Interferons and Multiple Sclerosis: Lessons from 25 Years of Clinical and Real-World Experience with Intramuscular Interferon-Beta-1a (Avonex)

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Abstract

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system. The interferons (IFNs) were discovered in 1957, and recombinant IFN-β-1b was approved by the US Food and Drug Administration as the first disease-modifying therapy (DMT) for MS in 1993. Since that time, clinical trials and real-world observational studies have demonstrated the effectiveness of IFN therapies. The pivotal intramuscular IFN-β-1a phase 3 trial was the first to demonstrate that a DMT could reduce accumulation of sustained disability in MS. Patient adherence to treatment is higher with intramuscular IFN-β-1a, given once weekly, than with subcutaneous formulations requiring multiple injections per week. Moreover, subcutaneous IFN-β-1a is associated with an increased incidence of injection site reactions and neutralizing antibodies compared with intramuscular administration. In recent years, revisions to MS diagnostic criteria have improved clinicians' ability to identify patients with MS and have promoted the use of magnetic resonance imaging (MRI) for diagnosis and monitoring. MRI studies show that treatment with IFN-β-1a, relative to placebo, reduces T2 and gadolinium-enhancing lesions and gray matter atrophy. Since the approval of intramuscular IFN-β-1a, several high-efficacy therapies have been approved for MS, though the benefit of these high-efficacy therapies should be balanced against the increased risk of serious adverse events. For some subpopulations of patients, including pregnant women, the safety profile of IFN-β formulations may provide a particular benefit. In addition, the antiviral properties of IFNs may indicate therapeutic opportunities for IFN-β in the treatment of viral infections such as COVID-19.

Key Points

- Since 1981, clinical and real-world observational studies have demonstrated the effectiveness of interferon therapies in reducing relapse rate, disability progression, and the number of new or newly enlarging lesions in patients with multiple sclerosis (MS).
- The pivotal intramuscular interferon-beta-1a phase 3 trial in 1996 (MSCRG) was the first to demonstrate that disease-modifying therapy could reduce the accumulation of sustained disability in MS.
- Other studies suggest that interferon treatment may improve cognition and benefit patients' quality-of-life.

Acknowledgements

1 Introduction to Multiple Sclerosis (MS)

1.1 Epidemiology and Symptomatology

MS is a chronic inflammatory demyelinating and neurodegenerative disease of the central nervous system (CNS) of unknown etiology with an estimated worldwide prevalence of >2.2 million cases as of 2016 [1, 2]. Symptoms of MS usually appear in adults between 20 and 50 years of age [3] and may include fatigue, visual impairment, motor weakness, ataxia, reduced mobility, tremor, sensory loss, pain, impaired genitourinary function, depression, and cognitive impairment [4]. These symptoms have a negative impact on patients' quality of life (QoL) by interfering with gainful employment, interpersonal relationships, intimate and leisure activities, and other daily activities [5, 6].

1.2 Pathogenesis

As the pathological mechanisms underlying the development of MS are not completely known, animal models have been used to derive hypotheses about associated oligodendrocyte biology and neuroinflammatory mechanisms of demyelination, axonal loss, and remyelination [7-9]. Human and animal immune responses differ in how they affect development and progression of CNS inflammation. Nonetheless, these animal models have yielded valuable insights, including elucidation of the role of processing and display of myelin-reactive antigens by antigen-presenting cells (APCs) and clarification of the differentiation of autoreactive CD4+ T lymphocytes into inflammatory Th1 and Th17 helper cells [10]. Th1/Th17 cell expansion and secretion of proinflammatory cytokines, such as interleukin 2 (IL-2) and interleukin 17 (IL-17), tumor necrosis factor-α, and interferon-γ (IFN-γ), promote and maintain an inflammatory state associated with MS [11]. Increased secretion of IL-17 by Th17 cells may also lead to reduced oligodendrocyte survival and thereby contribute to axonal demyelination as well [12]. Although the importance of TH17/IL17 in MS is debated, studies support its role in disease pathogenesis [13-15], and evidence suggests that IFN-β can inhibit Th17 cell development [16-18].

1.3 Risk Factors for MS

Epidemiological studies have identified geographic [19], environmental [20-22], and genetic [23] risk factors for MS. Genome-wide association studies show over 200 loci that may contribute to the genetic risk for MS, including major histocompatibility complex alleles and genes regulating IFN responses (reviewed in [24-27]). While some of the genetic loci and most of the identified environmental risk factors affect adaptive and/or innate immunity, no one risk factor is able to explain all cases of MS. This suggests that ≥1 risk factors may help to "trigger" MS in genetically susceptible persons [28, 29]. For example, viral initiation of abnormal inflammatory autoimmune cascades, such as from infection by Epstein-Barr virus, increases susceptibility to and severity of MS in genetically predisposed individuals [30].

2 IFNs in MS Therapy, with a Focus on Intramuscular (IM) IFN-β-1a

The IFNs were discovered in 1957 during investigations into mechanisms of viral interference [31]. In humans, IFNs form a family of secreted autocrine and paracrine cytokines [32] with diverse and essential roles in mediating antiviral activity, regulating cell growth and proliferation, and modulating immune responses [33, 34].

Based on sequence homology and signaling properties, IFNs can be grouped into three types. All type I IFNs bind to and signal through the same heterodimeric IFNAR1/IFNAR2 receptor [35, 36]. In addition to the type I IFNs, a single type II IFN, IFN-γ, signals through different receptor and elicits different cellular responses [37], though both types regulate inflammatory responses, primarily by signaling through the JAK-STAT family of signal

transducers [38]. The type III IFNs, which include IFN-λ1-4, primarily target epithelial cells and have antiviral and immunomodulatory functions [39]

The type I IFN-α and IFN-β subtypes share some, but not all, signaling properties and perform different roles in antiviral protection. IFN-β is the first IFN induced by viral infection; it then induces a second wave of IFN-β and IFN-α production. IFN-β and IFN-α play an essential role in controlling early viral spread following infection. Based on their antiviral and antiproliferative activity, the type I IFNs have been used to treat viral infections and certain malignancies [40]. However, the interactions between viruses and the IFN system are complex, as illustrated in chronic lymphocytic choriomeningitis virus (LCMV) infection in mice. LCMV infection results in induction of 2'-5' oligoadenylate synthetase-like 1 (OASL1), a global negative regulator of type I IFN expression, thereby modifying the IFN response and allowing a state of persistent viral infection [41] . In this case, LCMV clearance is accelerated by IFN-β but not IFN-α antibody blockade [42].

Epidemiological evidence for a viral trigger of MS, coupled with the known antiviral activity of type I IFNs [31, 43], formed the rationale for a small randomized controlled study of intrathecal IFN-β-1a versus placebo in 20 patients with MS reported in 1981 [44, 45] (Table 1). Over 1.5–2.0 years of observation, patients who received repeated intrathecal IFN-β-1a injections had fewer relapses and were more likely to show improvement in their clinical condition than patients who received placebo [44, 45]. Approximately 90% of the treated population required no additional injections nearly 4 years after the last intrathecal injection [46]. In 1984, a clinical trial of subcutaneous (SC) IFNα administration reported a trend toward reduced relapse rates [47]. These advances, coupled with the availability of biologically active recombinant IFNs [48], led to the pivotal clinical trials that resulted in US Food and Drug Administration (FDA) approval of recombinant SC IFN-β-1b (Betaseron®/Betaferon® and Extavia®) in 1993 [49-51] and recombinant IM IFN-β-1a (Avonex®) in 1996 [52] for treatment of relapsing MS (Fig. 1).

IFN-β-1b and IFN-β-1a were among the first disease-modifying therapies (DMTs) approved for treatment of relapsing forms of MS, ushering in the modern era of DMTs for MS. A third IFN, SC-administered IFN-β-1a (Rebif®), was approved in 2002 [53], and an SC-administered pegylated form of IFN-β-1a (Plegridy®), which has a longer half-life and thus requires less frequent dosing, was approved in 2014 [54] (Fig. 1). The beta IFNs are among the most widely prescribed DMTs for MS worldwide [55]. As of March 2020, >580,000 patients have been prescribed IM IFN-β-1a since its approval, representing >2,600,000 patient-years of exposure [56] .

The effectiveness of IFN-β in treating MS is presumed to be due to its complex effects on immunomodulatory signaling. IFN-β inhibits production of the inflammatory Th1 cytokines, IFN-γ and interleukin 12 (IL-12), by human dendritic cells [57, 58]. In patients with stable MS, long-term treatment with IFN-β (over an average of 8 years) suppresses expression of Th1/Th2/Th17 inflammatory cytokines and costimulatory proteins, reducing the "cytokine storm" [59]. Although stimulation of inflammatory cytokine release from Th1 cells is primarily associated with IFN-γ, the type I IFNs can also contribute to the production of Th1 cytotoxic mediators and enhance secretion of Th1-inducing IL-12 by monocytes and dendritic cells in response to acute viral infection [37, 60, 61], suggesting a mechanism for inflammation-induced MS exacerbations.

