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Application of Interferon Beta-1b in Multiple Sclerosis

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Abstract
Recombinant interferon beta-1b (IFNβ-1b) was the first approved disease-modifying therapy for patients with multiple sclerosis (MS) by the world regulatory agencies for medical drugs and devices. IFNβ-1b significantly decreases the inflammatory component of MS but still has doubtful effect on the neurodegenerative component. This article appraises the benefits of IFNβ-1b on clinical and imaging measures of disease. Upon only briefly discussing the side effects of the drug, it will conclude with some crucial scientific aspects warranting urgent investigations to precisely address the potentials of IFNβ-1b in MS patients.

Keywords
Multiple sclerosis, interferon beta-1b (IFNβ-1b), magnetic resonance imaging (MRI), inflammation, neurodegeneration

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Multiple sclerosis (MS) is a chronic illness of the central nervous system affecting approximately 2.5 million young people worldwide.1 Regarded as exclusively a white matter (WM) disease, clinicians are now facing the notion, known to pathologists for over a century, that MS may affect the gray matter (GM) as well.2 Currently, MS is an incurable disease. It is, however, to some extent treatable. The past 20 years have witnessed a remarkable expansion of the horizons of pharmacologic treatments aimed at delaying disease progression. Recombinant interferon beta-1b (IFNβ-1b) was the first disease-modifying therapy approved in MS by the US Food and Drug Administration (FDA).3 Today, IFNβ-1b is the drug for which clinicians have the most experience with in chronically treating patients.

This article will attempt to appraise the status of IFNβ-1b application in MS patients today. Upon reviewing the clinical-radiologic presentation of the illness and its evolution over time, the effects of IFNβ-1b on clinical and imaging measures of disease, as reported in the largest clinical trials, will be discussed. Then the side effects of the drug will briefly be covered. This review will conclude by addressing some crucial scientific aspects that are still open for investigation to estimate the actual potentials of IFNβ-1b treatment in MS patients.

Clinical-radiologic Presentation and Evolution of Multiple Sclerosis
The first clinically manifest event of MS is the relatively acute or subacute occurrence of one or more combined neurologic symptoms, lasting at least 24 hours, in the absence of fever and infection, and suggestive of demyelination and inflammation. Such an event, namely clinical relapse, defines the status of clinically isolated syndrome (CIS). This is not considered clinically definite MS (CDMS) until a second attack occurs. Approximately 44 % of CIS patients will remain free from a second attack within the following three years.4 Up to 10 % of CIS patients will not convert to CDMS over the course of the subsequent 20 years.5 Patients not converting to CDMS within the following three years may tend to have fewer active lesions during the six months following the first attack (see Figure 1) than those who do convert to CDMS.1

In 85–90 % of CDMS patients (MS hereafter) the disease starts and evolves with a relapsing-remitting (RR) course. RRMS is characterized by repeated and time-interleaved clinical relapses. These relapses may last from a few days to a few months and are sustained by inflammation directed against either the spinal cord or the brain tissue.

Contrast-enhancing Lesions and Clinical Attacks
Magnetic resonance imaging (MRI) mirrors inflammation by showing sharply demarcated focal WM contrast-enhancing lesions (CELS) in T1-weighted (T1-w) images obtained upon the injection of the contrast agent gadolinium-DTPA (see Figure 2A). CELs (brain CELs more than...
spinal cord ones) may be visible even in the absence of a clinically evident attack, with a clinical flare occurring on average with every 10 CELs. Nevertheless, as seen for CIS patients as well as MS patients, the higher the number of clinically silent CELs over monthly MRIs, the higher the likelihood that a clinical attack will occur later on.7

CELS may have different evolution over time. Such an evolution likely depends upon the degree of myelin destruction and axonal degeneration or repair. This may all take place by the time of the first occurrence and continue to evolve upon enhancement resolution. The average life-span of CEL visibility on imaging is nearly one month, with almost all CELs terminating as hyperintense chronic lesions in T2-w images8 (see Figure 2B). Nearly 20 % of CELs culminate in persisting hyposensitizes in T1-w images9 (see Figure 2C).

