Interferon-β₁b for multiple sclerosis

Jack Burks

Interferon-β₁b (Betaseron®/Betaferon®) was the first approved therapy for relapsing-remitting multiple sclerosis. The US Food and Drug Administration has expanded the indication to include relapsing forms of multiple sclerosis which encompasses secondary-progressive multiple sclerosis if relapses are present. In one scientifically sound head-to-head comparison (Independent Comparison of Interferon trial), Interferon-β₁b was shown to be clinically superior to low-dose Interferon-β₁a (Avonex®). Current studies are underway to compare it with a double dosage of Interferon-β₁b as well as glatiramer acetate. Neutralizing antibodies are more likely to occur with Interferon-β₁b, but their clinical significance has shown conflicting and confusing results making the utility of measuring neutralizing antibodies uncertain. Up to 12 years of follow-up data suggest that the drug remains effective on T2 magnetic resonance imaging burden of disease in those who stay on therapy. Initially, the major problem with Interferon-β₁b was a lack of tolerability due to high incidents of skin reactions and influenza-like side effects. Patient adherence has improved dramatically with the introduction of autoinjectors and protocol changes including initial dose escalation, prophylactic ibuprofen or acetaminophen, evening administration of drug and an attentive nurse support system. Interferon-β₁b remains a first-line treatment for relapsing-remitting multiple sclerosis and relapsing forms of secondary-progressive multiple sclerosis based on robust efficacy data and a long-term safety profile.


Multiple sclerosis (MS) is a chronic CNS disease usually beginning between the ages of 20 and 40 years, characterized initially by intermittent attacks resulting in a wide range of neurologic symptoms. Ultimately, most patients with relapsing-remitting multiple sclerosis (RRMS) transition to secondary-progressive multiple sclerosis (SPMS) after 10–20 years of symptoms. MS is a leading cause of disability in young adults, affecting over 1 million people [1,2]. Immunomodulating treatments in the past 10 years have been helpful to most patients, but the cause and cure remain elusive.

Multiple sclerosis definition challenged
Our understanding of MS has changed dramatically in the past few years. Previously, RRMS has been defined as a relapsing-remitting disease of CNS myelin caused by activated T-cells which induce inflammation, cytokines and macrophages.

This concept is now being challenged. First, although 80–85% of MS patients begin with a disease course characterized by exacerbations and remissions, magnetic resonance images (MRIs) are likely to show continuing damage during clinically asymptomatic periods. In addition, most of the patients who begin with a relapsing-remitting clinical course will convert to a progressive disease course called SPMS within 10–20 years [3,4]. Furthermore, normal-appearing white matter on brain MRIs demonstrates progressive damage by more specialized techniques such as magnetic resonance spectroscopy and magnetization transfer (MT)
imaging [5–7]. Therefore, many MS experts now believe that early and continuous CNS damage best characterize the pathogenesis of early MS in most MS patients.

Benign MS, where MS patients remain stable for over 20 years, can occur but are infrequent and not easy to predict, especially early in the disease course [8]. Patients with apparent mild MS early in the disease course can be devastated by a later attack. Therefore, many MS experts, the American Academy of Neurology and the National MS Society recommend early treatment of RRMS patients with evidence of active disease [9,10]. Recently, the concept that benign MS is unusual and hard to predict has been challenged by Mayo Clinic neurologists [11,12].

The second challenge to the RRMS definition involves the concept that myelin is the major target of the disease. In fact the damage in MS is not confined to myelin. Axonal and neuronal damage can occur, even at the earliest clinical signs of the disease [5,6]. For example, the MRIs in early MS often reveal axonal loss (black holes) [7]. Also, magnetic resonance spectroscopy shows a reduction of N-acetyl aspartate activity indicating axonal damage [13].

A third challenge to the definition of MS involves immunopathology. While inflammation is prominent early in the disease; later, clinical progress is not associated with abundant inflammation. Therefore, another pathologic process must be ongoing. This degenerative or apoptotic process is characterized by brain atrophy and clinical progression in spite of a paucity of new inflammatory lesions [14]. The cause of this degenerative pathology is unknown, but it is possible that early inflammation-induced damage may be partially responsible for later degenerative changes. For example, CNS cells that are damaged but not destroyed by inflammation can recover but may be destined to die earlier than if they had not been damaged. The situation may be similar to post polio syndrome where cells surviving from the original polio virus infection may undergo apoptosis or programmed death 20–40 years later. A progressive myelopathy ensues without recurrence of the viral infection [15]. If a similar phenomenon occurs in MS, the damaged cells may die after 5–25 years without the presence of additional inflammation.

Fourth, the concept that MS is a disease has recently been challenged. In fact, four separate pathologies have been identified, indicating the possibilities of four distinct disease processes [16]. Therefore, MS may be a syndrome rather than one specific disease. Proponents have indicated that these four distinct pathologies occur exclusive of one another. For example, if a patient has one type of pathology, they do not have evidence of the other three types of pathology. If confirmed, this may be one explanation as to why individual patients may respond differently to treatments.

Given this new data on the complexity and early severity of MS, new areas of research and treatment are likely to result in more specific treatments. In the meantime, four immunomodulating therapies and one immunosuppressant therapy have been approved by the US Food and Drug Administration (FDA). Another treatment, natalizumab (Tysabri™; formerly Antegren™), has been approved but the complete 1- and 2-year data set have not been published [10]. These therapies, while not curative, have improved the clinical course of MS in most patients. Long-term follow-up registries of treated patients indicate that patients continue to respond to treatments for many years [17,18].

