Interferons in the Treatment of Multiple Sclerosis

A Clinical Efficacy, Safety, and Tolerability Update

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Interferon beta (IFNβ) was the first disease-modifying therapy available to treat multiple sclerosis (MS), providing patients with a treatment that resulted in reduced relapse rates and delays in the onset of disability. Four IFNβ drugs are currently approved to treat relapsing forms of MS: subcutaneous (SC) IFNβ-1b, SC IFNβ-1a, intramuscular IFNβ-1a, and, most recently, SC peginterferon beta-1a. Peginterferon beta-1a has an extended half-life and requires less frequent administration than other available treatments (once every 2 weeks vs every other day, 3 times per week, or weekly). Large randomized controlled clinical trials have confirmed the efficacy of interferons for the treatment of relapsing MS. The most frequent adverse events in patients receiving IFNs include injection site reactions and flu-like symptoms. Patient education and mitigation strategies are key to managing these adverse events and supporting therapy adherence. With fewer injections needed, peginterferon beta-1a is associated with less frequent discomfort, which may translate to improved adherence, a major factor in treatment efficacy. Because the available interferon therapies differ in administration route and frequency of injection, switching among these therapies may be a viable option for patients who experience issues with tolerability. Although a variety of disease-modifying therapies are now available to treat relapsing MS, the efficacy and long-term safety profile of interferons make them an important first-line option for treatment. *Int J MS Care.* 2020;22:165-172.

Before the 1990s, treatment for multiple sclerosis (MS) largely comprised the management of relapses, primarily with systemic corticosteroids, and short-term management of symptoms.[1] The first two injectable interferon beta (IFNβ) therapies were approved in 1993 and 1996 and allowed clinicians to offer patients with MS a longer-term therapy designed to modify the course of the disease. Since then, the therapeutic landscape has expanded to include new drug targets and other disease-modifying therapies (DMTs), affording more treatment options. However, many patients continue to benefit from interferon therapy, experiencing reduced relapse rates and delayed disability.[2] A large body of data supports the long-term efficacy and safety of interferons for reducing the relapse rate, slowing disability worsening, and decreasing the number of central nervous system (CNS) lesions.[3-5] The role of interferons as the foundation of MS treatment is further evidenced by their use as active comparators in clinical trials evaluating newer MS therapies.[6,7]

Five IFNβ drugs are currently approved for the treatment of relapsing forms of MS: subcutaneous (SC) IFNβ-1b (Betaseron; Bayer HealthCare Pharmaceuticals Inc, and Extavia; Novartis Pharmaceuticals Corp), SC IFNβ-1a (Rebif; EMD Serono Inc), intramuscular (IM) IFNβ-1a (Avonex; Biogen Inc), and SC peginterferon beta-1a (Plegridy; Biogen Inc) (Table 1).[8-12] The US Food and Drug Administration approved the first four therapies before 2002 and approved peginterferon beta-1a in 2014.[8-12] The addition of this new formulation and dosing schedule necessitates reopening a dialogue regarding the IFNβs. Herein we provide a brief overview of the efficacy, safety, and tolerability of interferons for the treatment of MS, with an emphasis on newer clinical

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Table 1. Interferon beta therapies FDA approved for treatment of relapsing-remitting multiple sclerosis[8-12]

Drug	Trade name	Year of FDA approval	Route of administration	Dosing	Frequency	Pharmacokinetics
Interferon beta-1b	Betaseron	1993	Subcutaneous	0.25 mg	Every other day	$t_{½}$: 5 h T_{max}: 1-8 h
Interferon beta-1b	Extavia	1993	Subcutaneous	0.25 mg	Every other day	$t_{½}$: 5 h T_{max}: 1-8 h
Interferon beta-1a	Avonex	1996	Intramuscular	30 µg	Once weekly	$t_{½}$: 10 h T_{max}: 5-15 h
Interferon beta-1a	Rebif	2002	Subcutaneous	22 or 44 µg	3 times weekly	$t_{½}$: 50-60 h T_{max}: 8 h
Peginterferon beta-1a	Plegridy	2014	Subcutaneous	125 µg	Once every 2 wk	$t_{½}$: mean ± SD 78 ± 15 h T_{max}: 1-1.5 d

Abbreviations: FDA, US Food and Drug Administration; $t_{½}$, half-life; T_{max}, time to maximum concentration.

data, and discuss the continued role of IFNβ in the ever-expanding MS treatment algorithms.

