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REVIEW

Injectable interferon beta-1b for the treatment of relapsing forms of multiple sclerosis

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Abstract: Multiple sclerosis (MS) is chronic inflammatory and demyelinating disease with either a progressive (10%–15%) or relapsing-remitting (85%–90%) course. The pathological hallmarks of MS are lesions of both white and grey matter in the central nervous system. The onset of the disease is usually around 30 years of age. The patients experience an acute focal neurologic dysfunction which is not characteristic, followed by partial or complete recovery. Acute episodes of neurologic dysfunction with diverse signs and symptoms will then recur throughout the life of a patient, with periods of partial or complete remission and clinical stability in between. Currently, there are several therapeutic options for MS with disease-modifying properties. Immunomodulatory therapy with interferon beta-1b (IFN-β1b) or -1a, glatiramer and natalizumab shows similar efficacy; in a resistant or intolerant patient, the most recently approved therapeutic option is mitoxantrone. IFN-β1b in patients with MS binds to specific receptors on surface of immune cells, changing the expression of several genes and leading to a decrease in quantity of cell-associated adhesion molecules, inhibition of major histocompatibility complex class II expression and reduction in inflammatory cells migration into the central nervous system. After 2 years of treatment, IFN-β1b reduces the risk of development of clinically defined MS from 45% (with placebo) to 28% (with IFN-β1b). It also reduces relapses for 34% (1.31 exacerbations annually with placebo and 0.9 with higher dose of IFN-β1b) and makes 31% more patients relapse-free. In secondary-progressive disease annual rate of progression is 3% lower with IFN-β1b. In recommended doses IFN-β1b causes the following frequent adverse effects: injection site reactions (redness, discoloration, inflammation, pain, necrosis and non-specific reactions), insomnia, influenza-like syndrome, asthenia, headache, myalgia, hypoesthesia, nausea, paresthesia, myasthenia, chills and depression. Efficacy of IFN-β1b in relapsing-remitting MS is higher than that of IFN-β1a, and similar to the efficacy of glatiramer acetate. These facts promote IFN-β1b as one of the most important drugs in the spectrum of immunological therapies for this debilitating disease.

Keywords: multiple sclerosis, interferon beta 1b, mechanism of action, efficacy, safety

Introduction

Multiple sclerosis (MS) is chronic inflammatory and demyelinating disease with either progressive (10%–15%) or relapsing-remitting (85%–90%) course. Essential for diagnosis of its relapsing-remitting form is dissemination of clinical episodes in time (two or more episodes) and space (more than one focal lesion). Nowadays, diagnosis is routinely confirmed by magnetic resonance imaging, the diagnostic test with 95% sensitivity.[1]

Prevalence of MS varies geographically, and is more common in Western European and North American countries.[2] The most recent estimation of prevalence

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in USA was 100 symptomatic MS patients per 100,000 inhabitants,[3] and prevalence in England is even higher (118/100,000).[4] Prevalence of MS in the Middle East is much lower, ranging from 4/100,000 in Saudi Arabia and Libya to 39/100,000 in Jordan and 31.15/100,000 in Kuwait.[5] Low prevalence was also recorded in Panama (5.2/100,000),[6] with a female:male ratio of 8:1. Data on prevalence of MS are not available for the majority of Asian countries; however, a study from Japan reported a prevalence of 8.57/100,000, and studies in the Parsi community in India showed a prevalence of 21 to 58/100,000 inhabitants.[7] Such incomplete data led to a conclusion that prevalence of MS increases with latitude in both hemispheres,[2] but with obvious exceptions, like Israel (with MS prevalence of 46.2/100,000),[7] suggesting that prevalence of MS in a country depends more on national and racial origin of its inhabitants than on its latitude.

The male:female ratio among patients with MS ranges from 2.4:1 in Spain,[8] through 1.64:1 in Israel,[7] 1:2.25 in India[7] and 1:2.3 in Norway,[9] to 1:5 in Malaysia[7] and 1:8 in Panama.[6] Average age of onset is between 25 and 35 years of age (32.6 years in Spain,[8] 33 years in Japan,[7] 29 years in China,[7] 27 years in India,[7] and 34.7 years in Kuwait[7]).