Multiple sclerosis symptoms
Symptoms of MS can encompass any symptoms related to CNS damage [19,20]. Visual impairment, numbness, dizziness and fatigue are often the earliest symptoms. Other symptoms might include weakness, ataxia, cognitive dysfunction, spasticity, pain, vertigo, dysphagia, and bowel, bladder and sexual dysfunction. Less common symptoms include blindness, hearing loss and autonomic dysfunction. Depression is common in MS with an estimated sevenfold increase in suicide rates over the normal population [21]. Bipolar disease is also more common in MS patients.

Multiple sclerosis risk factors
The onset of the disease is usually between the ages of 20 and 40 years, although the disease may appear in children and can also be diagnosed after the age of 50 years [22]. Caucasians of northern European heritage are the most common ethnic groups. Women are two- to three-times more frequently diagnosed with RRMS than men. Women are likely to have less symptoms of the disease during pregnancy, but have an increased risk of an attack within the 6-month postpartum period. Hormonal research in MS has been initiated, but is in its infancy.

Geographical variability exists in that patients living in temperate climates who have northern and central European lineage constitute the highest risk group. Those who migrate from a high-to-low risk area remain at high risk after the move, if they move after the age of 15 years. Moving before the age of 15 years lessens their risk of MS [23]. An environmental exposure such as an infectious agent as a cause of MS, has been postulated for over 100 years. The current leading candidates are numerous viruses such as Epstein–Barr or Herpes Virus VI, as well as other infectious agents such as Chlamydia pneumoniae [24]. While an environmental exposure before the age of 15 years has been linked to MS, the first clinical episode may not occur until several years later.

A genetic predisposition to the disease has been identified in numerous studies. For example, the risk of MS in northern latitudes of the USA is one in 1000 (0.1%), but is 2–3% if a close biologic relative has MS. The concordance risk is 3–5% for a dizygotic twin but up to 30% for a monozygotic twin of an MS patient [25]. However, genetics is not the sole risk factor for MS and it is unlikely that a specific MS gene will be found as the etiology.

Immune pathogenesis
As discussed, the single pathology theory of MS is being challenged by those who have described four separate
pathologies \[16\]. Nonetheless, the pathologic process in RRMS apparently requires an initial cellular activation in the peripheral blood resulting in proinflammatory T-lymphocytes to proliferate. The activating stimulus is unknown but myelin or myelin-associated proteins are suspected. These activated cells then transverse the blood–brain barrier into the CNS to precipitate the damage. While T-lymphocytes and macrophages induce myelin and axonal damage in some patients, B-lymphocytes appear to mediate damage in other patients via antibody and activation of complement \[16\]. Clinically, these patients may be indistinguishable. In other patients, damage from lymphocytes is not apparent at biopsy or autopsy. These patients' brains demonstrate degenerative changes to oligodendroglia cells - the cells that produce myelin. Other researchers describe oligodendrocytes apoptosis as an initial event, preceding inflammation \[25\]. This diverse and complex pathology indicates that finding only one cause for MS is unlikely.

### Diagnosis & clinical disease course

Not surprising, the clinical course of MS is variable. Most patients' symptoms begin with relapses (RRMS) but they transform into a progression course later on (SPMS). Other patients have a progressive disease from onset called primary-progressive multiple sclerosis (PPMS). These patients tend to be older at onset and have more spinal cord than cerebral involvement. Other patients will begin with a progressive form of the disease and also have intermixed relapses. This uncommon course of MS is called progressive-relapsing multiple sclerosis (PRMS) \[26\].

A very small percentage of patients have a devastating disease course from onset with severe relapses as well as progression between relapses which leads to early disability and even death. This malignant form of the disease is called Marburg's Syndrome.

Benign MS is a term characterizing patients who have only a few mild attacks with complete recovery \[27\]. These episodes are widely dispersed in time and do not lead to progression later in life. The prevalence of benign MS is estimated at between 5 and 20\% of MS patients. Many MS experts believe less than 10\% of patients remain benign after 25 years. Other experts disagree and put the benign MS percentage higher \[12\]. Predicting which patients will have benign disease is difficult early in the disease course. Some patients who appear to have benign disease early, develop more serious symptoms after several years. Unfortunately, treatments later in the disease course may be less effective.

The existence of benign disease in a small subset of patients creates a therapeutic dilemma. Should all MS patients with relapses be treated or should only those patients who have severe relapses be treated early? Should clinically mild MS cases have their treatment delayed until more severe symptoms appear? The problem with this rationale is that damage that occurs early, even subclinical damage, may be permanent and lead to later progression of the disease. Also, early treatment is more effective in preventing relapses. Many neurologists believe patients should be treated after their first episode (clinically isolated syndrome [CIS]) if the MRI shows severe and/or continuous damage. By utilizing the MRI, the new McDonald MS Diagnostic Criteria allows for presumptive diagnosis of MS without a second clinical episode. Specifically, a CIS plus an abnormal MRI followed by another MRI in 3–6 months with new lesions meets their diagnostic criteria for MS \[28\].

### Therapeutic approach to multiple sclerosis

Symptom management is available for many of the common problems associated with MS. Medications for fatigue, spasticity, pseudo bulbar affect, depression, bladder problems and sexual dysfunction are helpful (Table 1). Drugs that improve cognitive dysfunction have shown some modest effect. Drugs for tremors, incoordination and weakness have been less successful. Complimentary and alternative medicine (CAM) approaches may be a helpful adjunct, although certain CAM herbs may stimulate immune activation and be detrimental. Fish oil, yoga, massage, hydrotherapy, hippotherapy and other CAM may aid MS patients \[29\].

