Interferon-β Treatment for Multiple Sclerosis

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Summary: Multiple sclerosis (MS) is the leading nontraumatic cause of neurologic disability in young adults. Interferon-β, approved for use in 1993, was the first treatment to modify the course and prognosis of the disease and remains a mainstay of MS treatment. Numerous large-scale clinical trials in early, active patient populations have established the clinical efficacy of interferon-β in reducing relapses and delaying disability progression. Although its mechanism of action remains incompletely understood, a reduction in active lesions seen on magnetic resonance imaging implies primary anti-inflammatory properties, a mechanism supported by basic immunologic research. Variation in individual patient responsiveness to interferon-β may be due to disease variability or differential induction of interferon-stimulated genes. The magnitude of the therapeutic effect appears to be similar among products, but the optimal dose, route, and frequency of administration of the drug remain uncertain. **Key Words:** interferon, multiple sclerosis, clinical trials.

INTRODUCTION

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system (CNS) characterized in its early stages by repeated autoimmune attacks incited by an as yet undiscovered trigger. With an estimated 400,000 individuals affected in the United States, and 2.5 million worldwide, it is the leading cause of nontraumatic disability in young adults.[1] Although MS was described well by Charcot[2] in the 1800s, effective disease-modifying therapies have been commercially available for just over a decade. Interferon-β was the first of these treatments to become available and remains the most widely prescribed disease-modifying therapy for MS today.

INTERFERON USE IN MULTIPLE SCLEROSIS

Interferon-β is a relatively small protein (approximately a tenth the size of immunoglobulin G), which exerts its complex effects by inducing a multitude of genetic and metabolic processes.[3] First described in 1957, interferon was named for its ability to interfere with the process of viral replication.[4] Early work profiling the immune response in the CSF of MS patients determined that the antibody response resembled that seen in response to a viral infection.[5] Although no causative virus was identified, it was known that endogenous lymphocyte interferon production was deficient in MS,[6] leading to the idea that exogenously delivered interferon might correct this deficit. Interferon was postulated to reduce IgG synthesis through a direct effect on plasma cells, while simultaneously modulating natural killer cell activity. These potential combined anti-inflammatory and antiviral mechanisms made interferon an attractive agent for MS clinical trials based on theories of MS pathogenesis.

All three human interferons (α, β, and γ) have been investigated in preliminary work. Interferon-γ was found to induce exacerbations in a pilot study, a discovery that led to its recognition as a cytokine endogenously responsible for inflammatory activity in MS.[7] Interferon-α was investigated through Phase III trials, but failed to provide the sustained benefit on relapse rate that interferon-β did.[8]

In 1982, Jacobs et al.[9] published the first report of interferon-β (delivered intrathecally) reducing relapse rates in patients with active relapsing MS. Despite debate about whether systemically administered interferons cross the blood–brain barrier (or need to, to exert their therapeutic effect), clinical trials of systemically administered interferon-β followed, and these established the efficacy of interferon-β in reducing relapse rates and slowing disease progression in relapsing–remitting MS.

MECHANISM OF ACTION

The biologic mechanisms by which interferon-β exerts its therapeutic effect in MS remain incompletely

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understood. From clinical trials in the various stages of the disease, however, we know that the most potent disease-modifying effects of the drug occur when it is used in the earliest, predominantly inflammatory stages of MS. As the disease shifts from predominantly inflammatory to predominantly degenerative in later stages,[10] the ability of interferon to slow disease progression appears to be less. These facts imply a largely anti-inflammatory mechanism of action.

The immunomodulatory mechanisms of interferon-β are multifaceted.[11] Generally, interferon-β inhibits the proliferation of T lymphocytes and reduces the production of proinflammatory cytokines, shifting the cytokine response from an inflammatory Th1 response to a favorable Th2 type.[12] Specifically, it is known to modulate the expression of major histocompatibility antigens, reduce the production of interferon-γ, increase both intracellular and CSF levels of interleukin-10, and lead to a decrease in interleukin-12 levels.[13,14]

Interferon-β reduces the migration of inflammatory cells across the blood–brain barrier, seen as a rapid decrease in gadolinium-enhancing lesions.[15] This is likely accomplished by indirectly reducing the quantity of functional endothelial adhesion molecules (ICAM and VCAM)[16] and by downregulating the production of chemokines and matrix metalloproteinases,[14] all of which decrease the ability of T lymphocytes to transmigrate across the blood–brain barrier.

The variability in therapeutic response to interferon across individuals suggests a differential effect based on either genetics or disease heterogeneity. In responders, a favorable response to interferon appears to be associated with reduced interferon-γ levels and decreased T cell proliferation after beginning therapy.[17,18] It is hypothesized that interferon-β acts by inducing gene expression, specifically through a large set of interferon-stimulated genes, and that the magnitude or pattern of interferon-stimulated gene induction determines an individual's response to the interferon-β. This hypothesis has led to a search for biomarkers which, if used clinically, might be useful in identifying interferon responders early in treatment.[19] Tumor necrosis factor-related apoptosis inducing ligand (TRAIL) shows sustained upregulation in interferon responders and has been proposed as one such biomarker.[20]

PHARMACOKINETICS AND PHARMACODYNAMICS

Parenterally administered interferon-β exerts its therapeutic effect through receptor binding and subsequent modulation of gene transcription, events that require a sustained exposure over time (multiple doses, over months to years) to achieve a clinical benefit. Serum concentrations of interferon-β after a single dose, whether administered intramuscularly or subcutaneously, peak at 12–16 hours after administration, then decline with an elimination half-life of ~10 hours.[21] The pharmacodynamic profile of interferon-β is commonly assessed by measuring the serum concentrations of neopterin, β2-microglobulin, or the antiviral protein MxA. These endogenous proteins are interferon-induced gene products that serve as useful biologic response markers.[22] After a single intramuscular dose of interferon-β1a, the serum concentration of neopterin reaches its peak at ~36 hours, plateauing between 36 and 72 hours and then steadily declining (although neopterin remains somewhat elevated, compared with baseline, as far out as 12 days after the dose).[21]

Although a single dose of interferon-β has measurable molecular effects *in vivo*, such traditional single-dose pharmacokinetic and pharmacodynamic studies are less relevant than in nonbiologic therapeutics, where achieving a steady-state serum concentration of drug is the goal. With biologic therapeutics, it is less clear how these traditional pharmacologic parameters relate to therapeutic response. Dynamic variables such as drug–protein binding, patient genetic heterogeneity, and the production of neutralizing antibodies contribute heavily to the determination of therapeutic efficacy in long-term use. These complex interactions are best investigated through well-designed clinical trials.