In animal models, IFN-β promotes the differentiation of T cells toward self-tolerance, favoring the CD4+/CD25+/FOXP3+ regulatory lineage [62]. Regulatory T cells expressing FOXP3 and other markers play a role in active maintenance of immunological self-tolerance, and deficiencies or dysfunction in these cells can contribute to autoimmune disease [63]. Reduced levels of FOXP3 mRNA and protein have been reported in CD4+/CD25+ cells isolated from patients with MS [64]. Within 6 months after starting therapy with IFN-β, including IM IFN-β-1a, naive CD4+ regulatory T cells increase, memory regulatory T cells decrease, and CD4 regulatory T-cell function is at least partially restored [65].

CD8+ suppressor/regulatory T cells play an important role in the resolution of inflammation, and nonspecific CD8+ suppressor cell function was first shown to be improved *in vitro* in lymphocytes from patients with MS treated with recombinant human IFN-β [66]. Autoreactive CD4+ T cells isolated from patients with MS express higher levels of IFN-γ than those from heathy controls and therefore appear to have a more "Th1-like" phenotype [67]. CD8+/CD25+/FOXP3+ regulatory T cells isolated from patients with MS inhibited the proliferation of these CD4+ autoreactive T-cells and the secretion of IFN-γ and IL-17 [68]. Patients in relapse have fewer CD8+/CD25+/FOXP3+ regulatory T cells in their cerebrospinal fluid (CSF) than patients in remission [68]. Although CD8+ regulatory T cells isolated from clinically quiescent treatment-naive patients with MS or healthy subjects similarly suppressed the proliferation of autoreactive CD4+ T cells, CD8+ cells isolated from patients during relapse were deficient in T-cell suppression [69], indicating that CD8 regulatory function is dynamic and may be influenced by MS disease activity.

IFN-β also promotes the production of anti-inflammatory cytokines. IFN-β-1a induces expression of interleukin-10 (IL-10), a potent anti-inflammatory and tolerogenic cytokine [70], in cultured peripheral blood mononuclear cells from patients with MS and healthy controls [71, 72]. Reduced levels of IL-10 are associated with an elevated risk of developing autoimmune diseases [73]. IL-10 levels in CSF decrease during MS relapse and increase during remission [74]. IFN-β-1a therapy increases serum IL-10 levels in patients with relapsing MS [75].

In animals with experimental autoimmune encephalomyelitis, recombinant IFN-β reduces the expression of vascular and intercellular adhesion molecules [76] and the inflammatory activity of dendritic APCs and decreases APC migration into the CNS [77]. In rat glial cell cultures, IFN-β inhibits the expression of matrix metalloproteinases by macrophages [78], impeding inflammatory cell migration into the CNS and reducing inflammation and damage within the brain.

Thus, type I IFNs have broad effects in reducing inflammatory cytokines, correcting defective regulatory cell function in MS, and reducing expression of molecules that allow penetration of the blood-brain barrier.

3 The Efficacy of IM IFN-β-1a: Clinical Studies

3.1 Multiple Sclerosis Collaborative Research Group (MSCRG)

The pivotal phase 3 MSCRG randomized clinical trial of recombinant IM IFN-β-1a versus placebo in patients with relapsing MS was the first large study designed to assess the effect of IFN treatment on physical disability [79]. Kaplan-Meier–estimated time to confirmed disability worsening (CDW) over 104 weeks of treatment (the primary study endpoint, defined as a 1.0-point increase from baseline Expanded Disability Status Scale (EDSS) score, confirmed after 6 months) was greater for patients treated with IM IFN-β-1a than with placebo (p=0.02). This was the first demonstration that a DMT could alter the course of relapsing MS by reducing the accumulation of confirmed disability.

The annualized relapse rate (ARR) decreased by 32% in patients who completed 104 weeks of treatment with IFN-β-1a versus placebo (0.61 vs 0.90; p=0.002). Over 52 weeks, reductions from baseline in the number and volume of gadolinium-enhancing (Gd+) lesions were greater for patients treated with IFN-β-1a than for placebo patients (both p=0.02). The magnetic resonance imaging (MRI) differences between the IFN-β-1a and placebo groups were sustained through the 104 weeks of treatment (p=0.05 for decrease in number of Gd+ lesions; p=0.03 for decrease in Gd+ lesion volume). A follow-up analysis demonstrated a significant reduction in the number of new or newly enlarging T2 MRI lesions with IM IFN-β-1a compared with placebo (p=0.002) [80]. Importantly, there were no major adverse events (AEs) related to IM IFN-β-1a treatment. Table 1 provides additional details.

3.2   Controlled High-risk Subjects Avonex Multiple Sclerosis Prevention Study (CHAMPS)

CHAMPS was a 3-year randomized controlled study that examined the effect of IM IFN-β-1a versus placebo in 383 patients after a first demyelinating episode involving either the optic nerve (optic neuritis), the brainstem/cerebellum, or the spinal cord (incomplete transverse myelitis) [81, 82]. After 3 years of treatment, the estimated cumulative probability of progression to the primary study endpoint, clinically definite MS (CDMS), which required either the occurrence of either a new visual or neurologic event or an increase (from month 1 of treatment) of ≥1.5 points in EDSS score, was significantly lower in the IM IFN-β-1a group than the placebo group (relative risk reduction 30%; rate ratio 0.56; 95% confidence interval [CI] 0.38–0.81; p=0.002) [81]. Over 18 months, IM IFN-β-1a treatment was associated with fewer Gd+ and new or newly enlarging T2 lesions as well as a diminished increase in T2 lesion volume (all p<0.001) [81]. In addition to providing evidence for the value of early DMT initiation, CHAMPS demonstrated the utility of early MRI scans in MS diagnosis and treatment monitoring.

A follow-up subgroup analysis of CHAMPS used a composite measure of either progression to CDMS (as specified above) or >1 new or newly enlarging T2 lesions on MRI. IM IFN-β-1a demonstrated benefit compared with placebo regardless of initial demyelinating event presentation [82]. Over 2 years, the estimated cumulative probability of reaching the composite outcome was 59% in the IFN-β-1a group and 81% in the placebo group (relative risk reduction 27.2%; rate ratio 0.47; 95% CI 0.36–0.62; p<0.001). Similar results were observed for subgroups with different initial demyelinating events (p<0.001 with optic neuritis; p<0.001 with brainstem/cerebellum event; p=0.004 with incomplete transverse myelitis) [82]. Table 1 provides additional details.

3.3   Long-Term Efficacy of IM IFN-β-1a in the MSCRG and CHAMPS Extension Studies

Of the 301 patients originally randomized in the MSCRG pivotal study, 172 (57.1%) completed the full 2 years. Follow-up studies evaluated the long-term efficacy of IM IFN-β-1a based on assessments performed 8 years and 15 years (ASSURANCE) [83] after original entry into the MSCRG trial. Of the 79 patients (41.4%) originally randomized to IM IFN-β-1a and the 81 patients (42.6%) who were originally randomized to placebo in MSCRG and re-assessed after 8 years, 13.8% had been DMT naive at MSCRG baseline [84]. At 8 years, a lower proportion of patients initially randomized to IM IFN-β-1a than to placebo had progressed to an EDSS score ≥4.0 (44.3% vs 65.4%; relative risk reduction 32.3%; p=0.007) or ≥5.0 (34.2% vs 54.3%; relative risk reduction 36.9%; p=0.01), demonstrating that early treatment with IM IFN-β-1a reduced the proportion of patients with EDSS progression (Table 2). At the 15-year ASSURANCE follow-up assessment, in 122 eligible patients (63 and 59 patients originally randomized to IM IFN-β-1a or placebo, respectively; 14 patients were deceased), those randomized to IM IFN-β-1a had better disability outcomes than those randomized to placebo on metrics including mean EDSS score (5.1 vs 5.7), increase from baseline in EDSS score (2.9 vs 3.3 points), and progression to EDSS score ≥4.0 (73.9% vs 79.1%), ≥6.0 (47.8% vs 58.2%), and ≥7.0 (24.6% vs 31.3%) [83]. At 15 years, patients with ongoing IM IFN-β-1a therapy had a lower mean EDSS score (4.4 vs 5.7; p=0.011) and a smaller mean increase in EDSS score from baseline (2.3 vs 3.3; p=0.011) than patients who had discontinued IM IFN-β-1a [83] (Table 2).