Mechanism of Action of Interferons

The interferon family of cytokines are secreted by many immune and nonimmune cell types, including macrophages, lymphocytes, fibroblasts, and endothelial cells.[2] Interferons possess immunomodulatory effects, as well as antiviral and antitumor properties. The type I family of interferons includes the IFNβs that are used to treat MS.[2]

The mechanism of action of IFNβ in people with MS is complex and not completely understood. Once IFNβ binds to specific cell surface receptors, several events occur, including increased expression of anti-inflammatory cytokines (eg, interleukin [IL] 4, IL-5, IL-10, IL-13, IL-27, and transforming growth factor beta) and downregulation of expression of proinflammatory cytokines (eg, IL-17, IFNγ, and tumor necrosis factor alpha), which helps stabilize dysregulated CNS inflammation.[13,14] The interferon-mediated shift from Th1/Th17 toward an anti-inflammatory profile may indirectly reduce neuronal demyelination, preventing further neuronal damage.[15]

Also, IFNβ acts on T cells by reducing T-cell activation as well as adhesion and penetration into the CNS through the blood-brain barrier.[16] In B cells and other antigen-presenting cells, IFNβ disrupts antigen presentation.[14] The overall effect of IFNβ on the brain is a shift in the balance from a proinflammatory Th1/Th17 response to a Th2 anti-inflammatory response, as well as a reduction in the number of inflammatory cells capable of crossing the blood-brain barrier.[13,14]

Peginterferon beta-1a is distinguished from other formulations by the addition of a polyethylene glycol (PEG) chain to the IFNβ-1a molecule.[1,17-19] PEG has been appended to a variety of molecules, and clinical research supports the safety and clinical value of pegylation; specifically, the improved stability and solubility of the pegylated molecule confers pharmacologic advantages such as reduced glomerular filtration rate and prolonged half-life.[20] In the case of peginterferon beta-1a, pegylation protects the IFNβ molecule from degradation and proteolysis, resulting in an extended half-life (Table 1), which, in turn, affects the pharmacokinetics and dosing interval.[1]

Pharmacokinetics, Dosing, and Adherence

The route of administration, dosing, and dosing frequency for the various interferons approved to treat relapsing-remitting MS (RRMS) are shown in Table 1.[8-12] The dosing frequencies of the interferon formulations differ from every other day (SC IFNβ-1b) to every 2 weeks (SC peginterferon beta-1a).

The greater stability of the pegylated formulation is reflected in the pharmacokinetics of peginterferon beta-1a, specifically its longer half-life (78 hours vs 5-60 hours) and time to maximum concentration (1-1.5 days vs 1-15 hours) relative to the nonpegylated interferon formulations (Table 1).[8-12] Single-dose phase 1 studies showed that peginterferon beta-1a has a longer terminal half-life, greater cumulative area under the curve, and higher maximum concentration than IM IFNβ-1a.[18] In the COMPARE study, an open-label, crossover, pharmacokinetic study in healthy individuals,[19] overall drug exposure over a 2-week dosing period was 60% higher after a single dose of peginterferon beta-1a than after six doses of SC IFNβ-1a. In addition, drug levels remained detectable throughout the 2-week dosing period with peginterferon beta-1a.[19]

Why is drug stability and dosing frequency an important issue with interferon treatment of MS? Studies of nonadherence (the proportion of patients who do not follow treatment according to the prescription) among patients receiving injectable MS therapies have shown nonadherence rates of 41% to 88%.[21,22] Nonadherent patients do not achieve the full efficacy of the treatment, with a negative effect on clinical outcomes, whereas patients who are more adherent to therapy show a reduced risk of relapse, lower rates of MS-related hospitalization, and decreased medical costs.[21,23,24]

Although anxiety over injections, difficulty with self-injections, and adverse events (AEs) also play a role in IFNβ nonadherence in patients with MS, injection frequency is, as in other chronic conditions, a major contributor to nonadherence.[22,25] Consistent with the role of injection frequency in adherence, among the nonpegylated IFNβs, a trend of declining adherence rates with increasing injection frequency has been reported, with average adherence rates of 69.4% for IM IFNβ-1a (once weekly), 63.8% for SC IFNβ-1a (three times weekly), and 58.4% for SC IFNβ-1b (every other day).[22] In the COMPARE study, injection site reactions (ISRs) and flu-like symptoms were more frequent with SC IFNβ-1a than with peginterferon beta-1a[19] (Figure 1) because of the higher injection frequency of SC IFNβ-1a. Based on the role of injection frequency and discomfort in leading to nonadherence,[22,25] the less frequent dosing allowed by the prolonged half-life of peginterferon beta-1a may lead to improved treatment adherence compared with other injectable therapies. However, real-world studies are needed to confirm that adherence improves with peginterferon beta-1a compared with nonpegylated interferons.