Rehabilitation has added a new dimension to improving function in MS patients in the last few years. The value of rehabilitation has been established for patients who undergo physical therapy, occupational therapy, speech therapy, cognitive therapy, recreational therapy and psychologic counseling. Improvement in quality of life and productively are added benefits \[19,20\].

Immunomodulating therapy has been the most prominent area of research in the past 15 years. Five agents are currently FDA-approved for MS therapy to reduce exacerbations and/or progression of the disease, and include:

- Interferon (IFN)-β1b (Betaseron®, Berlex Laboratories, USA; Betaferon®, Schering, Berlin, Germany). These two drugs are identical, but marketed under different generic names IFN-β1b
- IFN-β1a (Avonex®, Biogen/IDEC, USA) and (Rebif®, Serono, Geneva, Switzerland)

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<th>Table 1. Therapeutic approaches to multiple sclerosis.</th>
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<td><strong>Therapeutic approach</strong></td>
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<td>Symptom management</td>
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<tr>
<td>Rehabilitation/psychosocial support</td>
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<td>Immunomodulating therapy to reduce inflammation, relapses, and progression of the disease</td>
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<td>Immunosuppressive therapy with anticaner drugs for patients who experience a suboptimal response to immunomodulating therapies</td>
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<td>Newer experimental therapy strategies:</td>
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• Glatiramer acetate (Copaxone®, Teva Neurosciences, Israel)
• Natalizumab (Tysabri; formerly Antegen, Biogen/IDEC, USA)

The mechanisms of action of immunomodulation drugs are not fully understood. However, in peripheral blood they can shift the activated T-helper lymphocyte (Th1) cells which initiate proinflammatory activity to the Th2 cell, which initiates anti-inflammatory activity. In addition, β-IFNs reduce γ-IFN and reduce migration of activated T-cells from the blood stream into the CNS. These drugs are used primarily in the treatment of RRMS, although IFN-β1b has also been approved by the FDA for SPMS in patients who are still experiencing relapses. Their efficacy in PPMS has not been established. However, one small, preliminary randomized placebo-controlled 2-year study (73 patients) in Spain demonstrated that IFN-β1b reduced MRI damage and demonstrated a trend towards decreasing disability compared with placebo (22% of IFN-β1b-treated patients and 32.4% of the placebo group had progressed at 6 months) [30]. These data do not establish IFN-β1b as a treatment for PPMS.

Long-term efficacy is hampered because of the problem of keeping patients on placebo for several years. In fact, patients treated with placebos and then switched to treatment after 2–3 years, have more impairment several years later than those on treatment from the start of the studies. What is lost by delayed treatment may never be recovered.

Immunosuppressive therapy
Immunosuppressive (antineoplastic) agents such as azathioprine, cyclophosphamide and methotrexate have been used in MS patients for over 20 years with varying reports of success. However, these drugs are not FDA-approved for the treatment of MS in the USA. The only FDA-approved immunosuppressive agent is mitoxantrone which suppresses T-cells, B-cells and macrophages [31,32]. Usually given every 3 months intravenously, the length of treatment time is limited to 2–3 years due to potential cardiac toxicity at higher doses. In addition, potential infertility and the induction of acute leukemia in rare circumstances are deterrents. Most MS centers reserve mitoxantrone as a rescue therapy for treatment failures with immunomodulating drugs. Other immunosuppressive are undergoing clinical trials.

Steroid therapy
Steroids are still utilized for the treatment of acute MS relapses, even in patients on immunomodulating and immunosuppressive therapy. Adrenocorticotropic hormone and high doses of methylprednisolone intravenously improve the time to recovery of acute attacks, but may have little or no demonstrated effect on the disease long term. Some MS centers recommend high doses of methylprednisolone on an intermitted basis, either monthly or quarterly, as an adjunct to the immunomodulating therapy regimens when patients are perceived to be suboptimal responders [33]. This approach is an alternative to initiating mitoxantrone therapy in suboptimal responders on immunomodulating therapies. Steroids have not been approved by the FDA for long-term use in MS patients.

Interferon-β1b
IFN-β1b is the focus of this drug profile. The other immunomodulating therapies are not discussed except as they relate to IFN-β1b. IFN-β1b was the first FDA-approved immunomodulating therapy for RRMS in 1993. The initial interest in IFN-β1b resulted from it’s ability to decrease the production of γ-IFN which was shown to have a deleterious effect in MS patients [34]. It was also demonstrated to have antiviral and anticancer effects in addition to it’s immunomodulating properties.

IFN-β1b is a lyophilized protein produced by DNA recombinant technology using Escherichia coli bacteria. Containing 165 amino acids with the molecular weight of 18,500 Da, it lacks the carbohydrate side chain found in human IFN-β [35]. Combined with mannitol and human albumin, it has a neutral pH 7.2, and is stable at room temperature in the lyophilized form. Therefore, refrigeration is not needed. The dose per vial is 250 μg or 0.25 mg (million international units). The FDA-approved dose is 250 μg every other day given by subcutaneous injection.