T2-lesions have poor specificity with respect to the underlying pathological process and may represent areas with any degree of demyelination, axonal loss and repair. Conversely, T1-hypointense WM lesions persisting upon the enhancement resolution, namely persisting black holes (PBHs), are known to be pathologically more severe, since they are sustained by a higher degree of axonal loss.10 A subset of those PBHs appear as hyperintense lesions in cerebrospinal fluid tissue specific imaging11 (CSF-TSI, see Figure 2D). Lesions seen by CSF-TSI are likely a later event with two different components (inflammation and neurodegeneration) characterized by WM and GM tissue loss and leads to irreversible clinical deterioration and neurodegeneration. As a result of a long-standing insidious neurodegenerative process, patients also tend to present with cortical thinning12 and focal cortical lesions (see Figures 2E and 2F).13

The Role of Inflammation and Neurodegeneration

In about 10–15 % of patients, the disease starts and evolves with a primary progressive (PP) course. PPMS leads patients to disability acrretion and rapid brain and spinal cord tissue volume loss, with little inflammation visible by MRI.14 Cumulatively, MS presents with two different components (inflammation and neurodegeneration) of variable duration over time within individual patients. An initial phase of inflammation ultimately fades into an ominous and occult neurodegenerative process that leads patients to irreversible disability. At any stage of the disease, the two components may overlap and may be regulated by a complex, yet unknown, interplay. The relationship between inflammation and neurodegeneration in MS is one of the most complicated in medical science and likely regulated by a number of genetic, immunologic and environmental factors as yet unknown to clinicians and scientists.
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Numerous drugs have been tested and proven to be effective in defeating or at least controlling the inflammatory phase of MS, with little or unknown independent effect on the neurodegenerative component. IFNβ-1b belongs to this group of drugs.

Clinical and Imaging Parameters to Measure Disease Progression and Drug Efficacy in Multiple Sclerosis

Clinical Measures
The main clinical metrics used thus far for measuring IFNβ-1b’s effect in MS are:

- relapse rate;
- proportion of relapse-free patients;
- severity of relapse;
- disability progression according to the Expanded Disability Status Scale (EDSS);\(^9\)°
- proportion of patients free from EDSS change; and
- change in MS functional composite (MSFC) score.\(^9\)°

The meaning of clinical relapses was clarified earlier in this article. With respect to severity, the following measures are considered indicative of disease severity:

- extent of functional recovery;
- need to use steroid medication and/or hospitalize the patient; and
- number of days of hospitalization.

Numerous clinical scales are used to measure physical, cognitive and emotional disability of MS patients. Nevertheless, the ones commonly employed thus far are the EDSS and the MSFC scale.

The EDSS scale ranges from 0 to 10 with 0.5-step increases and quantifies MS-induced disability in the pyramidal, cerebellar, brainstem, sensory, bowel, bladder, visual and cerebral functional systems. EDSS steps 1 to 4.5 are indicative of MS patients who have independent walking ability. EDSS steps 5 to 9.5 are defined by severe impairment to ambulation. A sustained progression is defined as any change ≥1 for EDSS scores ≤5 and any change ≥0.5 for EDSS scores ≤5.5. The variables most commonly used to identify drug effects are: the proportion of patients who remain free from disability progression over three- or six-month time windows; time to sustained disability progression; group- and/or within-person differences over time in median EDSS scores.

The MSFC is a 3D scale that measures cognitive function, leg function/ambulation, arm/hand motor and co-ordination functions. The scale produces values that are translated into z-scores in reference to normative values. These scores are used for group comparisons or within-person comparison over a set time period.