The open-label extension study, CHAMPIONS, provided long-term efficacy data on patients originally enrolled in CHAMPS and randomized to placebo or IM IFN-β-1a treatment [85]. All CHAMPS patients who enrolled in CHAMPIONS (203 of 383 [53%]) were offered IM IFN-β-1a, regardless of their original assignment. After 5 years of treatment with IM IFN-β-1a, the cumulative probability of developing CDMS (as defined in CHAMPS) was lower in patients randomized to receive IM IFN-β-1a in CHAMPS (the immediate-treatment group) than in those

who initially received placebo (the delayed-treatment group; mean [standard deviation (SD)] 5-year incidence 36% [9%] vs 49% [10%]; *p*=0.03; Table 2).

Similar results were seen in a subset of CHAMPIONS patients at 10 years of follow-up [86]. The cumulative probability of developing CDMS was lower in the immediate-treatment group than in the delayed-treatment group (58% vs 69%; *p*=0.004). Patients in the immediate-treatment group also had a significantly lower ARR than those in the delayed-treatment group during years 5–10 (0.14 vs 0.31; *p*=0.03) and over the entire 10-year follow-up period (0.16 vs 0.33; *p*=0.02; Table 2). At 10 years, 81% of all patients had an EDSS score <3.0. There were no significant between-group differences for EDSS worsening or for any of the examined MRI outcomes (change in T2 lesion volume, number of Gd+ lesions, or number of new or newly enlarging T2 lesions) in years 5–10. The CHAMPIONS 10-year follow-up results suggest that early initiation of treatment more positively impacts MS disease course in high-risk patients than later initiation, though patients who initiate treatment later also receive important benefits. Over the 10-year follow-up period, IM IFN-β-1a was associated with a low percentage of serious AEs (SAEs) and no new safety concerns. (See also Section 6 below.)

4   Comparative Efficacy of IM IFN-β-1a

The efficacy of IM IFN-β-1a has been compared with other in-class DMTs in head-to-head studies, and IM IFN-β-1a has been used as a comparator in clinical trials of newer DMTs.

4.1   Head-to-Head Efficacy Comparison in EVIDENCE

EVIDENCE was a multicenter randomized controlled trial of the efficacy and safety of SC IFN-β-1a versus IM IFN-β-1a in patients with relapsing-remitting MS (RRMS) [87, 88]. In the primary clinical outcome, more patients receiving SC IFN-β-1a than IM IFN-β-1a were relapse free after 24 weeks (75% vs 63%; *p*=0.0005) and 48 weeks (62% vs 52%; *p*=0.009) [87]. Similarly, ARR was lower in the SC IFN-β-1a group than the IM IFN-β-1a group at 24 weeks (0.29 vs 0.41; *p*=0.022) and 48 weeks (0.54 vs 0.64; *p*=0.094). In the principal MRI outcome of EVIDENCE, more patients receiving SC IFN-β-1a than IM IFN-β-1a had no new MRI activity (no new Gd+ lesions or new or newly enlarging T2 lesions) at 24 weeks (*p*<0.001). However, in an analysis of 6-month CDW (defined as a ≥1.0-point increase in EDSS score) over 48 weeks, the proportions of SC IFN-β-1a and IM IFN-β-1a patients with disability progression did not differ significantly (5.9% vs 8.3%; *p*=0.23; Table 3) [87]. Between-group differences were maintained when EVIDENCE patients were followed for 64 weeks [88]. More SC IFN-β-1a than IM IFN-β-1a patients remained relapse free (56% vs 48%; *p*=0.023) and free of new or newly enlarging T2 lesions (58% vs 38%; *p*<0.001). However, as in the 48-week analyses, there was no significant difference in the proportions of SC IFN-β-1a and IM IFN-β-1a patients with 6-month CDW (16% vs 17%; *p*=0.710; Table 3).

An assessment using the composite no evidence of disease activity (NEDA) outcome measure (defined as no relapses, no 3-month confirmed EDSS worsening, no new Gd+ lesions, and no new or newly enlarging T2 lesions) showed that more patients treated with SC IFN-β-1a than with IM IFN-β-1a achieved NEDA (59.5% vs 41.2%; *p*<0.001) over 24 weeks in the EVIDENCE study [89].

4.2   Other Comparative Studies

TRANSFORMS was a 12-month, randomized, double-blind, double-dummy phase 3 efficacy study of fingolimod, an orally bioavailable functional sphingosine-1-phosphate–receptor antagonist, compared with IM IFN-β-1 [90]. In the primary study outcome, ARR at 12 months was significantly lower for patients receiving either 1.25 mg or 0.5 mg fingolimod than for those receiving IM IFN-β-1 30 μg IM (both *p*<0.001). However, in a key secondary outcome, there was no significant difference in the proportion of patients free of 3-month confirmed disability

progression on IM IFN-β-1 (92.1%) compared with 1.25 mg fingolimod (93.3%; *p*=0.50) or 0.5 mg fingolimod (94.1%; *p*=0.25; Table 3) [90].

Similar results were obtained in DECIDE, a randomized, double-blind, active-controlled phase 3 study of daclizumab, an anti–IL-2 receptor monoclonal antibody (voluntarily withdrawn from the market in March 2018), compared with IM IFN-β-1a [91]. ARR over 144 weeks, the primary study outcome, was lower with daclizumab than with IM IFN-β-1a, as was the number of new or newly enlarging T2 lesions over 96 weeks (both *p*<0.001). Paralleling the results of EVIDENCE and TRANSFORMS, there was no significant difference in the estimated proportions of patients with 3-month CDW between the daclizumab and IM IFN-β-1a treatment arms over 144 weeks of treatment (16% vs 20%; *p*=0.16; Table 3) [91].

RADIANCE was a 24-month, multicenter, double-blind, double-dummy phase 3 trial that compared the safety and efficacy of ozanimod, a sphingosine 1-phosphate receptor modulator, with IM IFN-β-1a [92]. Over 24 months, ARR was significantly lower in patients treated with ozanimod 1.0 mg than with IM IFN-β-1a (*p*<0.0001). Similarly, the adjusted mean number of new or newly enlarging T2 lesions per scan was significantly lower with ozanimod than with IM IFN-β-1a (1.84 vs 3.18; *p*<0.0001), as was the adjusted mean number of Gd+ lesions at 2 years (0.18 vs 0.37; *p*=0.0006). However, the proportion of patients with disability progression (defined as an EDSS score increase of ≥1.0 point confirmed after 3 or 6 months) did not differ significantly in the ozanimod and IM IFN-β-1a treatment groups (3-month CDW: 12.5% vs 11.3% [*p*=0.8224]; 6-month CDW: 9.7% vs 6.6% [*p*=0.1353]) [93].

Taken together, these comparative studies suggest that IM IFN-β-1a provides substantial long-term benefit to patients, as evidenced by the consistently low proportions of patients with 3- or 6-month CDW, despite the greater proportion of IM IFN-β-1a–treated patients with relapse or MRI activity compared with those treated with alternative DMTs. Broadly speaking, these results are consistent with the findings from a 10-year, longitudinal prospective study of 480 patients with RRMS or clinically isolated syndrome that brain atrophy, but not relapse activity, is associated with long-term disability progression [94]. The comparative data also call into question the assumption that on-therapy and off-therapy relapses and MRI activity have equivalent effects on clinical progression. The 16-year long-term follow-up of IFN-β-1b identified a similar dissociation between pre-study and on-study therapeutic efficacy as measured by relapse activity and MRI events and effects on long-term disease worsening as assessed by EDSS score progression or conversion to secondary progressive MS [95].

5   Brain Atrophy and Pseudoatrophy

Brain atrophy/brain volume loss (BVL) predicts long-term disability in MS [94, 96]. BVL is included in an expanded NEDA outcome measure, NEDA-4 [97]. However, reliable assessment of BVL can be difficult due to the variability and limited reproducibility of imaging methods. In addition, brain volume changes associated with aging in healthy individuals as well as those with MS make it difficult to identify the precise extent of pathological BVL attributable to MS [98]. Nevertheless, longitudinal imaging studies of BVL have found a larger annual percentage brain volume change (PBVC) in patients with MS than in normal controls (PBVC mean [SD] −0.51% [0.27] vs −0.27% [0.15]; *p*<0.0001) [99].