Mechanisms of action
The mechanisms of action are not fully understood. Much of the data represents in vitro findings after applying high doses of IFN-β1b (up to 3000 μg) which may not correspond to the in vivo situation. However, the following actions have been demonstrated with IFN-β1b:

• Reduces proinflammatory cytokines such as γ-IFN and tumor necrosis factor-α
• Increases secretion of anti inflammatory cytokines such as interleukin-10
• Enhances suppressor T-cell activity while inhibiting the proliferation of lymphocytes
• Downregulates antigen presentation which is needed for the activation of lymphocytes
• Inhibits lymphocyte trafficking through the blood–brain barrier to the CNS by down regulating very late after activation antigen 4 and intercellular adhesion molecule. (Activation of lymphocytes occurs in the peripheral blood. Therefore, these cells must be actively transported through the blood–brain barrier to enter the CNS to initiate a cascade of events resulting in CNS damage.)

In summary, IFN-β1b has immunomodulating effects and reduces trafficking of activated T-cells into the CNS at the blood–brain barrier level. Pharmacokinetic studies have been complicated since IFN-β1b is difficult to detect in the serum after subcutaneous inoculation [36–39]. Therefore, IFN-induced biologic response marker gene products such as neopterin, myxoinus antigen protein and β2 macroglobulin assays are used as surrogate markers. Every other day subcutaneous administration of IFN-β1b maintains relatively constant levels of surrogate marker activity.

Adverse effects
Adverse effects with IFN-β1b have decreased markedly since its introduction. Flu-like side effects and skin reactions were
problems for many patients treated with IFN-β₁b when it was initially approved in 1993 [35,40]. Subsequently, an autoinjector has been introduced which markedly decrease the skin reactions. In addition, flu-like side effects have been decreased with a combination of dose escalation at onset of treatment (starting at a quarter or half dose and gradually increasing to full dose after several weeks), evening drug administration, the prophylactic use of ibuprofen or acetaminophen during the first few weeks of therapy and attentive healthcare provider support (usually through nurses) [41]. The adherence rate has increased to approximately 90% overall after 1 year of treatment. Only 5% of patients stopped treatment due to adverse events.

IFN-β₁b may precipitate depression, however, this issue is complicated because over 50% of MS patients suffer from depression without immunomodulating therapy. In spite of the lack of conclusive proof that IFN-β₁b causes depression, any patient on IFN therapy who develops depression should be treated immediately. Also these patients should be evaluated for possible decreasing of the IFN dose or discontinuing therapy temporarily. Discontinuing IFN therapy is usually not necessary, if the depression is diagnosed early. Early detection of depression is enhanced by informing patients and their families of a potential relationship between IFNs and depression. Treatment of depression ideally includes both psychotherapy and medication in most situations.

Blood count and liver function abnormalities have also been detected in patients treated with IFN-β₁b [38]. Therefore, laboratory blood tests are recommended at regular intervals during IFN-β₁b therapy. While no standard protocol has been accepted, many clinicians check complete blood count and liver function tests at 3-month intervals for the first 6-12 months and at 6-month intervals for the next few years. Some physicians include thyroid function tests because of a possible link to thyroid dysfunction. Some patients may obtain more close scrutiny of laboratory tests if they have conditions affecting the liver, blood cells or thyroid.

Regarding use in pregnancy, IFN-β₁b is listed as a category C drug as no teratogenic effects have been demonstrated. However, it is known to be an abortifacient in animal studies. Women contemplating pregnancy should discontinue therapy until the baby is born. If a patient becomes pregnant while on IFN-β₁b, the drug should be discontinued until after the delivery. Breast feeding is not recommended while on IFN therapy, although it is not known if the drug is excreted in human milk.

Clinical trials with interferon-β₁b

Pivotal trial in RRMS

The approval of IFN-β₁b for RRMS was based primarily on a single pivotal Phase III, 2-year trial in North America [42,49]. This randomized, placebo-controlled, double-blinded study was extended to 5 years. Two doses (50 and 250 μg) of IFN-β₁b were injected every other day subcutaneously. MS patient were between the ages of 18-50 years, had the disease for more than 1 year, and had Expanded Disability Status Scale (EDSS) levels 0-5.5 (walk at least 100 m without rest or aid). They must have had two relapses over the preceding 2 years but no exacerbations in the preceding 30 days. In total, 372 patients were randomized to placebo, low-dose IFN-β₁b (50 μg) or higher dose (250 μg) subcutaneously every other day. Outcomes included relapse rate, proportion of the patient remaining relapse free, time to first relapse, duration and severity of relapses, changes in EDSS scores from baseline, and changes in T2 burden of disease on MRI. A subgroup of patients had frequent MRIs with and without gadolinium.

The results indicated that the 250-μg dose produced the best results overall. The relapse rate was reduced by approximately a third over 2 years with a 50% reduction in moderate and severe relapses per year. This effect persisted to 5 years, although the 5-year data included too few patients to show statistical significance in clinical parameters. Although not a primary end point, the 250-μg dose showed a nonsignificant trend towards slowing progression of disability. The MRI demonstrated a statistically significant benefit over the entire 5-year period. Specifically, IFN-β₁b showed a decrease of 9.3% in T2 lesion load compared with baseline versus an increase of 15% in T2 lesion load in the placebo group (p = 0.0002) at 2 years. Gadolinium lesions were markedly reduced (83%) in the frequent MRI subgroup of treated patients.

The presence of neutralizing antibodies (NAb) showed conflicting and confusing results. On a cross-sectional analysis, patients with NAb had higher exacerbation rates and more MRI lesions but were less likely to progress (p = 0.08) compared with patients without NAb. On longitudinal analysis comparing NAb+ period and NAb- periods, the NAb attenuating effects on the low-dose IFN-β₁b were more apparent than the standard dose (250 μg) [44].