Imaging Measures
The use of MRI provides a number of measurable disease parameters by means of which disease progression can be monitored. This is achieved with the use of conventional and non-conventional MRI techniques.\(^9\)°

Conventional MRI techniques include T1-w and T2-w spin echo images. They permit the identification and computation of acute and chronic WM lesions (see details later). These measures are currently mostly employed in clinical trials. WM lesion identification and computation is a sensitive method for assessing disease progression and at the same time is highly reproducible across different centers. Non-conventional MRI techniques allow one to obtain quantitative measurements of brain and spinal cord normal-appearing WM (NAWM), normal-appearing GM and lesions. One such technique is magnetization transfer imaging (MTI). Quantities derived from MTI, namely magnetization transfer ratios (MTRs), are considered to indirectly reflect the amount of demyelination and axonal loss within visible lesions as well as in regions of normal-appearing tissue and lesions.

Compared with conventional MRI techniques, non-conventional ones offer several challenges when one attempts their application in large multicenter clinical trials. First, scanning time may considerably increase. Second, results may suffer inter-center variability, therefore being poorly reproducible. Third, sophisticated image post-processing may be required for some of the non-conventional techniques, rendering their application in large clinical trials unpractical. To date, besides limited applications, which will be discussed later in the course of this review, no studies have attempted to investigate the effects of IFNβ-1b on MRI quantities derived from measurements on normal-appearing tissue and lesions.

A third image technique that is considered a non-conventional MRI technique but reflects the application of advanced post-processing analysis in conventional sequences, is the measurement of brain volume and its changes over time. Such a measurement is achieved by quantifying the so-called brain parenchyma fraction (BPF). This is given by the ratio of the sum of the WM and GM volumes over the volume of the entire brain, i.e. \(\frac{\text{WM}+\text{GM}}{\text{WM}+\text{GM}+\text{CSF}}\). The concept behind the application of BPF is that as the ventricles enlarge due to brain tissue shrinkage, the BPF decreases. BPF measurements have been successfully applied in large clinical trials.\(^9\)°

Types of Study Design
Different types of study design have been used in MS to detect the effect of IFNβ-1b. Study type depends upon two main factors:

- the number of subjects needed to treat in order to detect a significant effect on the chosen primary outcome measure; and
- ethical motivations that over time limit the possibility of assigning patients to the placebo control arm.

Two main types of study designs have been used to identify the effect of IFNβ-1b in MS thus far: randomized controlled trials (RCTs) and baseline versus therapy (BVT) studies.

Randomized Controlled Trials
In RCTs patients are randomly allocated to the ‘intervention’ or placebo group and both investigators and patients are blind with respect to the compounds administered. This type of study design provides important data regarding the efficacy of IFNβ-1b compared with placebo in reducing the number and severity of clinical relapses as well as newly-formed lesions on MRI.
RCTs led to the approval of IFNβ-1b by regulatory agencies for medical drugs and devices worldwide. They were subsequently slightly modified by substituting the placebo with another approved disease-modifying therapy. This type of ‘active comparator’ study allows the superiority of IFNβ-1b versus other standard-of-care or experimental compounds to be measured.

Baseline versus Therapy Studies
A BVT study is where each patient receives exposure to the drug after a natural history evaluation period. The main advantages offered by this type of study versus the RCTs are:

- each patient serves as his/her own control, thus minimizing the effect of inter-patient variability in measuring drug effect; and
- it generally requires a smaller number of subjects.

However, at the same time, BVT studies eliminate the blinding component of the RCT, thus potentially introducing the so-called Pygmalion type of bias. In MS, studies of this led to the initial identification of IFNβ-1b’s efficacy in decreasing the number of active lesions or CELs within individual patients.

Presently, in patients with MS, placebo-controlled trials can still ethically be prepared, but with restrictions. Specifically, for MS patients for whom established effective therapies exist, placebo-controlled trials should only be offered with rigorous informed consent if the patients refuse any of the existing therapies, have not responded to them, or if these treatments are not available for other reasons, such as cost.19

Interferon Beta-1b Effects on Clinical and Imaging Disease Parameters
This section discusses the effects of IFNβ-1b on clinical and imaging measures of disease seen in the main clinical trials. Clinical and imaging findings will be presented separately. For each type of finding, evidence obtained in each patient subgroup, i.e. CIS, RRMS and SPMS with and without superimposed relapses and PPMS, is discussed.