EVIDENCE FROM CLINICAL TRIALS OF INTERFERON-β

With an average clinical trial duration of 2 years, in a disease that affects patients over the course of their lives, most clinical trials of interferon-β have selected only highly active patients, to optimize the chances of finding a treatment effect on relapse rate or disability progression. In the pivotal trial of interferon-β1b, for example, the mean number of relapses for study participants was 3.4 in the 2 years before study enrollment.[23] Mean disease duration of the same patients was 2.9 years. Generalizing results from the early, highly active patients enrolled in studies to the larger MS population must therefore be done with caution. It is also difficult to generalize the clinical benefit measured during a 2-year clinical trial of interferon-β to its long-term use and benefit.

Relapsing–remitting MS

The pivotal trials of the different preparations of interferon-β (TABLE 1) in relapsing–remitting MS (RRMS) all used a randomized, double-blind, placebo-controlled design (TABLE 2).

The results of the pivotal phase III trial of subcutaneous IFNβ1b (Betaseron; Bayer Healthcare, Berlin, Germany) were published in 1993.[23] In this trial, 372 patients with RRMS were randomized to receive placebo, 1.6 mIU, or 8 mIU interferon-β1b subcutaneously every

TABLE 1. *Characteristics of Interferon-β Products and Comparison to Naturally Occurring Human Interferon-β*

	Natural Human Interferon	Recombinant Interferon β-1a	Recombinant Interferon β-1a	Recombinant Interferon β-1b
Trade name in U.S.A.	n/a	Avonex	Rebif	Betaseron
Route of administration	n/a	Intramuscular injection	Subcutaneous injection	Subcutaneous injection
Abbreviation	n/a	IFNβ1a-IM	IFNβ1a-SC	IFNβ1b
Synthesized in	Human fibroblasts	CHO cell line	CHO cell line	*Escherichia coli*
Number of amino acids	166	166	166	165
Sequence changes		None	None	Serine for cysteine at position 17
Glycosylated	Yes, human	Yes, nonhuman	Yes, nonhuman	No
Binding to serum albumin	Weak	Weak	Weak	Strong

CHO = Chinese hamster ovary.

other day. The primary endpoint, annual relapse rate, was 34% lower in the 8-mIU group. Magnetic resonance imaging (MRI) endpoints showed even greater benefits, with a 58% decrease in the active lesion rate per year. There was a dose–response effect on clinical and MRI outcomes (FIG. 1), but no effect on disability progression was noted, even after 5 years.[24]

The MS Collaborative Research Group study (MSCRG) randomized 301 patients to receive either IFNβ1a-IM (Avonex; Biogen Idec, Cambridge, MA) or placebo by intramuscular injection once weekly.[25] The primary endpoint in this study was time to onset of disability progression, sustained for at least 6 months. Enrollment began in November 1990.

After approval of IFNβ1b in 1993, ethical and logistical concerns related to continuing the MSCRG trial of IFNβ1a-IM were raised. Because the dropout rate (3%) was less than expected (10%), and because of the nature of the time-to-progression primary outcome measure, sufficient statistical power existed to analyze the results. When the trial was stopped, 172 participants (57%) had accrued 104 weeks of follow-up. The time to sustained Expanded Disability Status Scale (EDSS) progression was longer in the treatment group than in the placebo group ($P = 0.02$). The probability of disability progression was 21.9% in the treatment group, compared with 34.9% in the placebo group, a 37% relative decrease. The benefit on relapses appeared to be greater in participants who completed 104 weeks on the study (rate ratio = 0.68), compared with all participants (rate ratio = 0.82). This difference remains unexplained.

The Prevention of Relapses and Disability by Interferon-β1a Subcutaneously in Multiple Sclerosis study (PRISMS) randomized 560 patients to receive placebo, or IFNβ1a-SC (Rebif; Merck Serono, Geneva, Switzerland) 22 μg or 44 μg, by subcutaneous injection three times per week.[26] There was no stipulation for relapse stability before enrollment, so it is possible that some participants were in the recovery phase of a relapse at study entry.

The primary outcome measure (relapse count) was reduced in both treatment arms, compared with placebo, and the effect was similar to that seen in the IFNβ1b and IFNβ1a-IM studies (FIG. 2). The number of MRI T2-active lesions was lower in both the low-dose (67%) and high-dose (78%) groups, compared with placebo. Benefits on MRI outcomes were more pronounced for the 44-μg dose (FIG. 1). Time to confirmed progression of disability, sustained for 3 months, was delayed in the 22-μg group (risk ratio for progression = 0.68, 95% CI = 0.48–0.98) and the 44-μg group (risk ratio = 0.62, 95% CI = 0.43–0.91). At the end of 2 years, participants in the placebo arm were rerandomized to receive either 22 μg or 44 μg of IFNβ1a-SC.[27] Four years after enrollment, participants who were initially treated with placebo showed reductions in relapse count and MRI activity, but their time to sustained disability progression was shorter than that for participants treated with 44 μg throughout the entire study, indicating that the benefits observed after 4 years are greater with continuous rather than delayed treatment.[28]

Clinically isolated syndromes

Clinically isolated syndrome (CIS) refers to an initial demyelinating event that is suggestive of MS. These typically include optic neuritis, partial transverse myelitis, and brainstem demyelination. Patients who eventually go on to develop RRMS often have MRI evidence of prior, clinically silent demyelinating lesions, which

TABLE 2. *Phase III Studies of Interferon-β in Relapsing–Remitting Multiple Sclerosis (MS): Study Design Characteristics and Results*