Another difficulty in using brain atrophy as a therapeutic endpoint is the loss of brain volume during short-term (approximately 1 year) treatment with anti-inflammatory DMTs [100]. This phenomenon, termed "pseudoatrophy," presumably results from resolution of edema in brain along with reduction in the number or volume of inflammatory cells, including microglia [101]. For example, in MSCRG, a post hoc analysis observed that IM IFN-β-1a reduced the progression of brain atrophy, but only by the end of the second year of treatment [102]. It is possible that pseudoatrophy in year 1 masked improvements in BVL during this time.

Supporting this hypothesis, a 3-year prospective study of 386 patients treated with IM IFN-β-1a reported that the relative decrease from baseline in brain parenchymal fraction (BPF, a normalized measure of whole-brain atrophy) was 0.686% after 1 year of therapy, 0.377% after 2 years, and 0.378% after 3 years [103]. Subgroup analysis revealed that 68% of the decrease in BPF during the first year occurred during the first 4 months of treatment (0.482% decrease at 4 months; 0.710% change at 1 year). The pretreatment annualized rate of atrophy was 1.06%, whereas the yearly rate of atrophy was 0.33% from 4 months to 3 years of active therapy [103].

Gray matter (GM) atrophy may be the most clinically relevant component of overall brain atrophy in MS [104], as it correlates with physical disability [105] and cognitive impairment [106]. The thalamus is a GM region involved in sensorimotor, cognitive, and attentional circuit functions. A subgroup analysis of 39 patients found reduced thalamic volume in patients with MS compared with normal controls (p<0.0001) and a strong correlation between thalamic volume and cognitive performance [107]. A retrospective study of MSCRG patients with available whole brain atrophy (BPF) data during the second year of treatment showed significantly less GM atrophy with IM IFN-β-1a therapy than with placebo [108]. There was no significant difference in white matter (WM) atrophy, though pseudoatrophy was more apparent in WM than in GM.

6   Cognition

Cognitive impairment occurs frequently in MS, affecting up to 65% of patients [109]. Cognitive deficits adversely impact family and social relationships, work, and self-care [110]. Results from MSCRG provided early evidence that IM IFN-β-1a treatment could slow cognitive decline in patients with MS. At 2 years, IM IFN-β-1a treatment improved information processing speed and learning/memory as assessed by the Comprehensive Neuropsychological Battery compared with placebo [111].

In the CHAMPIONS 10-year follow-up, >95% of patients treated with IM IFN-β-1a showed cognitive stability, as assessed by the Paced Auditory Serial Addition Test (PASAT), over years 5–10 of the study [112]. Patient attrition over 10 years may have introduced selection bias into CHAMPIONS, but these results still seem notable, given that a small longitudinal study of patients with untreated early-onset MS showed cognitive decline in 46% of patients over 10 years [113]. It should also be noted that learning effects may have elevated PASAT scores in CHAMPIONS, and therefore these longitudinal cognitive test results should be interpreted with caution.

The DECIDE study of patients with RRMS treated with IM IFN-β-1a or daclizumab demonstrated improvements in processing speed on the Symbol Digit Modalities Test (SDMT) for both treatments over 96 weeks, with significantly greater improvements seen with daclizumab [114]. An analysis of the DECIDE patients treated with IM IFN-β-1a (n=922) showed an association between processing speed on the SDMT and cortical GM (CGM) and thalamic volume. With MRI results re-baselined at 24 weeks (to allow time for full clinical benefit and to adjust for pseudoatrophy), SDMT improvement at 96 weeks was more pronounced in patients with low (no greater than median) CGM loss over weeks 24–96 than in those with high (greater than median) CGM loss (p=0.0031). Similarly, SDMT improvement at 96 weeks was more pronounced in patients with low thalamic volume loss than in those with high thalamic volume loss (p=0.0445; Table 3) [115]. A recent systematic review of cognitive test performance outcomes in 44 studies revealed positive effects on cognitive test performance for DMTs in general; no significant differences between the effects were seen with any single DMT, including high-efficacy DMTs, and IFN-β [116].

7   Real-World Effectiveness and Adherence

Real-world observational studies provide data on long-term MS treatment outcomes and drug adherence in routine clinical practice settings and complement the information from randomized clinical trials [117]. Real-world data from a US claims database were used to investigate outcome measures in patients with MS who were stable (relapse free for 1 year) on any IFN-β therapy and then either switched to a different IFN-β therapy or kept on their existing therapy [118]. For the subset of patients who were stable on IM IFN-β-1a at baseline, ARR was twice as high in those who switched to a different IFN-β therapy (*n*=90) than in those who continued on IM IFN-β-1a (*n*=270) over 1 year of follow-up (0.14 vs 0.07; *p*=0.012). Patients who switched to a different IFN-β therapy also had lower medication adherence rates, as assessed by medication possession ratio (defined as the sum of all days' supplies for all fills of the drug in a particular time period divided by the number of days in that time period), than those who remained on IM IFN-β-1a (0.76 vs 0.92; *p*<0.001).

Adherence can have a major impact on treatment effectiveness, and multiple studies show poor adherence with self-administered medications for chronic diseases [119]. A retrospective claims database study of 6680 patients with MS initiating treatment with an IFN-β or glatiramer acetate (GA) found higher adherence in patients initiating IM IFN-β-1a than in those initiating the other DMTs (regression-adjusted odds ratio range, 0.656–0.829). Greater adherence with IM IFN-β-1a, possibly attributable to less frequent dosing, is consistent with the results of a questionnaire-based discrete-choice survey of 205 patients indicating that patients value a reduction in injection frequency just as much as a decrease in AEs or an improvement in efficacy [120]. A questionnaire-based study of IFN-β discontinuation using the North American Research Committee on Multiple Sclerosis (NARCOMS) registry found that treatment-adherent patients reported less disability progression with IM IFN-β-1a (44.4%) than with SC IFN-β-1a or SC IFN-β-1b (59.2% for the combined groups; *p*=0.007) [121]. Safety concerns prompted fewer patients to discontinue IM IFN-β-1a (22.3%) than SC IFN-β-1a (36.3%; *p*<0.001) or SC IFN-β-1b (37.8%; *p*<0.001). Adherence may be improved by patient education, though a non-interventional observational study of 731 patients with MS treated with IM IFN-β-1a found no significant difference in treatment adherence between those who participated in a drug patient management program, consisting of injection training, support, and quarterly visits for up to 12 months after initiation of therapy, and those who did not participate (84% vs 80%; *p*=0.3058) [122]. However, treatment cost savings were twice as great for treated patients who participated in the patient management program for 6 months as for non-participants [122].

8   Treatment Non-responders and Immunogenicity

A post hoc analysis of MSCRG suggested that the quartile of patients with the greatest MRI activity while taking IM IFN-β-1a could be categorized as "treatment non-responders" [123]. A single-nucleotide polymorphism study performed in 830 patients with MS treated with IFN-β, including 416 IFN-β responders (defined as patients with no relapses and no increase in the EDSS score over ≥2 years of treatment) and 414 non-responders (defined as patients with ≥1 relapses and an EDSS score increase of ≥1.0 point confirmed at 6 months over the same period), failed to demonstrate an association between polymorphisms located in type I IFN-induced genes, toll-like receptor pathway genes, or genes encoding neurotransmitter receptors and IFN-β response [124]. Since DNA links are not obvious in response to IFN-β-1a, response heterogeneity may be due to variation in expression of IFN-β-responsive genes. Short- and long-term transcriptome profiling of peripheral blood mononuclear cells isolated from patients with MS treated with IFN-β and followed for an average of 8.14 years (range 1–19 years) has been carried out in IFN-β-treated patients (complete or partial responders), DMT-naive patients (with stable or active disease), and healthy controls [59]. For IFN-β-treated patients, there were

short-term changes in the expression profile of 1233 coding and 664 non-coding sequences 4 and 24 hours after injection (fold-change ≥1.5 or ≤−1.5; $p<0.05$). Sequences associated with immune regulation, inflammation, antiviral responses, cell cycle progression, and promotion of apoptosis were the most significantly affected. Long-term alterations in 6434 coding and 2362 non-coding sequences were also identified in ≥1 of the treated and/or untreated MS groups compared with healthy controls. Nearly all (95%) of the differentially expressed sequences were identified only in the therapy-naive groups. In contrast, both the completely and partially IFN-β-responsive patients had a long-term expression profile similar to that of the healthy controls [59]. Such large-scale differential gene expression in response to IFN-β could account for the observed non-responders to IM IFN-β-1a. IFN signature gene expression has been suggested as a candidate biomarker to identify IFN-β-responsive patients, and it may also identify novel candidate proteins or target pathways for therapeutic intervention.