In the majority of clinical trials and post-marketing studies, IFNβ-1b has been administered at a dosage of 8 million international units, equivalent to 250 μg, subcutaneously, every other day (EOD). For the purpose of this review, this dosage is always referred to as the standard dose unless otherwise indicated. In addition, when specifying the purposes of this review, this dosage is always referred to as the standard dose unless otherwise indicated. In addition, when specifying the purpose of this review, this dosage is always referred to as the standard dose unless otherwise indicated.

Disability Progression
When one looks at the effect of a given drug in reducing disability progression, two important considerations need be kept in mind. First, disability changes during therapy might be linked to the indirect effect of a given drug in reducing the number and severity of clinical relapses, thereby leading to slower or lower accumulation of disability over time. Second, changes in disability might be due to a direct effect of the drug in promoting faster and more efficient remyelination or relenting demyelination. This will favor slower and less pronounced disability accumulation independently from the effect of reducing clinical relapse.

Compared with placebo, 250 μg subcutaneous IFNβ-1b EOD over a two-year time period significantly reduced the proportion of patients experiencing a sustained progression in disability among those with CIS, RRMS and SPMS with superimposed relapses.20,21 As seen with relapse rate, 250 μg was superior to 50 μg administered EOD.21 but was not inferior to the following subcutaneous regimens for remaining free from disability progression or having relevant beneficial changes in EDSS during therapy: 500 μg IFNβ-1b EOD,21 22 μg IFNβ-1a once weekly22 and 44 μg IFNβ-1a three times per week.23 Interestingly, on measures of disability progression by EDSS scores, 250 μg subcutaneous IFNβ-1b EOD
Superimposed relapses 28 or in those with PPMS. It is important to note that in an attempt to understand the long-term effect of IFN-β on MS, few studies have looked at the effect of IFN-β-1b on MSFC score. Over a two-year observational period, a significant improvement in MSFC score was seen in patients with CIS, a non-significant MSFC score improvement was seen between early- and late-treated patients after five years. Interestingly, such improvement was driven by the cognitive component of MSFC score that, more than any other component, may be affected by patient training.

In an attempt to understand the long-term effect of IFN-β-1b in MS patients (i.e. beyond five years) following completion of the pivotal trial, 372 RRMS participants were contacted by physicians and enrolled in a 16-year survey. Of the 372 patients initially enrolled, 260 (69.9% of the original group) had EDSS evaluations after 16 years of follow-up. These patients were taking various medications, as recommended by their physician. Although there is no statistical analysis in this long term follow-up, descriptive results indicate that continuous administrations of 250 μg IFN-β-1b tended to reduce the proportion of patients converting to SPMS and progressing to an EDSS >6. Conversely, patients who were exposed to 50 μg IFN-β-1b progressed faster and more frequently to SPMS and were more likely to end up with an EDSS score >6.

Imaging Measures

Magnetic Resonance Imaging Measures of Active Inflammation

In addressing the question of whether IFN-β-1b has an effect on blood–brain barrier (BBB) breakdown and inflammation, one should consider two important pathogenetic points. First, it is crucial to investigate and assess whether IFN-β-1b or any other given drug can prevent BBB breakdown. Such an assessment permits the anti-inflammatory and immunomodulating property of a given drug to be established. Second, it is important to examine the ability of IFN-β-1b to halt the WM changes preceding CEL occurrence before BBB breakdown and, later, promoting faster and better CEL recovery. The latter would ultimately provide evidence of the indirect effects of IFN-β-1b as neuroprotective agent.

With respect to the effect of IFN-β-1b before BBB breakdown, two main imaging outcome measures have been used thus far, namely number of CELs in T1-w post-contrast MRI and number of newly-formed lesions in T2-w images. From a statistical stand-point, defining new lesions as either active T2-lesions or CELs as MRI end-point does not seem to be substantially different for monitoring MRI activity in MS clinical trials. However, biologically, the advantage of CELs over newly-formed T2-lesions is given by the fact that CELs directly visualize the BBB breakdown while newly-formed T2-lesions may be only an indirect harbinger of an ongoing inflammatory process or inflammation that has occurred previously.