	IFN-β1b (Betaseron)	MSCRG IFN-β1a (Avonex)	PRISMS IFN-β1a (Rebif)	OWIMS (Rebif)
Design	Randomized, double-blind, placebo-controlled	Randomized, double-blind, placebo-controlled	Randomized, double-blind, placebo-controlled	Randomized, double-blind, placebo-controlled
Inclusion criteria				
MS diagnosis	Definite MS	Definite MS	Definite MS	Definite MS
Course	RR course	RR course	RR course	RR course
Age, yr	18–50	18–55	—	18–50
EDSS	≤5.5	1.0–3.5	0–5.0	0–5.0
Relapse	≥2 (in previous 2 yr)	≥2 (in previous 3 yr)	≥2 (in previous 2 yr)	≥1 (in previous 2 yr)
Treatment				
Agent, dose	IFN-β1b, 1.6 mIU; IFN-β1b, 8 mIU; placebo	IFN-β1a, 30 μg; Placebo	IFN-β1a, 22 μg; IFN-β1a, 44 μg; placebo	IFN-β1a, 22 μg; IFN-β1a, 44 μg; placebo
Route	Subcutaneous	Intramuscular	Subcutaneous	Subcutaneous
Frequency	Every other day	Weekly	2× per week	Weekly
Primary outcome	Annual relapse rate, proportion relapse-free	Time to EDSS progression ≥ 1.0 point, EDSS sustained 6 months	Relapse count	Number of combined unique active lesions at 24 weeks
Result				
Relapse	34% relative reduction (8 mIU)	32% relative reduction (completing 104 weeks); 18% relative reduction (all participants)	33% reduction (22 μg 3× per week); 37% reduction (44 μg 3× per week)	No reduction (22 μg weekly); 19% reduction (44 μg weekly), NS
Disability progression	No effect	Relative risk of progression sustained for 6 months = 0.63	Relative risk of progression sustained for 3 months = 0.68	Not reported
MRI lesions	58% reduction in active lesions	50% reduction in enhancing lesion number	78% reduction (44 μg 3×/wk); 67% reduction (22 μg 3×/wk)	29% reduction (22 μg weekly); 53% reduction (44 μg weekly) in number of combined unique active lesions

EDSS = Expanded Disability Status Scale score; MRI = magnetic resonance imaging; NS = nonsignificant.

strongly predict evolution to clinically definite RRMS following the initial clinical event.[29] Studies were undertaken to determine if disease-modifying therapies are effective at slowing the disease at this earliest stage, for the first time including lesions on cranial MRI as a study inclusion criterion (TABLE 3).

The Controlled High-Risk Subjects Avonex MS Prevention Study (CHAMPS) enrolled 383 patients with a CIS and abnormal MRI consistent with demyelination.[30] Patients received standard treatment with intravenously administered methylprednisolone for their CIS, and were randomized to receive 30 μg IFNβ1a-IM or placebo once weekly within 27 days of onset of the CIS. After a planned interim analysis at 22 months demonstrated a decreased rate of clinically definite MS (CDMS), the trial was terminated. The cumulative probability of developing MS was 35% in the treated group and 50% in the placebo group, resulting in a rate ratio of 0.56 (95% CI = 0.38–0.81, $P = 0.002$). At 18 months, the IFNβ1a-IM group had fewer new or enlarging lesions, and fewer gadolinium enhancing lesions ($P < 0.001$). Benefits were similar regardless of the type of initial event, sex, age, and baseline T2 lesion volume on MRI. Roughly half the patients from each arm chose to receive open-

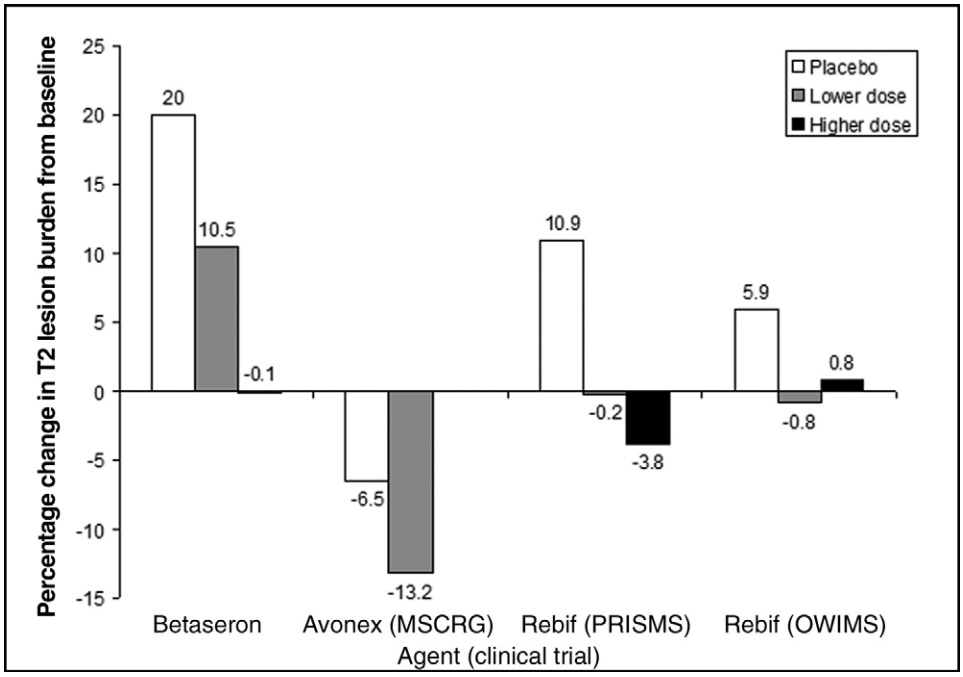

FIG. 1. Effect of interferon-β on T2 lesion burden in the pivotal RRMS trials.

label IFNβ1a-IM for three additional years as part of the Controlled High Risk Avonex Multiple Sclerosis Prevention Study in Ongoing Neurologic Surveillance study (CHAMPIONS).[31] At 5 years after initial randomization, the incidence of CDMS remained significantly lower in the early treatment group (36 ± 9%) than in the delayed treatment group (49 ± 10%).

The Early Treatment of Multiple Sclerosis study (ETOMS) randomized 308 patients within 3 months of CIS onset, each of whom had cranial MRI consistent with demyelination, to receive 22 μg IFNβ1a-SC or placebo once weekly for 2 years.[32] Clinically definite MS developed in 34% of the treatment arm and 45% of the placebo arm over 2 years (odds ratio = 0.52, 95% CI = 0.31–0.86, $P = 0.047$). The treated group also had a smaller increase in T2-lesion burden ($P = 0.002$).[33]

The Betaseron in Newly Emerging Multiple Sclerosis for Initial Treatment study (BENEFIT) randomized 487 patients to receive either IFNβ1b 250 μg or placebo subcutaneously in a 5:3 ratio.[34] Enrollment was permitted up to 60 days after onset of the first clinical event, and dose titration was performed over the first 16 injections to optimize tolerability of the treatment. The use of a standardized steroid treatment for the CIS was at the discretion of the investigator.

After 2 years, the probability of developing CDMS was 28% in the treatment group and 45% in the placebo group (hazard ratio HR = 0.50, 95% CI = 0.36–0.70, $P < 0.0001$), with a number-needed-to-treat (NNT) to prevent one case of CDMS over 2 years estimated to be 5.9. MRI measures supported treatment with interferon, with lower numbers of T2 and enhancing lesions in the treatment arm over the 2 years in patients treated with interferon. As of 2007, a 5-year open-label follow-up study of patients on treatment is ongoing.