Independent Head-to-Head Comparison Trial of Betaseron versus Avonex in RRMS

This Italian multicenter trial was independent of pharmaceutical company input or support. It compared IFN-β₁b versus IFN-β₁a in RRMS in a 2-year randomized, prospective study on 188 MS patients (Table 2) [45-47]. The outcomes included both clinical and MRI parameters. The MRI evaluations were blinded (class I data) but the clinical evaluations were not blinded (class III data). The results of this study are shown in Table 3. IFN-β₁b was shown to be more efficacious than IFN-β₁a in all categories measured over the 2-year period. Specifically, it demonstrated an approximate 50% difference in the blinded MRI outcomes and a 35-50% difference in the unblinded clinical outcomes. NAb tested in this study found no clinical or MRI effect of neutralizing antibody [45,48]. In other words, patients on IFN-β₁b with NAb still responded more favorably than patients on IFN-β₁a.

INCOMIN trial extension study: dose reduction; switch from IFN-β₁a to weekly IFN-β₁b

At the conclusion of the INDependent COMparision of Interferon (Betaseron vs. Avonex) in RRMS; INCOMIN study 27 patients who were stable on IFN-β₁b were randomized to
Table 2. Interferon-β_{1b} versus -β_{1a}: The Independent Comparison of Interferon Trial results at 24 months.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>β_{1a} (n = 92)</th>
<th>β_{1b} (n = 92)</th>
<th>%Δ</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relapse free (0–24 months)</td>
<td>30 (33%)</td>
<td>46 (48%)</td>
<td>+35</td>
<td>0.036</td>
</tr>
<tr>
<td>Change in lesion load (%)</td>
<td>+11.7</td>
<td>-2.8</td>
<td>-14.5</td>
<td>0.0001</td>
</tr>
<tr>
<td>Expanded Disability Status Scale progression (0–24 months)</td>
<td>28 (30%)</td>
<td>13 (14%)</td>
<td>-46</td>
<td>0.005</td>
</tr>
<tr>
<td>New T2 lesions (6–12 months)</td>
<td>33 (45%)</td>
<td>16 (21%)</td>
<td>-52</td>
<td>0.002</td>
</tr>
<tr>
<td>Gd+ lesions (6–12 months)</td>
<td>16 (22%)</td>
<td>7 (9%)</td>
<td>-56</td>
<td>0.03</td>
</tr>
<tr>
<td>T2 lesion free (0–24 months)</td>
<td>19 (26%)</td>
<td>42 (55%)</td>
<td>+53</td>
<td>0.0003</td>
</tr>
<tr>
<td>Gd lesion free (0–24 months)</td>
<td>18 (25%)</td>
<td>39 (51%)</td>
<td>+51</td>
<td>0.0008</td>
</tr>
</tbody>
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Interferon-β_{1b} demonstrated an overall superior efficacy versus interferon-β_{1a} (Avonex®) in this 2-year trial on clinical and magnetic resonance imaging parameters. Reproduced with permission from Darell. The Lancet 359(9218), 1452–1460 (2002).

remain on IFN-β_{1b} every other day or switched to IFN-β_{1a} once a week, for 1 year. The results are shown in Table 3 [47]. Although relatively few patients participated, a statistical significance was demonstrated for both clinical and MRI parameters. Patients who switched from the high-dose IFN-β_{1b} to once a week IFN-β_{1a} did worse than those patients who remained on IFN-β_{1b}. Specifically, in those patients who switch to IFN-β_{1a}, 77% had relapses, 23% progressed, and 85% had new MRI lesions during the 1-year following the switch. In the patients who remained on IFN-β_{1b}, 21% had relapses, 0% progressed and 36% had new MRI lesions in the same time period. The difference in the relapse rate and MRI were statistically significant. The difference in the progression of disability data was not statistically significant.

These two studies indicated that the high and frequent dosed IFN-β_{1b} was more effective than lower dose once per IFN-β_{1a}. Furthermore, patients who switched from the high-dose IFNIFN to the low-dose weekly IFN showed more worsening symptoms in 1 year than patients who remained on IFN-β_{1b}. The small numbers in this trial require confirmation in a larger Class I clinical trial.

**IFN-β_{1b} European SPMS Trial**

The European Secondary Progressive Trial IFN-β_{1b} was a randomized, placebo-controlled, multicenter, double-blind trial utilizing Betaseron 250 μg subcutaneously every other day (Figure 1) [49]. The time to confirmed progression of disability was defined as a 1 point increase in EDSS score sustained for at least 3 months or 0.5 increase in EDSS in patients whose baseline EDSS score was 6.0 or 6.5. Other end points included time to wheelchair (EDSS = 7), relapse rate, hospitalization, steroid use and MRI parameters. The trial was terminated early after an interim analysis showed that IFN-β_{1b}-treated patients had experienced a dramatic lengthening of time to confirmed progression versus placebo (p = 0.0008). More disabled patients demonstrated an equal benefit of treatment compared with the less disabled patients. Time to wheelchair was also increased in treated patients. Specifically, a third fewer patients in the Betaseron group were using a wheelchair compared with the placebo group. Relapse rate, hospitalization and steroid use were also less in the treated group. The MRI parameters showed that the T2 MRI disease burden decreased by 5% in the IFN-β_{1b} group versus an increase of 8% for patients on placebo (p > 0.0001). New active lesions were also markedly decreased in the treated versus placebo group (p = 0.0008).