The effect of IFN-β-1b on CELs has not been investigated in all clinical trials, mainly due to the cost of studying this. Monitoring CEL activity not only adds the costs of the contrast agent itself to the study, but also requires numerous monthly scans that certainly further increase costs. The effect of IFN-β-1b beyond BBB resolution and quality of inflammatory activity has only been assessed sporadically. This has been carried out by obtaining pre-therapy versus therapy-phase but also treated versus untreated patient comparisons in:

- the proportion of CELs converting into PBHs;
- the size of CELs formed during the different pre-therapy and therapy- phases; and
- the evolution of CEL by MTR measurements.

Interferon Beta-1b Effect on Lesion Quantity

That IFN-β-1b reduces the number of CELs, newly-formed and growing T2-lesions over a two-year time period has been extensively demonstrated in large RCTs performed in patients with CIS, RRMS, SPMS with and without superimposed relapses and PPMS. Such an effect was preserved on a yearly basis for up to four years in CIS patients, five years in RRMS patients, and four years in SPMS patients. The effect of 250 μg IFN-β-1b administered subcutaneously EOD on T2-lesions was similar to that of 500 μg subcutaneous IFN-β-1b EOD or 20 mg subcutaneous GA daily.
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Using both a fixed and a random effect model to investigate the distribution of active T2-lesion reduction over a three-year follow-up of SPMS patients with superimposed relapses, it has consistently been shown that between-patient response to IFN-β1b in T2-lesion reduction is highly heterogeneous. Reduction in T2 lesions account for only 57 % of the of the treatment’s effect on disability progression and 68 % of the effect on relapse rate reduction. Patients receiving treatment had >65 % chance of showing ≥60 % T2-lesion reduction but also a 7 % probability that there would be no reduction or even an increase in T2-lesion size.

When looking at the results of the small open-label BVT studies performed thus far, IFN-β1b administrations significantly decreased the number of new and total CELs for up to 19 months of follow-up. Similarly, a significant overall reduction in monthly CEL frequency was detected during therapy phases of 18 months (see Figure 3A) and 36 months (see Figure 3B) in comparison to a natural history phase of equal time.

As seen for the distribution of active T2-lesion reduction in SPMS, individual variability and month-to-month fluctuations in drug effects were also noted in these small studies, which relied upon CEL counting. Specifically, ≥60 % reduction in CEL activity was achieved and remained constant over three years in slightly more than 50 % of patients. An additional 13.7 % of individuals had a 60 % reduction in CEL activity after less significant changes initially. The remaining patients never reached ≥60 % reduction in CEL frequency.

Interferon Beta-1b Effect on Contrast-enhancing Lesion Quality

To evaluate the effect of IFN-β1b on CEL quality, several imaging measures were considered. The first such measure was the proportion of CELs evolving into PBHs. Studies performed by the National Institutes of Neurological Disorders and Stroke (NINDS) group on RRMS patients yielded contradictory findings depending on the group of patients studied. In a 72-month open-label BVT study performed on six patients with RRMS, patients were observed to have a significantly reduced likelihood of forming PBHs from CELs forming during therapy than during the pre-therapy phase. No similar significant effect was observed in a shorter 36-month follow-up study including 10 MS patients (eight RRMS and two with SPMS).

The ability of IFN-β1b to reduce the likelihood of PBH formation from CELs in RRMS has recently been confirmed by Filippi and colleagues in a large RCT whereby patients were assigned to receive either IFN-β1b or GA. The drugs were found to be equally significantly effective in protecting patients against PBH formation during therapy. Conversely, when patients with SPMS and superimposed relapses were examined, Brex and colleagues failed to find any significant decrease in the proportion of CELs converting into PBHs 18 months later compared with placebo. A more extensive and detailed description of IFN-β1b reducing the likelihood of CEL progression to PBH has been reported by the NINDS group.