Secondary progressive MS

Approximately 85% of patients advance to secondary progressive MS (SPMS), in which irreversible, steady progression of neurologic disability is present, with or without superimposed relapses.[35] Less robust effects have been observed for interferon-β in this stage of the disease. Especially in later stages of SPMS, there appears to be a dissociation of inflammatory disease activity and the development of physical and cognitive disability,[10] lessening the likely therapeutic potential of immune-modulating treatments such as interferon-β.

Five large-scale clinical trials have evaluated the effect of interferon-β in SPMS (TABLES 4 and 5). Inclusion criteria were similar but not identical. All focused on measuring the sustained progression of disability.

The European Interferon-β1b study randomized 718 patients with definite SPMS to receive 8 mIU IFNβ1b or placebo subcutaneously every other day.[36] Time to disability progression, measured by EDSS, was prolonged in the IFNβ1b group (726 days), compared with the placebo group (549 days, $P = 0.0008$). The proportion of patients experiencing progression was 21.7% lower in the treated group ($P = 0.003$) over the 2.5-year average follow-up.

The North American Interferon-β1b study randomized 939 patients with definite SPMS to receive IFNβ1b 8 mIU total dose, IFNβ1b 5 mIU/m^2, or placebo subcutaneously every other day for 3 years.[37] There was no difference between the treatment groups in time to con-

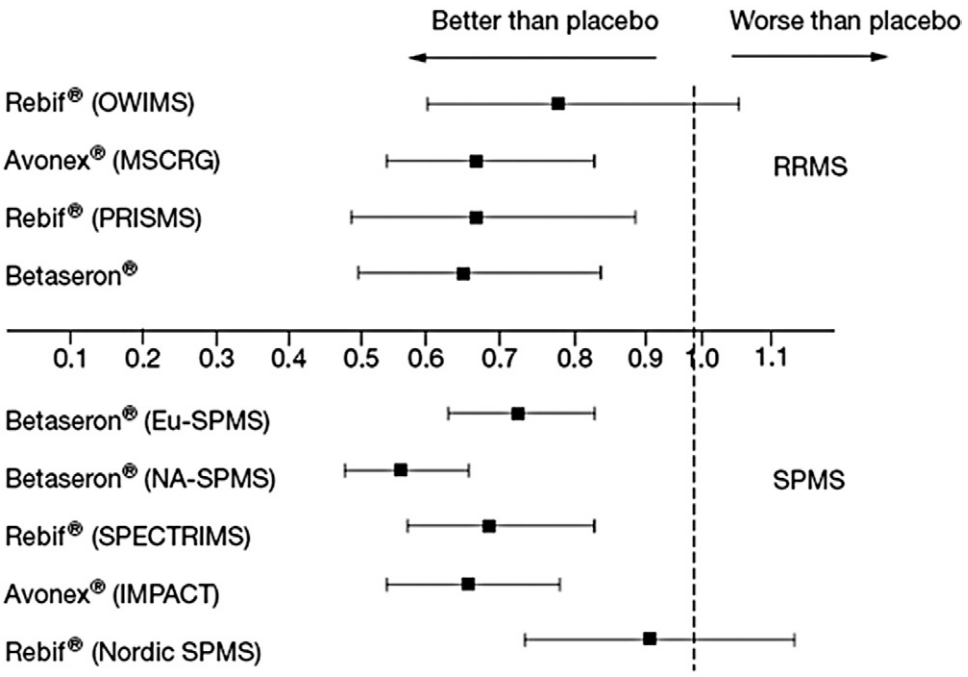

FIG. 2. Randomized controlled trials of interferon-β in multiple sclerosis: rate ratios and 95% CIs for annual relapse rates for highest dose studied. All data are for 2-year observations. Data are presented for the trials in relapsing–remitting multiple sclerosis (RRMS; *top*) and secondary progressive multiple sclerosis (SPMS; *bottom*). Rate ratios < 1 indicate a beneficial effect of active treatment compared with placebo. Rate ratios were <1 for all studies. The studies are: Eu-SPMS, European Secondary Progressive Multiple Sclerosis; IMPACT, International Multiple Sclerosis Secondary Progressive Avonex Clinical Trial; OWIMS, Once Weekly Interferon-β1a for Multiple Sclerosis; MSCRG, Multiple Sclerosis Collaborative Research Group; NA-SPMS, North American Secondary Progressive Multiple Sclerosis; PRISMS, Prevention of Relapses and Disability by Interferon-β1a Subcutaneously in Multiple Sclerosis; and SPECTRIMS, Secondary Progressive Efficacy Trial of Recombinant Interferon-β1a in MS. Reproduced with permission of Nature Publishing Group from Marrie RA, Rudick RA; Drug insight: interferon treatment in multiple sclerosis; Nat Clin Pract Neurol 2006;2:34–44.

firmed EDSS progression ($P = 0.71$); after a planned interim analysis, the trial was terminated early, for futility. A post hoc meta-analysis of the two IFNβ1b trials indicated that patients in the European SPMS study were younger and with shorter disease duration, more prestudy and on-study relapses, and greater MRI activity. The authors suggested that SPMS patients with either rapid disability progression or continuing relapse activity may be more likely to benefit from interferon treatment.[38]

The Secondary Progressive Efficacy Trial of Recombinant Interferon-β1a in Multiple Sclerosis study (SPECTRIMS) randomized 618 patients to receive 22 μg or 44 μg of IFNβ1a-SC or placebo subcutaneously three times per week for 3 years.[39,40] Although there was no significant effect on progression of EDSS, there was a small but significant benefit for relapse reduction.

The Nordic Secondary Progressive Multiple Sclerosis study (Nordic SPMS) randomized 371 patients to receive 22 μg of IFNβ1a-SC or placebo subcutaneously once weekly, a dose not previously tested in RRMS.[41] The trial was terminated early, after the release of the negative SPECTRIMS result, with the partial results revealing no difference in relapse rate or disability progression.

The International Multiple Sclerosis Secondary Progressive Avonex Clinical Trial (IMPACT) randomized 426 patients with definite SPMS to receive 60 μg IFNβ1a-IM or placebo intramuscularly once weekly for 24 months.[42] The primary outcome measure was change in the MS Functional Composite score (MSFC), an outcome measure that combines three domains: upper arm and hand function, cognition, and ambulation; it is expressed as a composite *Z*-score.[43] Two-year worsening in MSFC was reduced by 40.4% ($P = 0.033$) in the treatment arm; this was attributable largely to preservation of upper extremity function as measured by the nine-hole peg test. There was a significant reduction in relapses, but no difference between groups in the progression of EDSS. The MSFC may thus be a more sensitive measure of disability progression than the EDSS. Results from IMPACT did not achieve regulatory agency approval.