Subsequent conventional MRI and MT analysis of brain atrophy failed to differentiate between treated versus placebo-treated patients indicating that MRI and MT-MRI may not be a good stand alone measure of outcomes in SPMS trials [50–52].

Since the interim analysis showed a significant treatment effect, the trial was terminated early to allow patients on placebo to start IFN-β_{1b} treatment immediately. Of the treated patients, 28% developed NAb as measured on two consecutive assessments. Of NAb+ patients, 50% reverted to NAb- status and 80% of these patients remained NAb-.

An 8-year interim follow-up report demonstrated that patients, who returned for follow-up and were treated with IFN-β_{1b} from the beginning, had less progression of their EDSS over the 8-year period compared with the patients who were initially treated with placebo [53]. This study demonstrated that placebo-treated patients did not catch up to the levels of effectiveness of patients who were on IFN-β_{1b} from the beginning of the trial. In addition, this trial also demonstrated a positive effect on quality of life and cognition parameters in patients on IFN-β_{1b} [54].

**IFN-β_{1b} North American SPMS Trial**

The North American Secondary Progressive MS Trial was similar to the European trial with the exception of a third group who were treated with an IFN-β_{1b} dose based on body mass. In this study no difference in progression of disability was found between the placebo and treated groups [55]. However, the treated group demonstrated a favorable response in relapse rate and all MRI parameters. The discrepancy between the disability outcomes of these two SPMS trials is best explained by the fact that the European patients had more active disease and were earlier in their SPMS course compared with North American patients. These data indicate that earlier treatments in SPMS will more likely show positive effects on progression of disability than if treatments are delayed.
Interferon-β₁β long-term data in relapsing-remitting multiple sclerosis

No long-term, placebo-controlled, double-blinded, randomized studies are available because of the problem of keeping patients on placebo for years. However, one long-term follow-up on patients from the original IFN-β₁β pivotal trial in RRMS showed a 10.82 cc decrease in MRI T2 burden of disease from baseline after 12 years of therapy [18]. A control group of untreated patients from the same center had an increase MRI T2 burden of disease of 18.7 cc during this same time period. However, no difference in brain volume ratios was noted between treated and untreated patients. This long-term follow-up evaluation also showed that injection site reactions, flu-like symptoms, and NAbbs decreased dramatically over the 12 years of IFN-β₁β treatment. Specifically, 40% of IFN-β₁β-treated patients had NAbbs during the pivotal trial, but only 6% were NAb⁺ at the 8-year follow-up assessment [18]. These results reinforce the transient nature of NAbbs in most patients.

Another study evaluated disability progression and relapse rate among 83 RRMS and SPMS patients treated for an average of 8.8 years at the University of Alabama (AL, USA) [56]. IFN-β₁β reduced the annual rate of EDSS progression to 0. On occasion interview other long-term studies, no placebo controls were followed and an additional 43 patients were lost to follow-up or discontinued treatment. Nonetheless, it demonstrates that patients who stay on therapy can remain relatively stable for several years.

NAbbs with Interferon-β₁β

Do IFN-β NAbbs significantly affect clinical efficacy? An indepth analysis of the complex and conflicting NAb data is beyond the scope of this drug profile. However, a brief review of both sides of the debate is attempted. Data consistently demonstrates that IFN-β₁β is more likely to produce NAbbs than any other IFN-β product for MS. NAbbs reduce biologic markers such as myelin basic protein. The NAb effect on biologic markers is graduated versus an all-or-none phenomena (i.e., low levels of NAbbs have less effect than high levels of NAbbs). High levels of NAbbs occur infrequently, probably in less than 10% of patients on IFN-β treatment.

NAbbs have not been shown to affect progression of disability with IFN-β. Their effect on relapse rate has shown mixed results. The American Academy of Neurology and the MS Council addressed the issue of NAbbs in an evidence-based medicine review and found the clinical relevance of NAbbs data to be confusing and conflicting. They stated that the utility of measuring NAbbs is uncertain [10].

A 2003 consensus conference on NAbbs in London, UK identified concerns regarding efficacy if NAbbs were present. Their consensus statement (representing 70% of conference agreement) were published in a non-peer-reviewed and pharma-sponsored supplement in Neurology in 2003 [57]. They concluded that NAb assay controls and measurement units need to be standardized. Also they agreed that NAbbs reduce bioactivity and that persistently high levels of NAbbs will eventually lead to loss of clinical efficacy. Therefore, in NAb⁺ patients, consideration should be given to discontinue IFN-β therapy, in their consensus with 70% agreement.

In stark contrast to these recommendations, in September 2004 another review of NAbbs by authors not attending the London Conference concluded, 'The biological significance of anti-IFN NAbbs is not yet known, nor has it been proven conclusively that they affect the clinical response to IFN-β therapy. The presence of NAb is therefore not an indication that treatment should be changed. Indeed, any treatment decision should be based only on the clinical response to therapy' [58].