Efficacy of Interferon for MS Treatment

The DMTs represent a breakthrough in MS treatment insofar as they can modify the course of RRMS, lowering the rate of relapses and the number of magnetic resonance imaging (MRI) brain lesions and stabilizing or delaying MS disability.[2] Early studies of IFNβ therapies demonstrated reductions in relapse rates and severity of relapses and extended times to relapse and disability progression (Table S1, which is published in the online

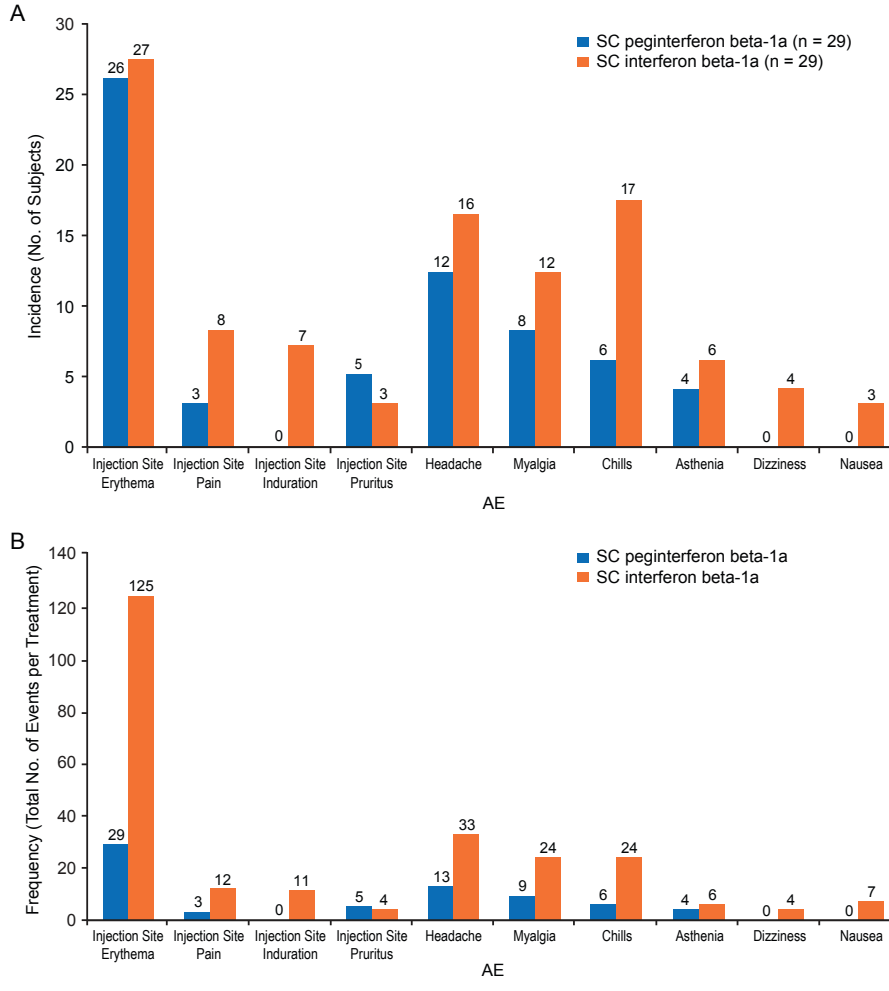

Figure 1. **(A) Incidence and (B) frequency of adverse events (AEs) related to study drug occurring in more than 10% of participants after treatment with either peginterferon beta-1a (n = 29) or subcutaneous (SC) interferon beta-1a (n = 29) in the COMPARE study[19]**

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version of this article at ijmsc.org).[3,26-32] Based on these early studies, the efficacy of IFNβ is generally accepted to be relatively consistent across the interferon class, yielding a decrease of approximately 30% in the annualized relapse rate (ARR).[35] In addition to shortening and preventing relapses, interferon therapies have also been shown to reduce new MRI gadolinium-enhancing (Gd+) brain lesions, decrease the risk of evolution of lesions into chronic black holes (markers of irreversible tissue injury), and reduce cognitive loss.[3,26,29,34,36-38] Furthermore, long-term interferon therapy has been shown to induce neuroprotectant proteins[39] and increase survival rates.[33]