In summary, interferon-β is effective in reducing relapses in SPMS, and may have a very modest effect in slowing disability progression, mainly in early SPMS with active brain inflammation. Younger patients and those who still have superimposed relapses or active MRI lesions are most likely to benefit from treatment.

Primary progressive MS

Primary progressive MS is characterized by the gradual accumulation of physical disability, without super-

TABLE 3. *Studies of Interferon-β in Clinically Isolated Syndrome: Study Design Characteristics and Primary Outcomes*

	CHAMPS (Avonex)	ETOMS (Rebif)	BENEFIT (Betaseron)
Design	Randomized, double-blind, placebo-controlled	Randomized, double-blind, placebo-controlled	Randomized, double-blind, placebo-controlled
Inclusion criteria			
Age, yr	18–50	18–40	18–45
Clinical	First-ever optic neuritis, partial transverse myelitis, brainstem, or cerebellar event	First neurologic event suggestive of MS, plus abnormal neurologic exam	First-ever monofocal or multifocal CNS event suggestive of MS
Imaging	≥2 clinically silent lesions, at least 3 mm, with one being periventricular or ovoid	(a) ≥4 white matter lesions on T2WI or (b) three white matter lesions plus one infratentorial or enhancing lesion	≥2 clinically silent lesions (≥3 mm), with one being periventricular, ovoid, or infratentorial
Randomization equalized by imaging burden?	Yes	No	Yes
Permitted treatment delay	14 days to steroids, 27 days to randomization	3 months	60 days
Treatment	IVMP for 3 days plus oral taper; Avonex 30 μg i.m. weekly	IVMP for moderate or severe exacerbations plus Rebif 22 μg once weekly	IVMP (at discretion of investigator) plus Betaseron 250 μg every other day
Primary outcome	Development of CDMS at 3 years	Development of CDMS at 2 years	Development of CDMS at 2 years
Result	Rate ratio = 0.56	Odds ratio = 0.61	Hazard ratio = 0.50

CDMS = clinically definite MS; IVMP = intravenous methylprednisolone.; T2WI = T2 weighted magnetic resonance imaging.

imposed relapses.[35] As already established from work in SPMS, interferon-β appears to be most effective in reducing the frequency of relapses, with a less robust effect on disability in the absence of relapses. One study randomized 50 patients with primary progressive MS to receive standard (30 μg) or high-dose (60 μg) IFNβ1a-IM once weekly.[44] The high-dose group experienced an unacceptable incidence of flu-like symptoms and liver enzyme elevations, as well as an accelerated rate of brain atrophy. There was no effect on the primary outcome measure of EDSS progression in either group; however, patients receiving 30 μg IFNβ1a-IM once weekly had a significantly lower rate of T2 lesion accumulation than those receiving placebo.[44]

Pediatric MS

Currently available interferon-β products have been systematically tested and approved only in adult populations. Experience in the pediatric population (ages 6–18) has recently been documented by several groups.[45–50] Safety was the primary focus of these studies, and although there are reports of incidental adverse events, adult doses appear to be well tolerated if started on an initial titration schedule. Some doses used in these studies vary empirically, based on the size of the child, ranging from one-third to full adult dose.

Efficacy data from these safety studies, though not the primary intent of the trials, indicated partial reduction in relapses and MRI activity similar to the adult population. Definitive efficacy trials for interferon-β in pediatric MS are lacking. Nonetheless, disease-modifying therapy (including interferon-β) is increasingly being used to treat children diagnosed with definite MS and ongoing clinical or MRI disease activity, given the potentially devastating long-term effects of brain inflammation in MS.[51]

Neuromyelitis optica

Neuromyelitis optica, or Devic's disease, is an entity pathogenetically distinct from MS and is primarily antibody-mediated.[52] Clinical signs include longitudinally extensive spinal cord lesions and bilateral optic nerve demyelination often resulting in blindness. Although the rarity of this disease precludes prospective randomized trials, interferon therapy for neuromyelitis optica has been found to be ineffective in small studies,[53] and in some cases detrimental.[54] Disease modification in neuromyelitis optica currently relies upon the empiric use of chronic steroids with or without azathioprine, and intermittent plasma exchange or intravenous immunoglobulin.

SIDE EFFECTS OF INTERFERON-β

The most frequently reported side effects of interferon-β are flu-like symptoms, which may include mus-

TABLE 4. *Studies of Interferon-β in Secondary Progressive MS: Study Design Characteristics*

	Eu IFN-β1b (Betaseron)	NA IFN-β1b (Betaseron)	SPECTRIMS (Rebif)	IMPACT (Avonex)	Nordic SPMS (Rebif)
Inclusion criteria					
Dx, course	Definite MS, SP	Definite MS, SP	Definite MS, SP	Definite MS, SP	Definite MS, SP
Age, yr	18–55	18–65	18–55	18–60	18–65
EDSS	3.0–6.5		EDSS 3.0–6.5 (and Pyramidal Functional System Score ≥ 2)	3.5–6.5	<7.0
Relapse	≥2 relapses or EDSS increase ≥1.0 step in previous 2 years	EDSS increase ≥1.0 step in previous 2 years	EDSS increase ≥1.0 step in previous 2 years	Progression in previous year	EDSS increase ≥1.0 step in previous 4 years or ≥0.5 step for EDSS 6.0–6.5
Treatment	IFN-β1b (8 mIU) or placebo, s.c., every other day	IFN-β1b (8 mIU) or IFN-β1b (5 mIU/m^2) or placebo, s.c., every other day	IFN-β1a (44 μg) or IFN-β1a (22 μg) or placebo, s.c., 3×/week	IFN-β1a, 60 μg placebo IM weekly	IFN-β1a (22 μg) or placebo, s.c., weekly
Primary Outcome	Time to EDSS progression: 1.0 step for EDSS 3.0–5.5 or 0.5 step for EDSS 6.0–6.5 sustained 3 months	Time to EDSS progression: 1.0 step for EDSS 3.0–5.5 or 0.5 step for EDSS 6.0–6.5 sustained 6 months	Time to EDSS progression: 1.0 step for EDSS 3.0–5.5 or 0.5 step for EDSS 5.5–6.5 sustained 3 months	2-year change in MS Functional Composite score	Time to EDSS progression: 1.0 step for EDSS <5.5 or 0.5 step for EDSS ≥5.5 sustained 3 months

Dx = diagnosis; EDSS = Expanded Disability Status Scale score; Eu = European; NA = North American; SP = secondary progressive.