A second imaging marker used to identify the effect of IFN-β1b on CEL quality is CEL size. The size of a given CEL is known to be an indirect indicator of the underlying disease pathology. Larger CELs have a greater tendency to evolve into PBHs, have lower MTRs and tend to be present in SPMS more than in RRMS patients. A relatively large study performed in the NINDS group during a short-term (six-month) time window, has shown that the effect of IFN-β1b in reducing the likelihood of CEL formation is not paralleled by its ability to reduce the size of CELs once formed. IFN-β1b reduced the number of CELs by 76.4 % over 18 months of therapy. This decrease however, was statistically greater for small lesions enhancing only once during therapy (82.3 %) than for larger ones enhancing multiple times (57.4 %).

A third imaging measure used to reliably track CEL evolution over time and investigate the ability of IFN-β1b to promote faster recovery is monthly measurements of MTR. The effect in CEL MTR is rather limited. As early as 12 months before the occurrence of enhancement, MTR starts to decrease. Such a pre-lesional decrease in MTR is not affected by IFN-β1b. In addition, the extent of CEL MTR recovery over time appears to be more evident if steroids are used in association with IFN-β1b.

Magnetic Resonance Imaging Measures of Neurodegeneration

In addressing the question of whether IFN-β1b has an effect on imaging measures of neurodegeneration, two important measures need to be considered. First, one should keep in mind measures of focal chronic lesions, such as lesion volume (LV) in T1-w (i.e PBHs) and T2-w images. Second, one should consider the effect of IFN-β1b in measures of global brain and spinal cord degeneration. These measures include brain volume loss (or BPF changes), whole-brain MTR, NAWM-MTR and cervical cord area measurements at the level of the second cervical vertebra or C2.

Interferon Beta-1b Effect on Focal Chronic Lesions

The role of IFN-β1b in reducing T2-LV is accompanied by a dual component. First, changes in T2-LV may reflect changes in chronic T2-lesions present prior to therapy. Second, those changes may only reflect the effect of the drug on newly formed lesions. In general, as previously stated, patients receiving 250 μg subcutaneous IFN-β1b EOD tend to form fewer new lesions (as seen in T2-w images). As a result, the difference in total T2-LV between treated and untreated patients at the end of the study may reach statistical significance. Such results were seen in patients with CIS, RRMS, PPMS with and without superimposed relapses, and in those with PPMS. Interestingly, in patients with CIS and RRMS, group differences remained significant throughout years four and five, respectively. As stated earlier, however, these results do not necessarily imply that IFN-β1b affects, by decreasing their size, the number of chronic lesions in T2-w images present at the time of the therapy start. Similarly, when one looks at the LV of PBHs, there are no reports to date that have sought to determine the role of IFN-β1b in preventing the formation of new PBHs or in decreasing the quantity of pre-existing PBHs, separately. Kappos and colleagues measured the volume of PBHs in CIS patients on therapy with IFN-β1b for up to five years and failed to demonstrate a drug effect. Conversely, Barkhof and colleagues measured the PBH volume changes over a three-year observation period in a subgroup of 95 patients with SPMS and superimposed relapses and found that the IFN-β1b-treated group had a significantly slower accumulation of PBHs at 36 months. These results were confirmed by Montalban and colleagues, who performed the same type of analysis in a cohort PPMS patients treated for 24 months with the same therapy regimen. O’Connor and colleagues found the same
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Interferon Beta-1b Effect on Global Disease—Brain Parenchyma Fraction and Magnetization Transfer Ratios

The reduction of brain atrophy accumulation over time with IFNβ-1b is controversial. At variable observational time periods, no significant differences in loss of brain volume were seen in treated versus untreated CIS (five years),29 SPMS with superimposed relapses (three years)20 or PPMS (two years).20 Conversely, IFNβ-1b seemed to protect the brain from atrophy better than GA in patients with RRMS.22 Similarly, over a three-year time period, an open-label study conducted in RRMS patients showed that IFNβ-1b successfully decreased brain volume loss with respect to pre-therapy phase.21