The presence of IFN-neutralizing antibodies (NAbs) has been associated with reduced therapeutic effectiveness [125-127]. The titer and frequency of developing anti-IFN-β NAbs varies with the particular IFN-β therapy, as well as with the frequency and route of administration [128]. During the MSCRG phase 3 trial, 22% of the IFN treatment group developed NAbs after 2 years. However, in the subsequent CHAMPS study of patients at risk of MS after a first demyelinating event, NAbs were detected in the serum of <1% of treated patients at 18 months and 2% of patients at 30 months [81]. This marked reduction in NAb frequency likely reflects improvements in the methodology of IFN-β-1a synthesis. In addition, IM administration may pose a lower risk of NAb development than SC administration. A 2017 meta-analysis of 36 studies that included >30,000 patients with MS receiving IFN therapy found that after ≥1 year of continuous treatment, the proportion (SD) of patients developing NAbs to IFN was lower in those treated with IM IFN-β-1a (4.7% [1.5%]; $n=188$) than in those treated with SC IFN-β-1a (21.4% [2.8%]; $n=716$; $p<0.001$) or SC IFN-β-1b (32.2% [3.3%]; $n=195$; $p<0.001$) [129]. Neutralization can depend on NAb titers, which also vary among IFN preparations. Over 2 years of treatment with PEGylated IFN-β-1a, <1% of patients developed NAbs, an incidence rate that may be due in part to a reduction in immunogenicity with pegylation [130].

9   Safety and Tolerability of IM IFN-β-1a

More than 25 years of clinical and real-world experience with IFN-βs for MS have demonstrated the long-term safety and tolerability of these therapies [131]. Over 10 years of treatment with IM IFN-β-1a in CHAMPIONS, a total of 34 SAEs in 25 patients were reported, none of which were considered likely to be related to treatment, and no new safety signals were identified [85, 86]. These results demonstrated the long-term safety of IM IFN-β-1a. A phase 4, multicenter, retrospective and prospective observational study found that similar proportions of patients receiving IM IFN-β-1a and SC IFN-β-1a reported AEs, though fewer patients treated with IM IFN-β-1a experienced injection site reactions (ISRs) [132].

Safety outcomes for IM IFN-β-1a and SC IFN-β-1a were also investigated over 1 year of treatment in the EVIDENCE study. ISRs were more frequent with SC IFN-β-1a than with IM IFN-β-1a, as were liver enzyme abnormalities, altered leukocyte counts, and the development of NAbs, though patient discontinuation rates were similar [88]. At the last assessment after 16 months of treatment, 21% of SC IFN-β-1a patients were persistently NAb-positive, compared with 3% of IM IFN-β-1a patients ($p<0.001$).

9.1   Flu-Like Symptoms and Injection Site Reactions

One of the most commonly reported AEs/safety concerns for each of the IFN-β therapies during clinical trials and post-marketing surveillance is flu-like symptoms (FLS) [49, 51-53]. This is not surprising, given that native IFNs are responsible for flu symptoms during infection by influenza

viruses [133, 134]. AEs such as FLS and ISRs are important factors in lack of adherence to IFN-β, typically ranking just below perceived lack of treatment effectiveness in importance. In MSCRG, FLS were the most common AE, reported by 61% of the IM IFN-β-1a group and 40% of the placebo group [79]. Similar proportions of patients had FLS during the first 6 months of CHAMPS [81]. A retrospective hospital chart–based study of 394 patients with MS treated with IFN-β for ≤8 years found that FLS and ISRs were the most often cited reasons for discontinuation [135]. Patients receiving IM IFN-β-1a are less likely to experience ISRs than patients receiving SC IFN-β-1a, so it was anticipated that patients receiving IM treatment would be less likely to discontinue medication as well [132]. Consistent with this, a NARCOMS registry study reported that patients treated with IM IFN-β-1a reported fewer discontinuations due to safety concerns than patients treated with SC IFN-β-1a or IFN-β-1b [121].

To reduce the negative impact of FLS and ISRs upon treatment adherence, successful strategies for mitigation and management of these AEs have been developed [136, 137]. Patient education that includes information about the frequency, severity, and management of FLS and ISRs may optimize treatment adherence and clinical outcomes [138-141]. The 12-month observational PERSIST study of 232 patients with MS demonstrated that the use of an IM IFN-β-1a autoinjector pen was also associated with high levels of persistence, compliance, adherence, and patient satisfaction, with little to no pain and minimal need for caregiver assistance [174].

10   Pregnancy

Women are disproportionately affected by MS and are often diagnosed and treated during childbearing years [142]. While patients can continue to take IFN-β before pregnancy, treatment choice during pregnancy planning and pregnancy and postpartum strategies regarding resumption of therapy are essential.

Recent observational data from European and Nordic (Finland and Sweden) healthcare registries of pregnant women with MS treated with IFN-β indicate that exposure to IFNs is not associated with adverse pregnancy outcomes. It should be noted that most exposure to IFN-β in these cases occurred before or during the first trimester of pregnancy [143, 144]. European MS registry data showed that 82.0% (777 of 948) of pregnancies in women who were treated with IFN-β resulted in live births without congenital anomalies. The prevalence of congenital anomalies (1.8% [17 of 948]), spontaneous abortions (10.7% [101 of 948]), and ectopic pregnancies (0.4% [4 of 948]) with live birth were within the ranges reported for the general population [143]. Similar results were obtained from the Nordic registries for pregnant women with MS exposed only to IFN-β compared with pregnant women with no exposure to any MS DMT. In the IFN-β-exposed and unexposed cohorts, live births with congenital anomaly occurred in 1.8% (12 of 666) and 4.0% (56 of 1397) of cases, respectively, spontaneous abortions in 8.3% (66 of 797) and 12.0% (197 of 1647) of cases, respectively, and ectopic pregnancies in 1.6% (13 of 797) and 3.2% (53 of 1647) of cases, respectively [145].

A separate analysis of Nordic registry data demonstrated that exposure to IFN-β did not affect infant outcomes (including birth weight, head circumference, and live birth with congenital malformation) compared with pregnancies with no exposure to any DMT. There was no difference in birth weight or infant head circumference between the exposed and unexposed cohorts [146].

Exposure to IM IFN-β-1a while breastfeeding does not appear to be associated with significant infant exposure. A small study of six breastfeeding patients with MS estimated, using the highest measured value of IM IFN-β-1a in breastmilk, that the relative infant dose was 0.006% of the maternal dose [147]. Similar results were recently reported for infant exposure to pegylated IFN-β-1a in breastmilk [148] .

Recently, the FDA and the European Medicines Agency approved updates to the IFN-β product information labels indicating that women may continue taking IFN-β during pregnancy and while breastfeeding [49-53, 149-151].

11   IFN-β and QoL

Patient-reported outcomes (PROs) have become increasingly important in therapeutic research and clinical practice in understanding of the effects of MS on patients' daily lives and how DMTs ameliorate those effects. PROs can include overall health status, MS symptom impact, physical and mental functioning, and health-related QoL (HRQoL). PROs are also applicable to comparative effectiveness research and real-world clinical settings [152].

Neurological symptoms experienced by patients with MS may interfere with daily life. Patients with MS rank their HRQoL lower than individuals with other neurological and chronic diseases or healthy individuals [6]. The effect of IM IFN-β-1a on HRQoL was evident in a retrospective evaluation of a subgroup of patients originally enrolled in MSCRG. QoL assessed by the Sickness Impact Profile, a validated patient-reported measure of overall health, remained stable with IM IFN-β-1a treatment over 2 years [153]. At the ASSURANCE year 15 follow-up assessment of patients who completed the 2-year pivotal phase 3 MSCRG trial, patients who stayed on IM IFN-β-1a, compared with patients who discontinued treatment, had better average scores on the physical component summary (39.3 vs 31.0; $p<0.0001$) and the physical functioning (53.0 vs 27.7; $p<0.001$), role-physical (46.0 vs 27.8; $p<0.05$), and general health (64.0 vs 51.4; $p<0.05$) subscales of the Short-Form Health Survey-36 [83].

Observational studies also demonstrate an association between IM IFN-β-1a treatment and improvements in QoL. A 2-year, prospective, observational phase 4 study in 284 patients found that IM IFN-β-1a treatment was associated with an increase in Multiple Sclerosis Quality of Life-54 (MS54QoL) physical domain score from 56.6 at baseline to 61.0 at 2 years ($p<0.05$). There was a trend towards improvement in MS54QoL mental domain score from 57.2 to 61.1 ($p=0.07$) over the same period [154]. In another observational retrospective study of 445 patients with RRMS treated with injectable DMTs, the Treatment Satisfaction Questionnaire for Medication showed that patient satisfaction ranged from 62% to 72%; of the patients treated with IM IFN-β-1a, 69% expressed overall satisfaction with their treatment [155].