Pathology and pathogenesis of MS

Both genetic background and environmental events are involved in the pathogenesis of MS. If a family member is affected by MS, the risk for his/her cousins to develop the disease increases in proportion to the shared genetic information between themselves and the affected person.[10] If a monozygotic twin develops MS, his/her brother or sister have 200 times greater risk of developing MS than members of the general population. Among the environmental factors, vitamin D deficiency and Epstein-Barr virus infection were the only ones for which causal links with MS were confirmed.[10,11]

The pathological hallmarks of MS are lesions of both white and grey matter in the central nervous system.[12] Early in our understanding MS, it was considered that myelin-specific, activated CD4+ T lymphocytes migrate from blood to brain tissue, bind to antigenic peptides presented by antigen presenting cells in the brain, clonally expand, and then attack oligodendrocytes, destroying myelin.[13] Now we know that neurons degenerate in the gray matter as well, and that this process is a major pathological correlate of clinical disability.[13] Neurons die due to loss of myelin protection, direct toxic action of immune cells, diminution of trophic support, metabolic changes and altered signaling.[13]

Clinical course of MS

The onset of the disease is usually around 30 years of age. The patients experience an acute focal neurologic dysfunction which is not characteristic, followed by partial or complete recovery. Acute episodes of neurologic dysfunction with diverse signs and symptoms will then recur throughout the life of a patient, with periods of partial or complete remission and clinical stability in between.[14] The majority of the patients (about 80%) have such relapsing-remitting type of MS (RRMS) in the beginning, which after 10 or more years is followed by progressive clinical disability with or without superimposed relapses and remissions (secondary progressive MS [SPMS]). In about 20% of the patients the disease is progressive from the beginning, sometimes with superimposed relapses and remissions (primary progressive/relapsing MS [PPMS/PRMS]).[15] Neurological impairment in the patients caused by the disease is quantified by the Kurtzke Expanded Disability Status Scale (EDSS)[16] score: EDSS score from 0.0 to 2.5 (no or few limitations in mobility), EDSS 3.0 to 5.5 (moderate limitations in mobility), EDSS 6.0 to 7.5 (walking aid or wheelchair necessary), EDSS 8.0 to 9.5 (confined to bed) and EDSS 10 (death).

Therapy of MS

Currently, there are several therapeutic options for MS with disease-modifying properties.[17] A few preparations of interferon beta (IFN-β) showed efficacy in decreasing frequency of relapses, especially if given early in the course of the disease; however, the disease progression to disability was not slowed. When compared head-to-head, different preparations of IFN-β showed similar efficacy in the majority of clinical trials, with a slight dominance of interferon beta-1b (IFN-β1b). Glatiramer acetate, a putative neurotrophic factor, has shown almost the same efficacy as IFN-β, and is used mostly when therapy with IFN-β is no longer possible, due to emergence of neutralizing antibodies against it.

Natalizumab, a humanized monoclonal antibody directed against α4-integrin, a protein present on leukocytes, reduces transmigration of these cells to inflamed areas of brain. It reduces relapse rate in MS patients to a similar extent as IFN-β and glatiramer, but serious adverse effects of the drug recorded in a few patients, fatal progressive multifocal leukoencephalopathy, led to restriction of natalizumab's use to cases which are resistant to treatment with both IFN-β and glatiramer.[17]

After immunomodulatory therapy with IFN-β, glatiramer and natalizumab loses its efficacy in a patient with MS or he/she becomes intolerant to it, the only approved therapeutic option is mitoxantrone.[18] Mitoxantrone is an immunosuppressant with a similar efficacy to immunomodulatory drugs, but with serious adverse effects such as cardiomyopathy or secondary leukemia. Its use is limited to patients with MS no longer responsive to immunomodulators, and its cumulative maximal dose must not exceed 100 mg/m^2, in order to avoid toxicity. Before each administration of mitoxantrone, an ultrasonography of heart is mandatory in order to detect early adverse effects on the myocardium and stop further therapy with the drug.