As seen with BPF, no significant effect of the whole brain and NAWM regions was seen to be exerted in MTR by IFNβ-1b in SPMS patients with superimposed relapses or PPMS after three and two years of therapy, respectively. Finally, no significant changes in spinal cord area measurements were seen to be exerted by IFNβ-1b in treated versus untreated patients over the course of two years of therapy.21

The effect of IFNβ-1b in reducing neurodegeneration, as measured by brain atrophy, is still being debated and is controversial. When visible, such an effect has been shown to be dependent on two main factors: time and the CEL-status of the patient. With respect to time, it is hypothesized that in the short term, IFNβ-1b may induce accelerated, non-tissue-related brain volume loss (i.e. pseudoatrophy) due to the reduction of CELs and inflammation-related edema.18,20 The actual biologic substrate of the effect of IFNβ-1b in reducing brain atrophy accumulation may become visible later on, once the edema is resolved.

With respect to CEL patient status, controversies and uncertainties still dominate. Exploratory subgroup analyses of the SPMS cohort of treated patients indicated that patients without CELs prior to therapy had a significantly greater reduction in cerebral volume in the placebo group compared with those with CELs prior to therapy. There was a trend towards greater reduction in cerebral volume, however, if the patient was on therapy. Although those differences did not reach a statistically relevant threshold, the trend suggests that in untreated patients no relation exists between inflammation and neurodegeneration. Conversely, when patients are taking IFNβ-1b, the reduction in inflammatory activity is paralleled by halting of brain volume loss. Similarly, monthly MRI analyses of individual RRMS cases performed in the NINDS group have shown that a decrease in the accumulation of brain atrophy is generally associated with decreases in the number of CELs.22

The fundamental question unanswered by all these studies is to what extent reduction in brain atrophy accumulation is merely sustained by CEL reduction or whether there is an additional effect independently exerted by IFNβ-1b. To this end, two patients who exemplify the complexity of the relationship between inflammation and neurodegeneration when IFNβ-1b is active are discussed here (see Figure 4). Both patients were monitored monthly with six MRIs prior to therapy and 12 MRIs during the first 12 months of therapy and one MRI at year 10 of therapy. The patient represented in Figure 4A–C had a substantial (≥60 % decrease) monthly decrease in CEL number, but his atrophy progressed at a rate of -0.55 % yearly. Such a progression rate is similar

in RRMS patients.21 With respect to the latter study, it is interesting to highlight that 250 μg subcutaneous IFNβ-1b EOD had a superior effect on T2-lesions but not on T1-lesions compared with 20 mg subcutaneous GA administered daily.21 In previous open-label BVT observational studies performed at the National Institutes of Health, a decrease in the number of PBHs forming de novo during therapy has been shown. Nevertheless, the longevity of PBHs arising during the natural history phase is no shorter than those formed during therapy. Consequently, according to these findings, the ability of IFNβ-1b to promote the formation of less aggressive CELs or a faster recovery over time should be questioned.21

The actual biologic substrate of the effect of IFNβ-1b in reducing brain atrophy accumulation may become visible later on, once the edema is resolved.
to that observed in untreated MS patients. Over the 10-year follow-up period, he shifted from RRMS to SPMS with an EDSS increase of 3.5 (from 2.5 to 6). Conversely, the patient in Figure 4D–F was not an optimal CEL responder during the first year of therapy but her atrophy progressed at a rate of -0.33 % per year, which is similar to what is observed in healthy subjects. Over the 10-year treatment period, her disease remained RRMS and she had an EDSS increase of 0.5 (from 1 to 1.5).

**Interferon Beta-1b Side Effects, Tolerability, and Resistance**

IFNβ-1b is a relatively well-tolerated drug. Its side effects are generally manageable with temporary drug discontinuation, although drug discontinuation is rarely necessary due to side effects. The most common side effects include lymphopenia, injection-site reaction, flu-like syndrome, headache, pain and thyroid dysfunctions.

