injection-site reactions, pain and pruritus were significantly more frequent in the GA treatment group than in the IFNβ-1b 250 µg group, but in the same way, the incidence of this reactions decreased over the study. The incidence of other adverse events such as fatigue, depression, arthralgia and paresthesia was comparable between treatment groups.

The evaluation of laboratory safety as elevations in liver enzymes abnormalities, in blood lipids and markers of thyroid function, as well as leukocytopenia were more frequently detected in patients treated with IFNβ-1b than in those treated with GA. Adherence to treatment was also assessed demonstrating that the adherence to treatment was high in all three treatment groups. The proportion of patients completing the anticipated treatment period ranged from 73% in the IFNβ-1b 500 µg group through 78% in GA group to 82% in the IFNβ-1b 250 µg group. No significant differences in discontinuation rates were observed among the groups.

The management of IFNβ-related side effects is of great importance to improve the patients’ treatment adherence. General precautions to reduce or avoid this side effect include the correct preparation of the injection solution and a proper injection technique. In all studies frequency and severity of adverse effects depend on the duration of treatment and they are at a maximum during the first weeks of treatment.

**Conclusions**

Results from rationally planned and statistically convincing studies in RRMS and CIS patients demonstrated that IFNβ-1b treatment has very favorable efficacy on clinical and MRI measures of disease activity and progression since very early stages of disease.

Early and continuous treatment with IFNβ-1b maintains persistent effectiveness and safety in the long term. A reduction in attack rate and a slight positive effect on the progression of disability were also demonstrated when IFNβ-1b was administered to patients in SP phase. Therefore IFNβ-1b still represents a key therapeutic option for MS patients, playing a fundamental role in all stages of the disease. No definitive relationship between development of NAbs and response to treatment has been demonstrated.

**Disclosures**

DP and VD declare no conflicts of interest. MT has received honoraria for speaking from Sanofi-Aventis, Biogen and Bayer Schering, and research grants from Merck Serono.