IFN-β1b preparations

A new preparation of IFN-β1b for subcutaneous administration (Extavia®; Novartis Pharmaceuticals UK, Limited) was approved for use in humans by the European Medicines Agency (EMEA) in May 2008, and by the Food and Drug Administration (FDA) in United States in August 2009, as a biosimilar drug (the original preparation of IFN-β1b, Betaseron® [Chiron corporation, Berlex, Inc., Schering AG] had been approved for human use for many years, and almost all clinical trials using IFN-β1b were conducted with Betaseron®). Extavia® is a recombinant IFN-β1b produced by genetic engineering from a strain of *Escherichia coli*. Given subcutaneously in a dose of 250 µg every other day, Extavia® is used for treatment of patients with a single demyelinating event with an active inflammatory process and with high risk of developing clinically definite MS, and for patients with severe RRMS ($\geq$2 relapses in 2 years) or active SPMS.[19]

Pharmacokinetics and mechanism of action

After subcutaneous administration, IFN-β1b is slowly and irregularly absorbed (maximum serum levels are measured 1–8 hours after injection), with an absolute bioavailability of 51%. It is distributed in an extracellular compartment, and degraded by the reticular-endothelial system in the liver. Total IFN-β1b clearance is about 30 $mL \cdot min^{-1} \cdot kg^{-1}$ and serum half-life around 5 hours.[20,21]

IFN-β1b in patients with MS binds to its specific receptors on surface of cells in the immune system, and then changes the expression of several genes. The expression of some genes is suppressed, leading to a decrease in quantity of cell-associated adhesion molecules, inhibition of major histocompatibility complex class II expression, and reduction in inflammatory cells migration into the central nervous system. Synthesis of proinflammatory cytokines is inhibited, and production of immunosuppressive ones is increased. Finally, T cells which attack neural structures, are inhibited by IFN-β1b[22] (Figure 1).

Efficacy

Efficacy in RRMS

Efficacy of IFN-β1b was tested in several placebo-controlled, randomized, double-blind, multicenter trials. In a phase 3 trial conducted by the IFN-β Multiple Sclerosis Study Group[23] IFN-β1b was given subcutaneously (250 µg or 50 µg every second day) to 372 patients with EDSS score less than 5.5 and at least 2 relapses in the last 2 years. The patients were treated for 2 years, and IFN-β1b reduced relapses (but only when given in higher dose – 250 µg) for 34% (1.31 exacerbations annually with placebo and 0.9 with higher dose of IFN-β1b) and made 31% more patients relapse-free for the study period (16% relapse-free with placebo and 25% relapse-free with IFN-β1b). The following adverse events were related to IFN-β1b: myalgia, sweating, malaise, fever and injection-site reactions, like redness and pain. Injection-site reactions were the most frequent adverse events, occurring at rate close to 70%, but also relatively mild. In this study, researchers noted emergence of neutralizing antibodies against IFN-β1b in blood of the patients who received this drug for prolonged periods. Up to 47% of the patients produced neutralizing antibodies, and became less responsive to IFN-β1b after 18 months of therapy. The study was extended for 3 years,[24] confirming sustainability of reduction in relapses after the higher dose (250 µg).

Efficacy in initial acute neurological dysfunction

A large randomized, placebo-controlled, double-blind, multicenter study was conducted in 18 European countries[25] on 483 patients, to test whether early treatment with 250 µg of IFN-β1b (within 60 days of initial acute neurological dysfunction) will slow down progression of clinically isolated neurological event to clinically defined MS. After 2 years of treatment, IFN-β1b reduced the risk of development of clinically defined MS from 45% (with placebo) to 28% (with IFN-β1b). IFNβ-1b also prolonged the time to second neurological event by 363 days (255 days in the placebo group, 618 days in the IFNβ-1b group).[20] The study was extended for 3 more years, and all patients received IFNβ-1b, with the aim of exploring the effect of the drug on progression of disability.[26] After 3 years, 37% of the patients who were receiving IFNβ-1b from the very beginning developed clinically defined MS, compared with 51% of the patients who were at first on placebo. Also, early treatment with IFNβ-1b