cle aches, fever, chills, headache, and back pain. These symptoms tend to appear from 2 to 8 hours after an injection, and resolve within 24 hours. The incidence of flu-like symptoms is ~50% for interferon-β1a[55,56] and ~75% for interferon-β1b.[57] Gradual titration of dose over the first 3–4 weeks of therapy, premedicating with acetaminophen or nonsteroidal anti-inflammatories, and giving the injection at bedtime are strategies that reduce the incidence of constitutional side effects.[58]

Injection-site reactions (pain, erythema, inflammation) are most common in the subcutaneously administered products, with an initial incidence of 85–92% that decreases with time.[56,57] The incidence of injection-site reactions in IFNβ1a-IM is <10%.[55] Although skin reactions tend to be mild, isolated cases of severe injection-site reactions (involving infection or necrosis) have been reported with IFNβ1a-IM, and occur with an incidence of ~3% with IFNβ1a-SC and ~5% with IFNβ1b.[59] Rotating and precooling injection sites, along with vigilant use of sterile technique, limits the frequency of injection-site reactions.[59]

Hepatotoxicity is a concern that warrants periodic surveillance of liver function tests prior to and after starting interferon-β. The mechanism appears to vary by patient, and is either dose-dependent or idiosyncratic, related to immune-mediated or metabolic mechanisms.[60] Alanine aminotransferase elevation is the most common laboratory testing liver function abnormality reported, with a de novo elevation occurring in approximately one-third of patients receiving any interferon-β preparation.[61] The dose frequency correlates with the probability of developing liver function abnormalities; therefore, the frequency of such abnormalities associated with IFNβ1a-IM is somewhat lower than with the more frequently dosed subcutaneous preparations.[61] The incidence of symptomatic abnormalities (presenting as jaundice) are fortunately rare.

Strategies used to deal with asymptomatic elevations of liver transaminases include dose reduction, laboratory testing surveillance, and temporary or permanent discontinuation of therapy, based on clinical judgment. Symptomatic or WHO Grade III elevations (>5 times the upper limit of normal) likely require discontinuation of therapy and hepatology evaluation.

TABLE 5. *Studies of Interferon-β in Secondary Progressive MS: Outcomes and Results*

	Eu IFN-β1b (Betaseron)		NA IFN-β1b (Betaseron)			SPECTRIMS (Rebif)			IMPACT (Avonex)		Nordic SPMS (Rebif)	
Outcome	PLC	8 mIU	PLC	8 mIU	5 mIU/m^2	PLC	22 μg	44 μg	PLC	30 μg	PLC	22 μg
Confirmed progression, %	54	45*	37	37	44	65	60	59	27	26	38	41
Relapse-free, %	36	43*	62	71*	67*	37	42*	44*	63*	74*	62	61
No new or enlarging T2 lesions, %	16	36*	31	30*	44*	24	36*	41*	42	63*	62	61
Median change in MSFC, %									−0.096	−0.16*		

MSFC = MS Functional Composite score; PLC = placebo.
*$P < 0.05$.

CHOOSING AMONG INTERFERON-β REGIMENS

Evidence exists for a therapeutic effect on reducing relapses and delaying disability for all the currently available interferon products in MS. There is a great deal of similarity in short-term efficacy data among products, and the ideal product and dosing scheme is still not agreed upon. Subtle differences among products and regimens may help guide therapeutic decisions.

Head-to-head comparison studies

There have been two prospective, randomized controlled trials comparing different interferon products.

The Independent Comparison of Interferon study (INCOMIN) was a comparison of RRMS patients randomized to receive IFNβ1b 250 μg every other day (n = 96) or IFNβ1a-IM 30 μg once weekly (n = 92) for 2 years.[62] The population recruited was similar to those in the pivotal trials of interferon-β: age 18–50 years, EDSS 1–3.5, and at least two relapses in the previous 2 years.

More participants remained relapse-free in the IFNβ1b group (51%) than in the IFNβ1a-IM group (36%) (rate ratio = 0.76, 95% CI = 0.59–0.9, P = 0.03). MRI results were similar to the clinical results, with 55% of IFNβ1b patients remaining free of new T2 lesions, compared with 26% of those treated with IFNβ1a-IM (rate ratio = 0.6, 95% CI = 0.45–0.8, $P < 0.0003$) over the study period. However, patients in the IFNβ1a-IM group had a greater lesion burden and more enhancing lesions on MRI prior to the start of the trial, as well as being older, with a longer disease duration and later age at diagnosis.

Another potential confounder of INCOMIN was that neither patients nor the clinical investigators conducting the assessments were blinded to treatment group. Blinding is especially crucial to reducing Type I error in clinical trials of MS therapeutics where patients and treating physicians may assume that more frequent treatments confer a greater therapeutic effect.[63] Also notable is that the proportion of IFNβ1b patients who remained relapse-free in INCOMIN was higher than in the phase III study (51 *vs* 31%), but the proportion of IFNβ1a-IM patients remaining relapse-free in INCOMIN was lower than in its pivotal trial. These discrepancies and lack of blinding make the results of INCOMIN difficult to generalize to the MS patient population.

The Evidence for Interferon Dose Response: European-North American Comparative Efficacy study (EVIDENCE) enrolled 677 patients to be followed for up to 48 weeks after being randomized to receive IFNβ1a-SC 44 μg three times per week (SC/TIW) or IFNβ1a-IM 30 μg once weekly (IM/OW). The primary endpoint was the proportion relapse-free after 6 months, although patients were followed for nearly a year (48 weeks). Clinical assessors but not patients were blinded to treatment assignment. The percentage of relapse-free patients over 6 months was higher in the SC/TIW group (75%) than in the IM/OW group (63%) over the first 6 months, and patients in the SC/TIW group also had fewer active MRI lesions over 6 months than did those in the IM/OW group.

An independent analysis of the data found that among patients who were relapse-free at 24 weeks, the proportion remaining relapse-free at 48 weeks was nearly identical in the two treatment arms, suggesting attenuation of the differential effect after 6 months.[64] Although the results of EVIDENCE are seemingly straightforward, application to the clinical setting is complicated, because IFNβ1a-SC was associated with higher frequency of neutralizing antibodies and adverse reactions, and advantages of treatment beyond 6 months were not demonstrated.