11.1   IFN-β and depression

Therapeutic use of IFNs has been associated with an increased risk of subjective feelings of illness, including fatigue and depression, collectively known as cytokine sickness behavior [156]. Neuropsychiatric side effects, including depression and suicide, were first identified in patients treated with IFNα for viral hepatitis infection [157, 158], and a 2012 meta-analysis confirmed a 25% incidence of major depressive episodes in patients who initiate treatment with IFNα [159]. While the labels for all MS IFN-β therapies carry a warning for depression and suicide, much of the evidence from the published literature does not support the association of IFN-β therapy with depression. A retrospective review of medical records from 2000–2007 of 112 patients with RRMS treated exclusively with IFN-β or GA found no change in baseline depression scores over 4 years and no exacerbation of depressive symptoms with either DMT [160]. Similarly, a cross-sectional study of 694 patients with MS found no significant relationship between depression levels and IFN treatment [161]. A systematic review of 10 studies found that while most of the included studies did not suggest an association between depression and IFN-β therapy, 3 studies indicated that patients with a prior history of depression may develop a major depressive episode during the first 6 months of treatment [162]. As noted in section 1.1, MS has a profoundly negative impact on patients' QoL, and persons with MS report lower QoL than those with other chronic conditions, including rheumatoid arthritis,

inflammatory bowel disease, epilepsy, and diabetes [163, 164]. The prevalence of depression is also greater in patients with MS than with other chronic conditions [165]; depression has been associated with increased neuroinflammatory activity and elevated levels of proinflammatory cytokines [156, 166, 167]. However, treatment of depression in patients with MS is associated with significant increases in QoL and improved adherence to treatment [168-171]

12 The Role of IM IFN-β-1a in the Current MS Therapeutic Landscape

12.1 Escalation Versus High-Efficacy Therapy

As the number of approved MS therapies has expanded, so has the complexity of treating MS. The newer therapies vary in efficacy, safety profile, and route and ease of administration [172]. The benefit of early treatment in MS highlights the importance of the choice of initial therapy [173]. Many factors play a role in treatment decisions, including age, sex, child-bearing potential, disease activity, comorbid conditions, previous DMT use, risk tolerance, and cost.

One common therapeutic approach is to use a first-line DMT that is considered safe and moderately efficacious (relative to higher-efficacy DMTs), followed by a period of monitoring and escalation to more efficacious treatment as disease activity necessitates [174]. Conversely, treating early with high-efficacy therapies may prevent the accumulation of irreversible long-term CNS damage [175]. However, high-efficacy therapies may be associated with greater risk of SAEs [176]. Thus, the decision whether to initiate treatment with high-efficacy medications or switch to them later must be balanced against the benefit-risk profile of each treatment approach and should be the result of a shared decision by healthcare providers and patients. The ongoing Determining the Effectiveness of earLy Intensive Versus Escalation Approaches for RRMS (DELIVER-MS) study, which began in May 2018 (with an estimated study completion date of September 2023), will compare the benefits and risks of starting treatment with an escalation approach versus initiating treatment with high-efficacy medications in patients with RRMS [177].

In another approach, after beginning treatment with a high-efficacy oral or infusible DMT as their initial therapy, patients may be switched to a first-line DMT after a period of stable disease or if/when AEs associated with the high-efficacy therapy occur. Initial treatment with immunosuppressive agents that target and ablate B-cell lymphocytes followed by long-term treatment with immunomodulatory DMTs, including IFNs ("induction therapy"), has been studied in randomized clinical trials (reviewed in [175]). In the randomized, partially placebo-controlled exploratory RESTORE study, patients with relapsing MS who were stable on natalizumab for ≥1 year were randomized 1:1:2 to continue natalizumab, switch to placebo, or switch to an alternate immunomodulatory therapy (IM IFN-β-1a, GA, or methylprednisolone). After 24 weeks, 40% of patients who switched to an alternate therapy or placebo had disease recurrence as assessed by new Gd+ lesions on MRI, including 1 of 14 patients receiving IM IFN-β-1a (7%), 8 of 15 patients receiving GA (53%), 21 of 52 patients receiving methylprednisolone (40%), and 19 of 41 patients receiving placebo (46%) [178].

12.2 Patient Subpopulations Who Might Benefit from IFN-β Therapy

As previously noted, IFNs are well tolerated in pregnant and nursing women. Women receiving DMTs that are contraindicated before/during pregnancy (i.e., fingolimod or teriflunomide) may, in consultation with their healthcare provider, consider IFN-β treatment for a "bridge" period after discontinuation of these DMTs. In addition, patients at high risk for serious infections, such as older patients with active inflammatory disease and patients with comorbidities that elevate the risks associated with higher-efficacy medications, may benefit from the established safety profile of IFN-β.

Given the role of IFNs in native immune responses to viral infections, it is not surprising that the antiviral properties of IFN-βs have been investigated in MS. Sera from patients treated with IM IFN-β-1 (*n*=23) had lower levels of latent neurotropic human herpes virus 6 (HHV6) cell–free DNA and higher levels of anti-HHV6 immunoglobulin M antibodies than sera from untreated patients with MS or healthy individuals [179].

In response to the novel coronavirus first identified in late 2019 (COVID-19), it has been hypothesized that type I IFNs (including IFN-β-1a) may, in combination with other antiviral agents, be effective for the treatment of human coronavirus infection, including infection by Middle East respiratory syndrome coronavirus (MERS-CoV) and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2, the causative agent of COVID-19), if administered early in the infection (reviewed in [180]). Recently, a small, prospective randomized study of patients hospitalized with COVID-19 infection found a reduction in the duration of viral shedding and hospital stay and greater alleviation of symptoms in patients treated with a combination of lopinavir, ritonavir, ribavirin, and IFN-β-1b compared with those treated with lopinavir and ritonavir treatment alone [181]. A recent observational study of confirmed or suspected COVID-19 cases in 625 patients with MS with currently taking a prescribed DMT demonstrated a lower risk of COVID-19 infection in patients currently taking an IFN-β therapy than would be expected based on the size of the overall MS population [182]. With respect to management of patients with MS, it is important to note that most DMTs, including IFN-β, do not appear to have major short- or long-term impacts on immune protection against COVID-19 [183, 184]. However, adjustments to dosing schedules may reduce the risk of viral infection and allay other concerns of patients with MS being treated during the COVID-19 pandemic [185].

The well-established safety profile of IFN-β DMTs suggests that they may be useful in patients with comorbidities that can be exacerbated by certain MS therapies. The age of the MS patient population is increasing due to the increased use of efficacious therapies for MS and better interventions for MS-related comorbidities [186, 187]. A small number of people are diagnosed later in life than most patients with MS with what is referred to as "late-onset" MS [188, 189]. Aging is frequently accompanied by immunosenescence, a functional reduction in function of the innate and adaptive immune systems [190]. In particular, a paucity of recent thymocyte emigrants, as well as changes in B cells and CD4+/CD8+ T cells in MS, can compound the immunosuppressive effect of some DMTs. Elderly patients with MS frequently also have age- and disease-related comorbidities that can complicate their management [191]. IFN-βs may have potential advantages in the treatment of this elderly MS population.

13   Conclusions

Since the discovery of the antiviral role of IFNs in 1957, research has demonstrated that IFN-β has immunomodulatory effects [192] and promotes the production of anti-inflammatory cytokines [71, 72] and multiple immune regulatory pathways [59]. MSCRG, the pivotal IM IFN-β-1a phase 3 trial, was the first to study to show that a DMT could improve disability outcomes in MS [79]. Clinical trials and real-world observational studies have since demonstrated the effectiveness of IM IFN-β-1a for treating MS [81, 82, 85, 86, 118, 121, 129, 193]. Treatment with IM IFN-β-1a is associated with significant reductions in the number and volume of T2 and Gd+ MRI lesions [79, 80] and GM atrophy relative to placebo [108]. Head-to-head comparisons of several newer MS therapies with IM IFN-β-1a have consistently found no significant between-group differences with regard to disability outcomes [90, 91]. Finally, cognitive benefits [111, 112] and QoL improvements [153, 83, 154] have been observed with ≥2 years of treatment with IM IFN-β-1a.

In the years since the approval of the IFN-βs, the MS therapeutic landscape has changed dramatically [194]. This changing landscape presents both challenges in terms of balancing

efficacy with safety and opportunities to develop individualized long-term treatment strategies for persons with MS.