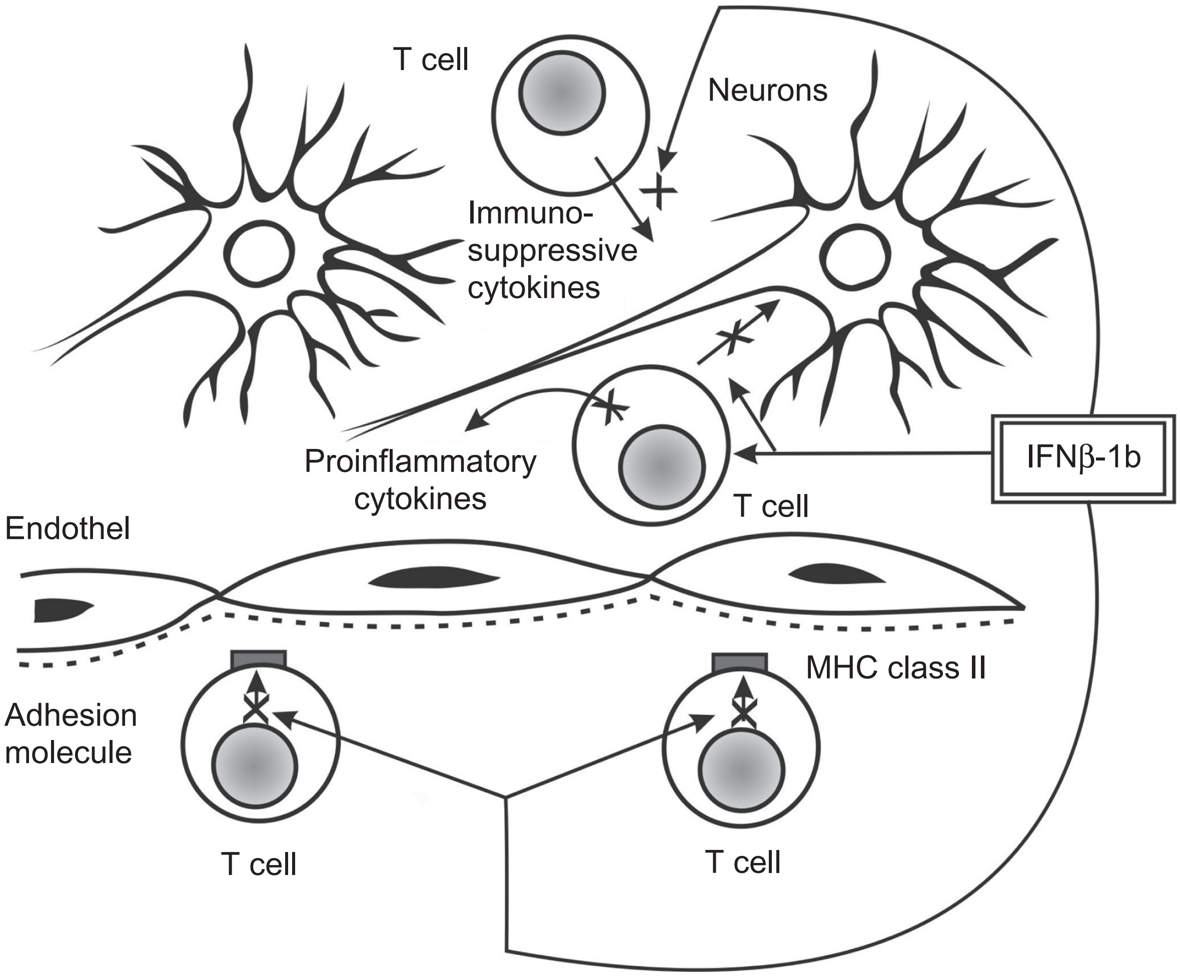

Figure 1 Mechanism of action of interferon beta-1b.

resulted with only 16% percent of patients who developed progression of disability, while 24% of patients who were at first on placebo and later on IFNβ-1b experienced progression of EDSS score.