In 2014, the 2-year, double-blind, parallel-group, phase 3 ADVANCE study (with a placebo-controlled design for the first 48 weeks) was conducted at 183 sites in 26 countries to assess the safety and efficacy of peginterferon beta-1a.[26] In this study, 1512 patients with RRMS were randomly assigned to receive placebo (n = 500), peginterferon beta-1a every 2 weeks (n = 512), or peginterferon beta-1a every 4 weeks (n = 500) in year 1. At year 2, all the placebo-receiving patients were randomized again to receive peginterferon beta-1a either every 2 weeks or every 4 weeks. During year 1, patients receiving peginterferon beta-1a had significantly fewer relapses than those taking placebo; the adjusted ARR was 0.256 in the every-2-weeks group, 0.288 in the every-4-weeks group, and 0.397 in the placebo group (rate ratio vs placebo: 0.644 [P = .0007] for every 2 weeks and 0.725 [P = .0114] for every 4 weeks).[26] These results support the efficacy of peginterferon beta-1a for the treatment of RRMS, with less frequent administration required than with other available treatments. In year 2, the ARR was further reduced with every-2-weeks dosing (to 0.178) and was maintained with every-4-weeks dosing (at 0.291), indicating that peginterferon beta-1a efficacy is maintained beyond 1 year.[16] In the phase 3 ATTAIN extension study, year-by-year ARRs remained low over 6 years in patients treated with peginterferon beta-1a every 2 weeks.[40]

Interferon therapies are commonly used as comparators in clinical trials of new therapies[6,7,41]; however, no head-to-head trials have definitively shown a difference in efficacy among the interferon therapies. Of those studies that have been conducted, most have shown no difference, and for those that have shown a difference (eg, INCOMIN, EVIDENCE),[42,43] limitations in study design—namely, a lack of double-blinding—may restrict interpretation of the findings. The lack of blinding in these trials may have influenced patients and/or investigators when measuring subjective outcomes such as relapse and disability progression.[44] Results from INCOMIN and EVIDENCE were also compromised by baseline imbalances between study groups. In EVIDENCE, the groups differed in the number of active lesions, and statistical significance was mostly found in outcomes related to lesion activity. In each case, the group with better performance was the group with fewer mean lesions at baseline.[44] INCOMIN study groups differed in the number of T2 lesions, disease duration, the proportion of patients with Gd+ lesions, age at disease onset, and sex. The study group in INCOMIN that had worse relapse- and MRI-related outcomes also had more T2 lesions, had longer disease duration, and were older at disease onset, and a higher percentage were male. The latter two factors have been associated with adverse disability outcomes.[44]

A recent meta-analysis indicated that the efficacy and safety profiles of peginterferon beta-1a are comparable with those of IFNβ-1a, IFNβ-1b, and glatiramer acetate in patients with RRMS.[45] Indirect comparisons have reported better clinical outcomes with peginterferon beta-1a than with SC or IM IFNβ-1a.[46,47]

No evidence of disease activity (NEDA), increasingly considered the primary aim of MS treatment, is a composite of three measures of disease activity: no relapses, no disability progression, and no MRI activity (ie, new or enlarging T2 and Gd+ lesions).[48-50] In post hoc analyses of the EVIDENCE study, a head-to-head trial of SC and IM IFNβ-1a, more patients achieved clinical NEDA (defined as no relapses and no increase of ≥1.0 point in Expanded Disability Status Scale score from baseline sustained for 12 weeks) and MRI NEDA (defined as no new or newly enlarging T2 lesions) over 72 weeks with SC IFNβ-1a than with IM IFNβ-1a (clinical NEDA: 46.7% vs 33.3%; MRI NEDA: 48.6% vs 25.6%).[51] In the ADVANCE study, higher rates of overall NEDA, a composite of clinical NEDA (defined as no relapses and no increase in Expanded Disability Status Scale score of ≥1.0 point in patients with a baseline score of ≥1.0, or an increase of ≥1.5 points in patients with a baseline score of 0.0, confirmed after 12 weeks) and MRI NEDA (defined as no Gd+ lesions and no new or newly enlarging T2 lesions), were achieved by patients who received continuous treatment with peginterferon beta-1a every 2 weeks for 2 years (36.7%) than

by patients who received peginterferon beta-1a every 4 weeks for 2 years (23.0%) or delayed treatment (placebo in year 1 and peginterferon beta-1a in year 2; 15.8%).[34] Differences in study design and NEDA definitions prevent comparison of NEDA rates across studies; however, these data generally support the possibility of achieving NEDA with interferon treatment.