Very few patients exhibit depression and suicidal ideas. Compared with IFNx, which circulates for longer than IFNβ-1b in the blood, depression does not occur de novo in patients treated with IFNβ-1b. Despite this, care needs to be taken in those patients with depressive symptoms prior to therapy, since these patients may exhibit suicidal ideas as therapy starts. This topic is only briefly expanded upon, since numerous extensive reviews and post-marketing studies have been compiled on the topic.36,38,39 Specifically, it is recommended that readers consult an important long-term (16-year) follow-up study on the safety and tolerability of IFNβ-1b very recently published40 and several informative reports on the effect of IFNβ-1b on the quality of life of MS patients.36,38,41 Today there is class III evidence that RRMS patients taking IFNβ-1b 50 µg or 250 µg subcutaneously EOD for up to five years, with subsequent unspecified treatment, have fewer deaths after 16 years of follow-up than similar patients on placebo for up to five years, with subsequent unspecified treatment.

An important aspect associated with therapy with IFNβ-1b is the development of neutralizing antibodies (NABS). NABS may occur after as little as six months of therapy and persist for a few years. Whether NABS are the cause or epiphenomenon of therapy failure is still a controversial question that, similarly to the topic of side effects, has been extensively debated in the literature.36,38,39

**Conclusions**

IFNβ-1b is one of the most widely used and effective therapies for preventing disease progression in MS. Despite this, several uncertainties remain in the clinical community regarding the actual therapeutic potential of IFNβ-1b. Undoubtedly, the combined effort of basic and clinical scientists is warranted to provide insights into the several still-unanswered questions.

**Interferon Beta-1b Beside Blood–Brain Barrier Breakdown**

Both imaging and clinical evidence thus far prove that when the inflammatory component of MS still plays the major visible pathogenetic role, IFNβ-1b seems to have a key effect in preventing the occurrence of new flares. However, the effect of IFNβ-1b on neurodegeneration and disability accretion remains controversial. In addition, it is unclear whether the effect of IFNβ-1b in halting neurodegeneration progress is independent of its indirect effect on inflammation or is an epiphenomenon. Studies designed to elucidate this topic have never been conducted and are certainly warranted.

**Interferon Beta-1b Before Blood–Brain Barrier Breakdown and Beyond its Resolution**

Limited and discouraging evidence is available on the (in)ability of IFNβ-1b to affect NAWM pre-lesional or outside-lesion MRI quantities. Further knowledge on such topic would ultimately allow one to understand:

- to what extent IFNβ-1b alters the disease course before CELs become visible; and
- the need to treat patients without visible CELs.

Serial imaging studies in large patient cohorts examining the effect of IFNβ-1b on the changes occurring in NAWM before a lesion develops and once its enhancement resolves are crucial.

**Interferon Beta-1b and Gray-matter Disease**

No evidence exists thus far on the role of IFNβ-1b in affecting focal and diffuse GM disease in MS. Lack of such knowledge impedes elucidation of the neuroprotective properties of the drug. Nowadays, numerous quantitative and non-quantitative MRI techniques are available to identify part of the cortical lesions and topographically measure selective damage to the GM. Using these techniques in the context of clinical trials is the next step.

**Interferon Beta-1b Beyond Clinical Relapses and Physical Disability**

Although the effect of IFNβ-1b in decreasing the occurrence of new clinical relapses and relenting physical disability progression is established, no evidence is available on its ability to halt other disease-associated symptoms. Among these symptoms, cognitive and emotional disability play a substantial role in affecting the life of MS patients. Exploring the interplay between IFNβ-1b and these symptoms is hence crucial in order to define the actual potential of the drug.

Current knowledge yields the conclusion that in patients with MS, IFNβ-1b partially affects the quantity of disease but probably leaves its quality unaltered. Conversely, quality of disease leads patients to irreversible disability as much as, if not more than, its quantity.

The combined effort of clinicians and basic scientists is required to disentangle this topic, which will ultimately permit understanding the role of IFNβ-1b, if any, in the complex interplay between inflammation and neurodegeneration in MS.
Multiple Sclerosis

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