An extension study to EVIDENCE followed participants continuing on IFNβ1a-SC, as well as those initially assigned to IFNβ1a-IM who were willing to switch to IFNβ1a-SC for the extension phase.[65] Of the patients initially assigned to IFNβ1a-IM, 223 switched to IFNβ1a-SC (73%) and were followed (along with 272,

TABLE 6. *Percentage of Patients Exhibiting Positive Titers of Neutralizing Antibodies in Major Clinical Trials of Interferon-β*

Agent (Study)	Trade Name	Average Follow-Up	Dose	Route	Frequency	Antibodies, %
IFNβ1a (CHAMPS)	Avonex	22 months	30 μg	IM	Once weekly	2
IFNβ1a (EVIDENCE)	Avonex	48 weeks	30 μg	IM	Once weekly	2
IFNβ1a (EU dose comparison)	Avonex	3 years	30 μg	IM	Once weekly	2.3
IFNβ1a (IMPACT)	Avonex	2 years	60 μg	IM	Once weekly	3.3
IFNβ1a (EU dose comparison)	Avonex	3 years	60 μg	IM	Once weekly	5.8
IFNβ1a (INCOMIN)	Avonex	2 years	30 μg	IM	Once weekly	6
IFNβ1a (MSCRG)	Avonex	2 years	30 μg	IM	Once weekly	22
IFNβ1b (INCOMIN)	Betaseron	2 years	250 μg	SC	Every other day	22
IFNβ1b (NA-SPMS)	Betaseron	3 years*	250 μg	SC	Every other day	23
IFNβ1b (EU-SPMS)	Betaseron	3 years	250 μg	SC	Every other day	27.8
IFNβ1b (BENEFIT)	Betaseron	2 years	250 μg	SC	Every other day	29.9
IFNβ1b (NA-SPMS)	Betaseron	3 years*	160 μg/m^2	SC	Every other day	32
IFNβ1b	Betaseron	3 years	250 μg	SC	Every other day	45
IFNβ1b	Betaseron	3 years	50 μg	SC	Every other day	47
IFNβ1a (OWIMS)	Rebif	24 weeks	22 μg	SC	Once weekly	5.3
IFNβ1a (PRISMS)	Rebif	2 years	44 μg	SC	Three times per week	12.5
IFNβ1a (SPECTRIMS)	Rebif	3 years	44 μg	SC	Three times per week	14.7
IFNβ1a (OWIMS)	Rebif	24 weeks	44 μg	SC	Once weekly	16.3
IFNβ1a (SPECTRIMS)	Rebif	3 years	22 μg	SC	Three times per week	20.6
IFNβ1a (PRISMS)	Rebif	2 years	22 μg	SC	Three times per week	23.8
IFNβ1a (EVIDENCE)	Rebif	48 weeks	44 μg	SC	Three times per week	25
IFNβ1a (ETOMS)	Rebif	2 years	22 μg	SC	Once weekly	ND
IFNβ1a (Nordic SPMS)	Rebif	3 years*	22 μg	SC	Once weekly	ND

IM = intramuscular; ND = not determined; SC = subcutaneous.
*Terminated early.

or 91%, of those initially assigned to IFNβ1a-SC) for an average of 32 additional weeks. The post-transition relapse rate was 26% lower in the IFNβ1a-SC group and 50% lower in the initial IFNβ1a-IM group. An overall decrease in relapse rates in both groups suggests regression to the mean.

Willingness to switch treatments infers an a priori expectation that the new treatment will be more powerful, or some dissatisfaction with the prior treatment, which further complicates interpretation. Indeed, initial IFNβ1a-IM patients who chose to enter the extension were less likely to be relapse-free, with higher preswitch relapse counts than their counterparts who did not switch.

The INCOMIN and EVIDENCE trials compared products with multiple variables, including preparation, total dose, administration frequency, and route of administration, so it is difficult to make any conclusions about which of these individual variables contribute to clinical responsiveness.

The European Dose Comparison Study compared two doses of a single product (IFNβ1a-IM, 30 *vs* 60 μg) administered in the same fashion.[66] The study enrolled 802 patients with RRMS or SPMS using a randomized, double-blind design and found no difference in EDSS progression or number of new T2 lesions after 36 months or during the 1-year extension. Thus, there is no evidence that 60 μg is more effective than the standard 30 μg weekly IFNβ1a-IM dose.

Neutralizing antibodies

One factor that relates to differential efficacy among patients is development of neutralizing antibodies (NAbs) targeted against the interferon-β molecule. NAbs occur commonly as a complication of biologic therapies. They interfere with receptor binding and with receptor-mediated biological responses. The presence of interferon-β NAbs reduces the bioavailability of interferon-β and the biological response to injections, although the clinical consequences of this have remained controversial.[67]

NAb titers have been measured in all major clinical trials of interferon-β (TABLE 6). Increasing titers have been correlated with reduced efficacy on relapse rate and MRI endpoints in a number of these and other trials.[27,68–70] Patients in the European Dose Comparison Study who developed NAbs experienced greater EDSS progression (mean change of 0.89) than those who remained NAb-negative (mean change of 0.29) over 48 months ($P = 0.001$). Post hoc analysis of the PRISMS study indicated that NAb-positive patients experience greater disability progression.[71]

In shorter trials, the effect of NAb status on relapse rate and disability progression is less apparent, although

the effect on MRI measures remains evident.[72] This is probably multifactorial. First, the clinical efficacy of interferon-β is modest. Demonstrating significant attenuation of a modest effect requires large sample sizes, a situation that predisposes to false negative results. The consistent observable effect of NAbs on MRI lesions occurs because the effect size on MRI measures is approximately double the relapse effect. Second, the difficulty observing clinical correlates of NAbs may be due to the kinetics of interferon-β NAbs, which do not appear until the second half of the first treatment year and are most prevalent at 12–18 months into treatment.[73] Thus, the impact of interferon-β NAbs on efficacy may emerge only during the second year of a clinical trial, and so would be diluted by data from the first year. These two factors have undoubtedly led to an underappreciation of the importance of interferon-β NAbs.

The development of NAbs appears to be highly variable and dependent on the patient and on the specific product, preparation, and dosing schedule used. In general, the overall rate of NAb development associated with the once-weekly recombinant interferon-β1a intramuscular injection appears to be lower than that for more frequently dosed subcutaneous interferon-β preparations.

Although an international panel recently determined that insufficient evidence exists to officially recommend the practice of measuring NAbs in patients on treatment,[74] many experts in the field routinely measure and use NAb status to guide their choice of therapy in patients suboptimally responding to treatment.