Compliance with Ethical Standards

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Table 1 Pivotal clinical trials of IM IFN-β in MS

Study	Design	Treatment	Patients	Study duration	Key data	References
IT study of IFN-β	Multicenter, randomized, open label, PBO controlled	IFN-β 10^6 IRU/m^2 at each lumbar puncture semiweekly for the first 4 weeks and once per month for the next 5 months	MS (n=20)	IFN-β: 1.8–2.0 years PBO: 1.5–1.7 years	At 6 months, patients who received IT IFN-β were more likely to show improvement in their clinical condition than those who received PBO (p<0.036)	Jacobs et al., 1981 [44]; Jacobs et al., 1982 [45]
MSCRG	Multicenter, randomized, double blinded, PBO controlled	IFN-β-1a 30 μg IM QW for up to 104 weeks	RMS (n=301)	104 weeks	Clinical outcomes: Over 104 weeks, the time to 6-month CDW was greater in patients treated with IM IFN-β-1a than with PBO (p=0.02). At 104 weeks, estimated proportion of patients with 6-month CDW was 21.9% with IM IFN-β-1a and 34.9% with PBO. In patients followed for ≥104 weeks, ARR was 0.61 with IM IFN-β-1a and 0.90 with placebo (p=0.002)	Jacobs et al., 1996 [79]
					MRI outcomes: After 1 year of treatment, IM IFN-β-1a treatment caused greater reductions than PBO in the number (67.2% vs 31.5% reduction; p=0.02) and volume (72.5% vs 55.9% decrease; p=0.02) of Gd+ lesions. Differences were sustained over 2 years of treatment (reduction in number of lesions: 74.8% vs 28.9%; p=0.05; reduction in volume of lesions: 70.9% vs 44.1%; p=0.03)	
					Follow-up MRI analyses: After 2 years, IM IFN-β-1a patients compared with PBO patients had a lower mean (SD) number of new or newly enlarging T2 lesions (3.2 [3.6] vs 4.8 [4.4]; p=0.002)	Simon et al., 1998 [80]

CHAMPS	Multicenter, randomized, double blinded, PBO controlled	IM IFN-β-1a 30 μg QW for 3 years	Patients who had a first acute, clinical demyelinating event (*n*=383)	3 years	Clinical outcomes: After 3 years of treatment, the estimated cumulative probability of CDMS was lower with IM IFN-β-1a than with PBO (RRR 30%; RR 0.56; 95% CI 0.38–0.81; *p*=0.002)	Jacobs et al., 2000 [81]
					MRI outcomes: At 18 months, IM IFN-β-1a patients had less increase than PBO patients in the volume of T2 lesions (28 mm^3 vs 313 mm^3; *p*<0.001), fewer new or newly enlarging T2 lesions (mean [SD] 2.1 [3.2] vs 5.0 [7.7]; *p*<0.001), and fewer Gd+ lesions (0.14 [1.5] vs 1.4 [3.6]; *p*<0.001)	
					Subgroup analyses: Over 2 years, IM IFN-β-1a had a lower estimated probability of reaching a composite endpoint of CDMS *or* >1 new or newly enlarging T2 lesions than PBO (RRR 27.2%; RR 0.47; 95% CI 0.36–0.62; *p*<0.001) in the overall CHAMPS population. Analysis of patients based on the initial demyelinating event demonstrated similar estimated probabilities for the composite endpoint (optic neuritis adjusted RR 0.50 [*p*<0.001]; brainstem/cerebellum adjusted RR 0.41 [*p*<0.001]; spinal cord adjusted RR 0.40 [*p*=0.004]); RR adjusted for T2 lesion volume and number of Gd+ lesions at baseline	Beck et al., (2002) [82]

ARR annualized relapse rate, *CDMS* clinically definite multiple sclerosis, *CDW* confirmed disability worsening, *Gd+* gadolinium enhancing, *IFN* interferon, *IM* intramuscular, *IRU* interferon reference units, *IT* intrathecal, *MRI* magnetic resonance imaging, *MS* multiple sclerosis, *MSCRG* Multiple Sclerosis Collaborative Research Group, *PBO* placebo, *QW* once weekly, *RMS* relapsing multiple sclerosis, *RR* rate ratio, *RRR* relative risk reduction, *SD* standard deviation.

Table 2 Long-term extension and follow-up studies

Study	Design	Treatment	Patients	Study duration	Key data	References
MSCRG 8-year follow-up	Multicenter, open-label extension	IFN-β-1a 30 μg IM QW for 8 years	RRMS treated for 2 years in MSCRG (*n*=203)	8 years	EDSS: A lower proportion of patients randomized to IM IFN-β-1a than to placebo progressed to an EDSS score ≥4.0 (44.3% vs 65.4%; RRR 32.3%; *p*=0.007) or ≥5.0 (34.2% vs 54.3%; RRR 36.9%; *p*=0.01)	Rudick et al., 2010 [195]
MSCRG 15-year follow-up (ASSURANCE)	Multicenter, open-label extension	IFN-β-1a 30 μg IM QW for 15 years	RRMS treated for 2 years in MSCRG (*n*=122)	15 years	EDSS: Patients initially randomized to IM IFN-β-1a had better disability outcomes than those randomized to placebo on metrics including mean EDSS scores (5.1 vs 5.7), EDSS increase from BL (2.9 vs 3.3), and progression to EDSS score ≥4.0 (73.9% vs 79.1%), ≥6.0 (47.8% vs 58.2%), and ≥7.0 (24.6% vs 31.3%). Patients currently receiving IM IFN-β-1a had a lower mean EDSS score (4.4 vs 5.7; *p*=0.011) and a smaller mean increase from BL EDSS score (2.3 vs 3.3; *p*=0.011) than those no longer receiving IM IFN-β-1a	Bermel et al., 2010 [83]
CHAMPIONS 5-year follow-up	Multicenter, open-label extension	IFN-β-1a 30 μg IM QW for 5 years	Clinically defined 1st demyelinating event, then treated in CHAMPS (*n*=203)	5 years	CDMS: The cumulative probability of development of CDMS was lower in patients randomized to IM IFN-β-1a than to PBO in CHAMPS (5-year incidence 36% ± 9% vs 49% ± 10%; HR 0.65; 95% CI 0.43–0.97; *p*=0.03). MRI outcomes: At 5 years, IM IFN-β-1a patients had fewer new or newly enlarging T2 lesions than PBO patients (median [Q1, Q3] 3.5 [0.5, 8.5] vs 6.0 [2.0, 13.0]; *p*=0.05). Changes in T2 lesion volume from BL (median [Q1, Q3] 646 [105, 2599] mm^3 increase vs 827 [107, 4112] mm^3 increase; *p*=0.10) and the proportion of patients with ≥1 Gd+ lesion (29% vs 30%; *p*=0.81) were similar between the two groups	Kinkel et al., 2006 [85]

| CHAMPIONS 10-year follow-up | Multicenter, open-label extension | IFN-β-1a 30 µg IM QW for 10 years | Clinically defined first demyelinating event treated in CHAMPS (*n*=155) | 10 years | CDMS: Patients randomized to immediate treatment with IM IFN-β-1a in CHAMPS had a lower cumulative probability of CDMS than those randomized to PBO (delayed treatment) (58% [95% CI 48–68%] vs 69% [95% CI 61–78%]; unadjusted HR 0.64 [95% CI 0.48–0.87]; *p*=0.004)

ARR: Between years 5 and 10, the immediate-treatment group had lower mean (SD) ARR than the delayed treatment group (0.14 [0.21] vs 0.31 [0.41]; *p*=0.03) and over the entire follow-up period (0.16 [0.18] vs 0.33 [0.41]; *p*=0.02)

EDSS: After 10 years of follow-up, 81% of patients had an EDSS score <3.0 (immediate treatment 82% vs delayed treatment 80%; *p*=0.61)

MRI outcomes: At 10 years, there was no significant difference between groups in the number of new or newly enlarging T2 lesions (median [IQR] immediate treatment 5 [1–12] vs delayed treatment 7 [3–17]; *p*=0.50), and most patients had no Gd+ lesions (immediate treatment 81%; delayed treatment 80%). From year 5 to year 10, there was no significant difference between groups in the change in T2-weighted lesion volume (median [IQR] immediate treatment 1752 [460-4621] mm^3 vs delayed treatment 917 [199-3060] mm^3; *p*=0.26) | Kinkel et al., 2012 [86] |

ARR annualized relapse rate, *BL* baseline, *CDMS* clinically definite multiple sclerosis, *CI* confidence interval, *EDSS* Expanded Disability Status Scale, *Gd+* gadolinium enhancing, *HR* hazard ratio, *IFN* interferon, *IM* intramuscular, *IQR* interquartile range, *MRI* magnetic resonance imaging, *MSCRG* Multiple Sclerosis Collaborative Research Group, *PBO* placebo, *QW* once weekly, *RRMS* relapsing-remitting multiple sclerosis, *RRR* relative risk reduction, *SD* standard deviation