Efficacy in SPMS

In two studies (European[27] and North American[28]) IFN-β1b (250 μg subcutaneously every second day, for 2 years) was tested in patients with SPMS. Only in the European study time to increase in the EDSS score for 1 point was longer in IFN group compared with placebo group, ie, annual rate of progression was 16% in IFN group compared with 19% in placebo group. The difference was not significant in the North American trial. Also, the mean annual relapse rate in the European study was lower in the IFN-β1b group (0.42) than in placebo group (0.63). Despite conflicting results of these two studies, IFN-β1b was approved by the FDA and the EMEA for treatment of SPMS.

Comparison with IFN-β1a

The efficacy of IFN-β1b in MS was compared with efficacy of IFN-β1a in 156 patients with RRMS. The patients with initial value of EDSS score less than 4 were followed for 12[29] and 18[30] months, and relapse rate was the primary outcome. Although the relapse rate before enrollment of the patients was similar in both IFN-β1a and IFN-β1b group, after 12 months of treatment relapse rate in IFN-β1b group was significantly lower (0.61 per year) than relapse rate in IFN-β1b group (0.85 per year). Besides, after 12 months of treatment, only IFN-β1b significantly reduced the EDSS score. Dominance of IFN-β1b over IFN-β1a was maintained after 18 months of follow-up.[30]

Higher efficacy of IFN-β1b compared to IFN-β1a was also shown in a multicenter, randomized clinical trial with 188 patients with RRMS.[31] The patients were treated for 2 years, with either 30 μg of IFN-β1a per week subcutaneously, or with 250 μg of IFN-β1b every other day, subcutaneously. After 2 years, 51% of study patients who received IFN-β1b remained relapse-free compared to 36% of study patients who were given IFN-β1a (relative risk of relapse 0.76).

Comparison with glatiramer acetate

When compared with glatiramer acetate in patients with RRMS, IFN-β1b showed similar efficacy. In a large, randomized, prospective, multicenter clinical trial[32] with 2447 patients suffering from RRMS, 3-year therapy with 250 μg of IFN-β1b every other day, subcutaneously, led to the same relapse rate as 500 μg of IFN-β1b every other day, subcutaneously, or 20 μg of glatiramer acetate subcutaneously, every day. Small clinical study with 75 patients, which compared IFN-β1b with glatiramer in patients with RRMS, had for primary outcome number of combined active lesions on NMR per patient per scan during the first year, including all enhancing lesions and non-enhancing new T2/fluid-attenuated inversion recovery lesions, and for secondary outcomes the number of new lesions and clinical exacerbations over 2 years. After completion of the study, there were no differences among the groups in new lesions or clinical relapses for 2 years.[33]

Dosing schedule of IFN-β1b

Patients with RRMS should receive initially 62.5 μg subcutaneously every other day for 3 doses; then the dose should be doubled and given every other day for the next 3 occasions. The following 3 doses are given also every other day subcutaneously, and are 3 times higher than the initial dose. Finally, the patients continue to receive 250 μg every other day subcutaneously, for approximately 5 years. The dose of 250 μg every other day was shown to be more effective in clinical trials than either the lower or higher doses.[23–25,27,28] It is not known yet whether the therapy should be continued after 5 years.[17,19]

Safety and tolerability

In recommended doses IFN-β1b causes the following frequent adverse effects (frequency is given in parenthesis): injection site reactions (redness, discoloration, inflammation, pain, necrosis and non-specific reactions) (85%), insomnia (31%), influenza-like syndrome (34%), asthenia (34%), headache (32%), myalgia (26%), hypoesthesia (26%), nausea (16%), paresthesia (16%), myasthenia (11%), chills (8%), depression (8%), back pain (5%), increased liver enzymes (11%), lymphopenia (11%), fever (5%), and pain in extremities (3%).[34,35] In pediatric populations, the most common adverse events recorded in clinical trials are influenza-like syndrome (35%), abnormal liver function tests (26%), and injection site reactions (21%).[36] During treatment with IFN-β1b, a number of patients develop neutralizing antibodies; however, their clinical significance was not proven in clinical studies, making the utility of measuring neutralizing antibodies uncertain,[37] leaving decisions about treatment with IFN-β1b to be made on clinical grounds.[38] Apart from neutralizing antibodies, about 7% of patients during treatment with IFN-β1b develop auto-antibodies, primarily against thyroid and hepatic structures.[39] However, emergence of the auto-antibodies was not linked to thyroid or liver function alterations.[40]

Although there are no published studies of interactions between IFN-β1b and other drugs, there are reports that IFNs reduce the activity of hepatic cytochrome P450-dependent enzymes.[19] Therefore, one should be careful when using IFN-β1b in combination with drugs which are metabolized by the cytochrome P450 system, and whose therapeutic index is narrow.