Safety and Tolerability

Treatment of MS with IFNβ has a long record of safety, with millions of patients treated across more than 2 decades.[52,53] The most common AEs with a consistently higher incidence with interferon than with placebo are injection site erythema, influenza-like illness, pyrexia, headache, myalgia, chills, and injection site pain.[8-12] Most reported AEs are mild or moderate in severity.[16,54]

The AEs that most significantly limit the use of interferon treatment are flu-like symptoms and ISRs. The exact mechanism of ISRs with interferon use is not known; however, results of a study using skin biopsy samples obtained from patients with MS suggest that IFNβ SC injection may trigger inflammatory skin reactions through local chemokine induction, followed by rapid movement of immune cells to the injection site.[55] Such ISRs as injection site erythema, pain, induration, and pruritus have been observed to occur less frequently in patients receiving IM than SC MS therapies.[56,57] (See the next section for further discussion on managing flu-like symptoms and ISRs.)

Peginterferon beta-1a has demonstrated a favorable tolerability profile compared with SC IFNβ-1a with respect to ISRs.[18] In the COMPARE study (in healthy individuals), the most common ISR, injection site erythema, occurred with similar incidence but lower frequency with peginterferon beta-1a compared with SC IFNβ-1a. Peginterferon beta-1a was better tolerated than SC IFNβ-1a with respect to flu-like symptoms,[19] with myalgia and chills as the most common AEs reported with both treatments (Figure 1). Numerically lower AE incidences, frequencies, and incidence rates with peginterferon beta-1a compared with SC IFNβ-1a were as expected given the differences in frequency of administration. In year 1 of the phase 3 ADVANCE study,[26] rates of the most common ISRs and flu-like symptoms were similar in the peginterferon beta-1a every-2-weeks and every-4-weeks groups, including injection site erythema (62% and 56%, respectively), influenza-like illness (47% in both groups), pyrexia (45% and 44%, respectively), headache (44% and 41%, respectively), injection site pain (15% and 13%, respectively), and injection site pruritus (13% and 11%, respectively). The randomized phase 3b ALLOW study characterized flu-like symptoms in 201 patients with RRMS transitioning from nonpegylated IFNβ therapies to peginterferon beta-1a; it found that 90% of patients did not have new or worsening flu-like symptoms, most were mild to moderate, the median onset time after injection was 10 hours, and the median duration was 17 hours.[58]

Notwithstanding this long history of safety, not all patients with MS are responsive to IFNβ therapies; in fact, 30% to 50% are nonresponsive.[59] Nonresponse may be attributed to genetic, pharmacologic, or pathogenic factors. One main factor in nonresponsiveness is the presence of neutralizing antibodies to IFNβ.[60] Overall, the prevalence of neutralizing antibodies in patients treated with different nonpegylated interferon therapies ranges from less than 5% to almost 45%, with SC IFNβ-1b associated with the highest neutralizing antibody levels (30%-40%) and IM IFNβ-1a with the lowest neutralizing antibody levels (2%-6%).[61] Pegylation of molecules has generally been shown to reduce drug immunogenicity, antigenicity, and toxicity.[20] Consistent with this, in the peginterferon beta-1a phase 3 ADVANCE trial,[26] the incidence of anti-interferon neutralizing antibodies remained low in both active treatment groups (<1%), and the proportion of patients developing neutralizing antibodies was at the low end of the range of immunogenicity observed with any of the nonpegylated interferon MS therapies.[62,63]

Management of Interferon AEs

Patients taking interferon may experience several AEs, including headaches, muscle aches, flu-like symptoms, and ISRs, which can all negatively affect the patient's quality of life and desire to continue treatment. To maximize interferon treatment adherence and, thus, therapeutic efficacy, it is important to proactively manage AE symptoms (particularly flu-like symptoms and ISRs) in all patients, including those switching between interferon and noninterferon DMTs, those switching between IM and SC IFNβs, and those naive to DMT treatment. Table 2 summarizes recommended pharmacologic and nonpharmacologic mitigation strategies for common AEs associated with IFNβ therapies.[64-66] The primary management strategy for flu-like symptoms and ISRs is gradual dose titration over 4 to 6 weeks. Analgesics and/or antipyretics, such as ibuprofen or acetaminophen, are often administered concurrently to prevent