Table 3 Head-to-head studies of comparative efficacy

Study	Design	Treatment	Patients	Study duration	Key data	References
EVIDENCE	Multicenter, randomized, parallel group, assessor blinded	IFN-β-1a 44 μg SC TIW for 24 weeks IFN-β-1a 30 μg IM QW for 24 weeks	RRMS, IFN naive (*n*=677)	48 weeks	Relapses: A greater proportion of SC IFN-β-1a than IM IFN-β-1a patients was relapse free after 24 weeks (75% vs 63%; OR [95% CI] 1.9 [1.3–2.6]; *p*=0.0005) and 48 weeks (62% vs 52%; OR [95% CI] 1.5 [1.1–2.1]; *p*=0.009). ARR in the SC IFN-β-1a and IM IFN-β-1a groups was 0.29 vs 0.41 (*p*=0.022) at 24 weeks and 0.54 vs 0.64 (*p*=0.094) at 48 weeks	Panitch et al., 2002 [87]
					Disability progression: No significant difference was seen between the SC and IM IFN-β-1a groups in the proportion of patients with 6-month CDW over 48 weeks (5.9% vs 8.3%; HR [95% CI] 0.70 [0.39–1.25]; *p*=0.23)	
					MRI outcomes: More patients receiving SC IFN-β-1a than IM IFN-β-1a had no new Gd+ lesions or new or newly enlarging T2 lesions at 24 weeks (48% vs 33%; *p*<0.001)	
					NEDA: At 24 weeks, more patients treated with SC IFN-β-1a achieved NEDA than those treated with IM IFN-β-1a (59.5% vs 41.2%; OR [95% CI] 2.32 [1.64–3.28; *p*<0.001). When all 6-monthly scans over 24 weeks were taken into account 35.0% of SC IFN-β-1a patients achieved NEDA compared with vs 21.6% of IM IFN-β-1a patients (OR [95% CI] 2.28 [1.52–3.41]; *p*<0.001)	Coyle et al., 2017 [89]
				64 weeks	Relapses: Over an average follow-up time of 64 weeks, more SC IFN-β-1a than IM IFN-β-1a patients were relapse free (56% vs 48%; OR [95% CI] 1.5 [1.1–2.0]; *p*=0.023); ARR was lower with SC IFN-β-1a than with IM IFN-β-1a (0.54 vs 0.65; *p*=0.033)	Panitch et al., 2005 [88]
					MRI outcomes: More patients receiving SC IFN-β-1a than IM IFN-β-1a had no new or newly enlarging T2 lesions (58% vs 38%; OR [95% CI] 2.4 [1.7–3.3]; *p*<0.001)	
					Disability progression: No significant difference between the SC IFN-β-1a and IM IFN-β-1a groups was seen in the	

					proportion of patients with 6-month CDW (16% vs 17%; p=0.710)	
TRANSFORMS	Multicenter, randomized, comparative, double blind, double dummy, parallel group	Oral fingolimod 1.25 mg QD for 12 months Oral fingolimod 0.5 mg QD for 12 months IFN-β-1a 30 µg IM QW for 12 months	RRMS (*n*=1153)	12 months	Relapses: ARR was lower in the 1.25 mg fingolimod group (0.20; 95% CI 0.16–0.26) and the 0.5 mg fingolimod group (0.16; 95% CI 0.12–0.21) than the IM IFN-β-1a group (0.33; 95% CI 0.26–0.42; *p*<0.001 vs both fingolimod groups). Disability progression: There was no significant difference in the proportion of patients without 3-month CDW with IM IFN-β-1a (92.1%; 95% CI 89.4–94.7%) vs fingolimod 1.25 mg (93.3%; 95% CI 90.9–95.8%; *p*=0.50) or fingolimod 0.5 mg (94.1%; 95% CI 91.8–96.3%; *p*=0.25)	Cohen et al., 2010 [90]
DECIDE	Multicenter, randomized, double blind, active controlled	Daclizumab 150 mg SC Q4W for 96–144 weeks IFN-β-1a 30 µg IM QW for 96–144 weeks	RRMS (*n*=1481)	144 weeks	Relapses: ARR over 144 weeks was lower with daclizumab than with IM IFN-β-1a (0.22 vs 0.39, *p*<0.001). The estimated proportion of patients free from relapse at 144 weeks was greater for daclizumab than IM IFN-β-1a (67% vs 51%; HR [95% CI] 0.59 [0.50–0.69]) MRI: Patients treated with daclizumab had fewer new or newly enlarging T2 lesions at 96 weeks than those treated with IM IFN-β-1a (mean [95% CI] 4.3 [3.9–4.8] vs 9.4 [8.5–10.5]; *p*<0.001) Disability progression: There was no significant difference in the estimated proportion of daclizumab or IM IFN-β-1a patients with 3-month CDW after 144 weeks (16% vs 20%; HR [95% CI] 0.84 [0.66–1.07]; *p*=0.16)	Kappos et al., 2015 [91]
					Cognition: IM IFN-β-treated patients with low CGM loss showed greater improvement in processing speed on SDMT from week 24 to week 96 than those with high CGM loss (mean [SE] 3.86 [0.784] vs 1.49 [0.932]; *p*=0.0031). Patients with low thalamic volume loss showed greater improvement in processing speed on SDMT from week 24 to week 96 than those with high thalamic volume loss mean [SE] (4.03 [0.769] vs 1.66 [0.935]; *p*=0.0445)	Benedict et al., 2019 [115]

RADIANCE	Multicenter, randomized, double-blind, double-dummy, active-controlled, parallel group	Oral ozanimod 0.5 mg QD for 24 months Oral ozanimod 1.0 mg QD for 24 months IFN-β-1a 30 μg IM QW for 24 months	RMS (*n*=1320)	24 months	Relapses: ARR over 24 months was lower for patients treated with ozanimod 1.0 mg than with IM IFN-β-1a (0.17 vs 0.28; *p*<0.0001). MRI: Patients treated with ozanimod 1.0 mg had fewer new or newly enlarging T2 lesions per scan over 24 months (adjusted mean [95% CI] 1.84 [1.52–2.21] vs 3.18 [2.64–3.84]; RR [95% CI] 0.58 [0.47–0.71]; *p* < 0.0001) and fewer Gd+ lesions at 24 months (adjusted mean [95% CI] 0.18 [0.12–0.27] vs 0.37 [0.26–0.54]; RR [95% CI] 0.47 [0.31–0.73]; *p*=0.0006) Disability progression: There was no significant difference in the proportion of ozanimod or IM IFN-β-1a patients with 3-month CDW (12.5% vs 11.3%; HR [95% CI] 1.05 [0.71–1.54]; *p*=0.8224) or 6-month CDW (9.7% vs 6.6%; HR [95% CI] 1.44 [0.89–2.31]; *p*=0.1353)	Cohen et al., 2019 [92]

ARR annualized relapse rate, *CDW* confirmed disability worsening, *CGM* cortical gray matter, *CI* confidence interval, *Gd+* gadolinium enhancing, *HR* hazard ratio, *IFN* interferon, *IM* intramuscular, *MRI* magnetic resonance imaging, *NEDA* no evidence of disease activity, *OR* odds ratio, *QD* once daily, *QW* once weekly, *RMS* relapsing multiple sclerosis, *RR* rate ratio, *RRMS* relapsing-remitting multiple sclerosis, *SC* subcutaneous, *SDMT* Symbol Digit Modalities Test, *SE* standard error, *TIW* three times weekly

Fig. 1 Timeline of key developments in the history of interferon (IFN). *FDA* Food and Drug Administration, *IM* intramuscular, *IT* intrathecal, *MSCRG* MS Collaborative Research Group, *RCT* randomized controlled trial, *SC* subcutaneous; [a]Krause and Petska, 2005 [196]; [b]Isaacs et al., 1957 [31]; [c]Jacobs et al., 1991; 1992 [44, 45]; [d]SC IFN-β-1b (Betaseron® and Extavia®), 1993 [49, 51]; [e]Jacobs et al., 1996 [79]; [f]IM IFN-β-1a (Avonex®), 1996 [52]; [g]Jacobs et al., 2000 [81]; [h]SC IFN-β-1a (Rebif®), 2002 [53]; [i]Kinkel et al., 2012 [86]; [j]SC pegylated IFN-β-1a (Plegridy®) [54]; [k]Cohan et al, 2018; Fox et al., 2012; Gajofatto et al., 2009; Einarson et al., 2017 [129].

Figure 1. Timeline of key developments in the history of interferon (IFN)