Patients receiving IFN-β1b perceive depression, influenza-like reactions and pain due to injection site reactions as most disturbing.[41] When starting an IFN-β1b therapy, a treatment discontinuation rate ranging from 14%–44% could be expected.[42] However, there is a considerable inter-individual variation among patients in perception of both the systemic and local side-effects, which is why it is important to identify early the patients who need more support or other interventions to maintain compliance.[43] Patient adherence is improved dramatically if the drug is administered subcutaneously by auto-injectors; besides, if the dose is gradually increased at the start of the treatment, if ibuprofen is used prophylactically and the drug is administered in the evening, the patients are more compliant.[37] The patients with MS dependent on a wheelchair are at increased risk to become non-adherent to the treatment due to the adverse effects of IFN-β1b.

If a patient receiving IFN-β1b becomes depressed, treatment of the depression with either psychotherapy or antidepressant medication decreases risk of discontinuing IFN-β1b by about 4.4-fold.[44] Psychotherapy is used as a treatment option more frequently in university and academic group practice-based MS clinics than in a regular health system.

Cost/effectiveness of IFN-β1b

Because of the considerable cost of IFN-β1b therapy its cost/effectiveness is still an open issue, which depends on duration of therapy, an accurate estimate of long-term benefit and prices of health services in health care settings. In US health care settings, if IFN-β1b is given for the lifetime of a patient, incremental cost per quality-adjusted life year gained (compared to symptom management alone) is $310,691, which is within the range of incremental cost/effectiveness recorded for other biologic agents for MS ($258,465, $303,968 and $416,301 for subcutaneous glatiramer, intra-muscular IFN-β1a and subcutaneous IFN-β1a, respectively).[45] If the costs are calculated per relapse avoided in patients with RRMS, IFN-β1b, subcutaneous IFN-β1a and glatiramer are more favorable than intra-muscular IFN-β1a ($87,061; $80,589 and $88,310; respectively).[46] When IFN-β1b is used in some of the European Union (EU) countries for 20 years, the costs per quality-adjusted life-year gained will be less than €50,000. Large differences in costs between the US and the EU could be explained by much higher prices of drug administration services in the USA.[47] However, if IFN-β1b and other biologic agents are used for patients in a country passing through socio-economic transition, neither IFN-β1b nor other biologic agents are cost/effective, due to extremely low prices of relapse treatment, which is prevented by IFN-β1b.[48]

Tolerance to IFN-β1b

After at least 1 year of IFN-β1b therapy,[49] about one fifth of the patients with MS develop tolerance to this drug, manifested as an increase in the relapse rate.[50] The tolerance correlates well with emergence of neutralizing antibodies, which are produced by the patient's immune system and bind to IFN-β1b, preventing its action.[51] It was noted that this tolerance spontaneously abates after several years of continuous treatment, coinciding with disappearance of neutralizing antibodies from the patients' sera.[20] Therefore, a finding of neutralizing antibodies against IFN-β1b in serum of MS patients is not an indication for discontinuing therapy with this valuable drug.

Conclusions

Extavia®, an IFN-β1b for subcutaneous self-administration, was recently approved for treatment of relapsing-remitting or active secondary progressive MS, thus enlarging the spectrum of immunological therapies for this debilitating disease. Its efficacy in RRMS is higher than that of IFN-β1a, and similar to the efficacy of glatiramer acetate. Higher efficacy and similar safety compared with other drugs of the same class, mean that IFN-β1b has a significant segment of the drug market for MS, which is shared between the older product Betaseron® and Extavia®. Considering the high incidence of injection site reactions to IFN-β1b, a future target should be the development of an IFN-β1b preparation with improved local tolerability and maintained systemic efficacy.

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