Sorenson and colleagues published NAb data in 2004 that concluded, 'Our findings suggest that the presence of NAbbs against IFN-β reduces the clinical effect of the drug. In patients who are not doing well on IFN-β, the presence of such antibodies should prompt consideration about change of treatment' [59]. Their study included 541 patients on any IFN-β up to 60 months where NAbbs were measured every 12 months. The most recent NAb review paper which included the same authors from the London Consensus Group was published in another non-peer-reviewed and pharma-sponsored supplement to Neurology in December 2004. They reiterated the London Group position, 'The potential development of NAbbs is an important consideration in selection and monitoring treatment of MS.' However they

Table 3. Independent Comparison of Interferon Trial Extension: dose reduction study interferon-β₁β to -β₁α (Avonex®) switch trial.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Switch from interferon-β₁β to -β₁α</th>
<th>Continuous interferon-β₁β</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exacerbation rate</td>
<td>0.09*</td>
<td>0.02*</td>
</tr>
<tr>
<td>Patients with exacerbation (%)</td>
<td>77</td>
<td>21</td>
</tr>
<tr>
<td>Patients with sustained Expanded Disability Status Scale worsening (%)</td>
<td>23 (not significant)</td>
<td>0 (not significant)</td>
</tr>
<tr>
<td>Patients with magnetic resonance imaging activity (%)</td>
<td>85*</td>
<td>36*</td>
</tr>
</tbody>
</table>

*Statistically significant p < 0.05.

Patients who switched from interferon-β₁α (Avonex®) at the conclusion of the Independent Comparison of Interferon Trial had increased disease activity over 1 year when compared with patients who remained on interferon-β₁α (n = 27). Reprinted with permission from Barbero P et al. J. Neural. Sci. 222(1-2), 13-19 (2004).
also stated that, ‘Long-term prospective studies are needed to further define the clinical effects of NABs on patients receiving disease-modifying therapies for MS’ [60].

Given the controversy, conflicting data and strong opinions on both sides of the NAB issues, this author is influenced by the remarks of biostatisticians at the London NAB conference. Cutter stated, “To date, no studies have been adequately designed to prospectively answer the question of NABs…” and ‘cross-sectional studies elicit associations and not cause’ [61,62]. Petkau, another biostatistician at that conference, also expressed concerns about the validity of conclusions based on the currently utilized NAB cross-sectional analysis [62]. He stated that these analyses lack statistical power in small subgroup comparisons of NAB+ patients. In addition he pointed out, ‘The cause of any difference detected by such comparisons is unclear because these subgroups may differ on baseline covariates (possibly unmeasured) predictive of NAB development and reduced efficacy’ [62]. In summary, these statisticians in London were concerned about the validity of the cross-sectional NAB data, design and analysis of the NAB studies and assumptions that NAB associations might be portrayed as NAB causes. Their concerns should not be overlooked but rather addressed scientifically before making conclusions on the clinical relevance of NABs. Their remarks crystallize the problem of trying to make clinical decisions based on inadequate and conflicting data.

Unfortunately, this is not an academic issue. If NABs are clinically relevant and NAB+ patients respond remarkably better than NAB- patients, strategies to reduce NABs may be readily available without discontinuing IFN-β therapy. For example, pulse methylprednisolone [63] or low-dose oral immunosuppressive agents such as azathioprine or methotrexate might alleviate the potential problem. Also, inducing tolerance by increasing the IFN dose may be another option that has some supporting data [58].

Until the issue is settled by adequate data, there will likely remain two camps with strongly opposing opinions based on selected data favoring their views. Therefore, this author recommends that clinical decisions be based on patient response to therapy and not NAB status. While the (theoretical) negative clinical response to NABs may lag behind the appearance of NABs, NABs are usually transient and, paradoxically, are usually negative in patients who are not responding well to IFN-β1b therapy [64,65].

The author agrees with part of Sorensen’s conclusions (above) ‘In patients who are doing well on IFN-β, the presence of such antibodies should prompt consideration about change of treatment’ except that the author believes that NABs should not drive the treatment decision. In any patient who is not doing well, prompt consideration for a therapeutic change is warranted with or without NABs. Most suboptimal responders to IFN-β1b do not have NABs [64]. In fact, less than 10% of this group had high levels of NAB. Then why measure NABs?

In conclusion, until the NAB issue is clarified scientifically, the author recommends initiating therapy with the treatment the clinician believes has the best efficacy data, without regard to the controversial NAB issues. Furthermore, if a patient is responding well to treatment, the author would not change their therapeutic regimen based on a NAB+ test result. On the other hand, the author would not hesitate to change their therapeutic regimen if the author believed the patient was not responding well to a therapy, even if the test were NAB-. The potential use of IFN NAB testing in clinical practice awaits data that scientifically establishes a clinical effect, if any, of NABs.

**Regulatory affairs**

IFN-β1b has approved FDA indications for the treatment of relapsing forms of MS (including RRMS and SPMS with relapses).

**Expert opinion & five-year view**

IFN-β1b was the first approved treatment for RRMS. Recently, FDA indication approval was added for relapsing forms of MS, (including SPMS with relapses). Advances in the tolerability and nursing support systems have increased adherence dramatically in the last few years. Only 5% of patients discontinue IFN-β1b due to adverse events, if given properly [41].

The data supporting the efficacy of IFN-β1b is robust. The American Academy of Neurology independent evidence-based medicine review on immunomodulating drugs for MS contains the following [10]:

- IFNs have more robust disability progression data than Copaxone (B vs. C recommendation).
- Higher dosed and more frequent administrated IFN-β1b (Betaseron) and the IFN-β1a (Rebif) have more robust efficacy data than the low-dose weekly IFN-β1a (Avonex) (B recommendation).
- Route of administration does not appear to modify efficacy.
- NABs are more prevalent in the high-dose IFNs compared with low-dose IFN, but clinical relevance data is conflicting. Furthermore, the utility of even measuring NABs is uncertain.