Table 2. Mitigation strategies for the most common adverse events associated with interferon beta therapies[64-69]

Adverse event	Pharmacologic therapies	Nonpharmacologic therapies
FLSs	• Gradual interferon up-titration with concomitant medication for FLSs • FLS medications: Recommended: NSAID (eg, ibuprofen), acetaminophen Alternative: pentoxifylline • As necessary: temporarily decrease interferon dose; concomitant oral prednisone	• Alter injection timing (eg, administer in evening) • Administer at room temperature • Hydration • Caffeine • Ensure good nutrition • Rest • Cold water showers/baths
ISRs	• Oral: acetaminophen, diphenhydramine, dimethindene • Topical: lidocaine + prilocaine	• Educate patients • Rotate injection site • Ensure proper injection depth and angle • Ensure aseptic injection technique • Use small needle size • Use autoinjector device • Warm medication to room temperature and ensure drug is fully dissolved • Apply ice to site after injection

Abbreviations: FLS, flu-like symptom; ISR, injection site reaction; NSAID, nonsteroidal anti-inflammatory drug.

the onset of symptoms.[67,68] It is especially critical that patients be educated regarding the timing and impact of flu-like symptoms and ISRs and how to reduce/prevent such AEs using over-the-counter medications and other self-care practices, such as hydration, diet, and rest.[64] Most patients who experience flu-like symptoms or ISRs can administer doses in the evening, such that they sleep through the time during which they would otherwise experience symptoms.[67-69] Understanding the timing of AEs may be of particular importance when considering the potential for patients treated with PEG-IFNβ-1a to potentially experience flu-like symptoms or ISRs of extended duration.[58]

Role of Interferons in Current MS Therapeutic Landscape

As in many therapeutic areas, in MS there is debate about whether to begin therapy with safer agents and then escalate treatment as necessary or to begin treatment with the most effective therapies available.[70] Given the number of available therapies, recent consensus guidelines recommend individualized therapy choice made based on discussion with the patient and consideration of patient characteristics, disease severity, drug safety profiles, barriers to adherence, and accessibility of the drug.[71] Guidelines from the American Academy of Neurology and the European Academy of Neurology recommend that patients with MS offered a first-line therapy such as IFNβ or glatiramer acetate be switched to a higher-efficacy DMT (eg, alemtuzumab, fingolimod, or natalizumab) if and when breakthrough disease activity occurs.[71,72] However, when a treatment switch is desired for reasons unrelated to efficacy (eg, tolerability or convenience), a lateral switch from one first-line DMT to another, rather than escalating therapy, is an acceptable treatment strategy.[54,73-75] In the ALLOW study, most patients (89.6%) who made a lateral switch (from a nonpegylated interferon to PEG-IFNβ-1a) did not have new or worsening flu-like symptoms.[58] In that study, patients switching from a more frequent to a less frequent injection also reported increases in treatment satisfaction.[65] In separate analyses, however, switching patients who were stable on an interferon therapy for at least 1 year to another interferon therapy was shown to potentially lead to worse clinical outcomes (with peginterferon beta-1a not included in the analyses) due in part to decreased adherence to the switch medication.[76]

PRACTICE POINTS

- Interferon beta, which is available in several formulations, plays an important role as standard-of-care, first-line therapy for relapsing forms of MS.
- Interferons have demonstrated efficacy on clinical outcomes, and their long-term safety profiles are well established.
- The most common adverse events associated with interferon beta therapy—flu-like symptoms and injection site reactions—can be managed through patient education and mitigation strategies.

Because reasons for switching were not identified and patients were followed up for only 1 year after switching, individual patient needs must continue to be weighed when considering a treatment switch.

Summary

Even with the wide array of DMTs currently available, IFNβ therapy still plays an important role in the treatment of patients with MS. Interferons have been shown to improve clinical outcomes, and their long-term safety profiles make them standard-of-care, first-line therapy for MS. Although patients with RRMS may benefit from interferon treatment, individual response, in terms of both efficacy and AEs, is unpredictable, and it is necessary in many cases to switch treatments to stabilize disease. New real-world data are continuously being collected comparing IFNβ drugs in terms of efficacy, tolerability, and the effects of switching, as well as the relative incidence of flu-like symptoms and ISRs. Both flu-like symptoms and ISRs have been shown to be manageable through patient education and monitoring and pharmacologic and nonpharmacologic intervention. □

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