Effect on brain atrophy

Brain atrophy measured on MRI is a sensitive and reproducible measure of irreversible tissue destruction in MS. Early accumulation of brain atrophy has been shown to correlate with physical disability,[75] and brain atrophy measures are now common secondary outcome measures in MS clinical trials.[76]

In the pivotal trial of IFNβ1a-IM, whole-brain atrophy was measured using the brain parenchymal fraction method in 68 patients randomized to interferon-β1a and 72 patients randomized to placebo.[77] There was a 55% reduction in brain atrophy (−0.233% in IFN, compared with −0.521% in placebo) seen with interferon therapy in the second year of therapy, but no effect during the first year. Analysis of a subgroup that underwent frequent MRIs during the first year of a separate trial of IFNβ1a-IM showed that 68% of the first-year brain parenchymal fraction decrease occurred during the first 4 months of treatment. This suggests that anti-inflammatory mechanisms and resolution of edema contribute to a sort of pseudoatrophy soon after starting interferon therapy.[78]

A large-scale randomized trial of IFNβ1a-SC dosed 22 μg once weekly showed a beneficial effect on whole-brain atrophy, an effect seen after 2 years of treatment.[33] The rate of brain parenchymal volume decrease for patients on placebo was −0.83% during the first year and −0.67% during the second year. Respective values for treated patients were −0.62 and −0.61%, with a treatment effect seen after 2 years ($P = 0.0031$).

By contrast, a post hoc analysis of the initial phase III trial of the same medication with more frequent and higher dosing in 519 patients with RRMS found no effect from three times per week IFNβ1a-SC on brain atrophy progression between treatment groups over 2 years.[79] In a post hoc analysis of an open-label, randomized dose comparison trial of IFNβ1a-SC (11 *vs* 33 μg subcutaneously, three times per week) in 52 patients with RRMS, there was a significant decline in brain volume in both dosage groups during the 2 years of the study, and no difference in change in brain volume between doses.[80]

Data collected over three years in an open-label study of IFNβ1b in 30 patients with RRMS showed a delayed reduction in cerebral atrophy rates over time within a group of patients treated with IFNβ1b.[81] No placebo group was included, so patients served as their own controls. Brain volumes at baseline (taken as the average of 6 monthly measures prior to study entry) decreased 1.35% during the first year of the study (an average of 12 monthly measurements), then remained relatively stable during the second and third years of follow-up.[81] A trial of IFNβ1b in 95 patients with SPMS[82] showed no significant treatment effect overall on cerebral volumes, but the authors did identify a significant effect in the subgroup of patients who had gadolinium-enhancing lesions at study entry.

Thus, once-weekly interferon-β appears to limit the rate of brain atrophy in RRMS and CIS, an effect that is confounded during the first year by resolution of brain edema and inflammation. Beneficial effects of three times per week or every-other-day interferon-β on limiting the rate of brain atrophy have not been observed.

Proposed mechanisms by which interferon-β may limit brain atrophy include limiting immune-mediated destructive inflammation,[83] increasing nerve growth factors,[84] or limiting toxic mechanisms such as pathologic iron deposition.[85]

LONG-TERM DATA ON INTERFERON EFFICACY

Scientific justification for the widespread use of interferon-β in humans was based upon the efficacy established in the phase III trials discussed above, each with a duration of 1–3 years. Given the demonstrated short-term benefits of interferon use in MS, long-term placebo-

controlled trials are ethically difficult to justify. There remains a gap in our knowledge of whether the beneficial effects seen in the pivotal trials of these medications predict long-term benefits, and whether and how the timing of therapy (early or late within the course of the disease) modulates that effect. Open-label, long-term follow-up studies, though not ideal, aid in our understanding of these effects.

An 8-year follow-up of 172 patients completing 2 years in the pivotal IFNβ1a-IM trial was conducted to determine the long-term effects of initial assignment to placebo or IFNβ1a-IM 30 μg once weekly.[86] A larger proportion of patients in the original placebo group (42%, compared with 29% in the treatment group) advanced to an EDSS $\geq$ 6 by the 8-year follow-up—even though a higher percentage of patients in the initial placebo group were on disease-modifying therapies over the 6-year open-label interval—indicating a lasting advantage of early treatment.

In a 2-year extension of the pivotal trial of IFNβ1a-SC titled PRISMS-4, patients in one of the two initial treatment groups (22 μg or 44 μg SC/TIW) remained blinded and patients in the initial placebo group were rerandomized to one of the two treatment arms.[27] Time to sustained disability progression was prolonged by 18 months in the group treated with 44 μg SC/TIW, relative to all patients untreated for the initial 2 years (P = 0.047). Relapse rate and measures of MRI lesion burden were also higher in the group initially assigned to 2 years of placebo. These results suggest advantages to early treatment, in that the group initially assigned to placebo consistently lagged behind the treatment group despite being on the same treatment for the second half of the study. After 8 years of follow-up after the PRISMS study, a trend to reduction in reliance on a unilateral walking aid was observed in the early treatment group, but the magnitude of this effect was small.[87] New data are emerging that suggest early and consistent treatment with interferon-β may have important effects on survival and disease progression over as many as 16 years.[88]

A recent observational study used propensity score weightings to adjust survival curves in determining the long-term effects of interferon treatment.[89] The investigators followed over 1500 patients with RRMS (1103 treated with interferon-β and 401 untreated) for up to 7 years. Patients treated with interferon-β experienced a significantly lower rate of conversion to SPMS (HR = 0.38, 95% CI = 0.24–0.58, $P < 0.0001$), and a lower incidence of progression to EDSS 6.0 (requiring unilateral walking assist) (HR = 0.60, 95% CI = 0.38–0.95, $P < 0.03$). Treatment with interferon-β was associated with a delay of 3.8 years in conversion to SPMS and 2.2 years before reaching EDSS = 6. This study suggested long-term benefits on disease progression with interferon-β treatment.

CONCLUSION

The development of interferon-β has proven to be a major advance in MS therapeutics, benefiting thousands of patients worldwide. There is strong evidence that in RRMS, treatment with interferon-β reduces relapse frequency and slows disability progression significantly. In patients with a clinically isolated syndrome, treatment with interferon-β delays the occurrence of a second event and onset of definite MS. Patients with early SPMS, especially those who still experience relapses, may also benefit from treatment. We are just now beginning to understand how the interferon-β effect on MRI measures correlates with clinical results, and how short-term clinical and imaging variables may predict long-term outcomes.

Beneficial effects are tempered by the fact that injections of interferon-β are both expensive and inconvenient. Many attempts have been made to weigh the relative costs of untreated MS against the cost of interferon injections.[90–94] These attempts are difficult because of the heterogeneity of the MS patient population and innumerable costs of a disease that disables young people in the prime of their lives. For such patients, an imperfect therapy with partial benefit is useful—but not ideal. Future understanding of factors that predict which patients are interferon responders should aid in the informed selection of therapy on an individual basis, and MRI can help to measure that response to therapy. There is a great need for new treatments with a more complete therapeutic effect, but given its track record and relative safety, interferon-β remains a mainstay of MS therapy into the foreseeable future.

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