Do the two high-dose IFN-β (Betaseron and Rebif) have equal efficacy? The two high-dose IFNs have not been compared in a head-to-head trial and cannot be directly compared using their pivotal trial data because of intertrial variability and different patient cohorts. However, reviewing the individual pivotal trial data reveals no substantial efficacy difference between the two high-dose IFNs. Both drugs are generally well tolerated. IFN-β1a is available in a prefilled syringe that needs refrigeration while IFN-β1b must be mixed but does not require refrigeration. Injection site pain is more common with IFN-β1a (Rebif) [66,67]. The etiology of the IFN-β1a pain is unknown but may be primarily related to an acidic pH of 3.8.

Following the American Academy of Neurology evidence-based medicine review, the first scientifically robust head-to-head trial was conducted in Italy (INCOMIN Trial). This trial demonstrated that IFN-β1b was substantially more efficacious than IFN-β1a (Avonex) and that NABs did not reduce clinical or MRI efficacy [45,58]. In this study, the MRI data were class I while the clinical data were only class III because the clinical evaluators were not blinded.

A second trial (class I clinical and MRI data) of high-dose IFN-β1a (Rebif) given three-times weekly versus low-dose weekly IFN-β1a (Avonex) also demonstrated that the higher dose IFN was clinically superior [68].

In addition, the Italian head-to-head INCOMIN Trial extension study illustrated that those patients on high-dose IFN-β1b, who switched to low-dose weekly IFN-β1a, deteriorated clinically and by MRI in a 1-year extension study. Therefore, reducing the dose (or discontinuing treatment) may be deleterious.

The issue of the clinical relevance of neutralizing antibody remains controversial because of the lack of adequate data. Until the issue is clarified, my current recommendation is to keep patients on treatment if they are clinically stable, regardless of NAb status.

There may be benefits in increasing the recommended dose of IFN-β1b in those patients where suboptimal response and/or NABs are a concern. In a recent study, patients who had continued MRI activity or a relapse after 6 months of IFN-β1b and who had the dose increased by 50% to 375 μg showed a positive MRI response compared with those who remained on the 250 μg dose [58].

Another recent study demonstrated the safety and short-term MRI benefits of double-dose IFN-β1b (Betaseron Efficacy Yielding Outcomes of a New Dose [BEYOND] Safety Trial) [69,70]. Subsequently, the BEYOND Trial is comparing regular-dosed IFN-β1b, double-dose IFN-β1b and glatiramer acetate. In other words, the ceiling effect of IFNs may not have been reached and that higher doses may produce even better results. The higher dose may also decrease NAB formation as is the case for IFN-β1a (Rebif) [71]. The BEYOND Trial should put into perspective the relative efficacy of IFN-β1b versus glatiramer acetate.

Another trial underway involves patients on low-dose weekly IFN-β1a (Avonex) switching to high-dose IFN-β1b (IFN-β1a vs. IFN-β1b Observations of Efficacy Trial). These patients are being randomized to stay on weekly IFN-β1a or switch to high-dose IFN-β1b in a class I study design. This will help answer the question concerning the best therapeutic strategy for patients currently on low-dose IFN-β1a. Should they stay on low-dose IFN-β1a or would they get a further benefit if they were switched to high dose IFN-β1b?

Another ongoing IFN-β1b trial compares IFN-β1b with placebo in patients with Clinical Isolated Syndrome (BEtaseron in Newly Emerging multiple sclerosis For Initial Treatment Trial). Can high-dose, high-frequency IFN-β1b delay or prevent recurrent attacks and MRI damage?

### Key issues

- Interferon IFN-β1b was the first approved treatment for relapsing-remitting multiple sclerosis and has over 15 years of safety data.
- The combined efficacy data in relapsing-remitting multiple sclerosis and relapsing secondary-progressive multiple sclerosis is robust. It has US Food and Drug Administration approval for relapsing forms of MS, which include secondary-progressive multiple sclerosis with relapses.
- IFN-β1b has shown superior efficacy over low-dose IFN-β1a (Avonex®) in a scientifically sound head-to-head trial over a 2-year period.
- Adverse events resulting in discontinuation of IFN-β1b have been reduced to only 5% after 13 months of treatments utilizing new protocols, autoinjectors and extensive nursing support.
- Neutralizing antibodies are more likely to appear with IFN-β1b than other immunomodulating therapies, but the clinical significance is uncertain. Until this controversy is resolved, the author recommends that treatment decisions be based on clinical outcomes and not neutralizing antibody tests.
- Notable class I trials are underway involving IFN-β1b:
  - To evaluate the efficacy of even higher dosages of IFN-β1b: Preliminary data are positive. This trial also includes a glatiramer acetate arm
  - To evaluate the efficacy of switching patients on weekly low-dose to high-dose IFN-β1b
  - To evaluate the effect of IFN-β1b on patients with clinically isolated syndrome
  - To analyze 15 years of data from patients on the pivotal trial
Over the next 5 years a number of other treatments are being or will be tested in clinical trials. Some of these treatments are oral medications and some are given parentally but at prolonged intervals such as every 1-12 months. If these show similar or enhanced efficacy to the current immunomodulating therapies, prescribing patterns will likely change. For example, α4-integrin antagonist selective adhesion molecule inhibitor has been recently approved (Tysabri) [72,101]. Its position in MS treatment will be further clarified when the 2-year data is presented in April 2005.

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* of interest
** of considerable interest

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