Interferon β for Multiple Sclerosis

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Despite that the availability of new therapeutic options has expanded the multiple sclerosis (MS) disease-modifying therapy arsenal, interferon β (IFN- β) remains an important therapy option in the current decision-making process. This review will summarize the present knowledge of IFN- β mechanism of action, the overall safety, and the short- and long-term efficacy of its use in relapsing remitting MS and clinically isolated syndromes. Data on secondary progressive MS is also provided, although no clear benefit was identified.

From the first report of intrathecal interferon (IFN) use by Jacobs et al. (1981) and the approval of IFN- β -1b (Betaseron) in 1993 (The IFNB Multiple Sclerosis Study Group 1993), IFN- β therapies became the first major therapeutic class of drugs developed for use in multiple sclerosis (MS) (Weinstock-Guttman 2013). Additional IFN- β -based products, including intramuscular (IM) IFN- β -1a (Avonex, Biogen), subcutaneous (SC) IFN- β -1a (Rebif, EMD Serono), and PEGylated IFN (PEG-IFN)- β -1a (Plegridy, Biogen) have expanded the repertoire of IFN- β Food and Drug Administration (FDA)-approved drugs. Even though IFNs only partially attenuate the relapse rate and slow the progression of the disease, they

opened a new era of therapeutic interventions that has reshaped the natural history of the disease (Trojano et al. 2007; Cree et al. 2016). The complex and heterogeneous immunological milieu of the MS disease process may explain the partial effectiveness of IFN- β in a subset of patients. Therefore, a better understanding of the pathophysiology of the disease itself and of the IFN- β -mediated signaling pathways will ultimately lead to more effective and safer treatment decisions. This article summarizes the 25-year-old successful use of IFN- β treatments for MS. In particular, this article reviews the mechanism of action (MOA), clinical efficacy, safety profile, and adherence of IFN- β therapy in MS.

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Figure 1. Molecular mechanisms of action of interferon β (IFN- β). Decrease of cellular expression of adhesion molecules (VLA-4) and cleavage of endothelial vascular cell adhesion protein (VCAM) results in decrease in cell sequestration through the blood–brain barrier. Additional decrease of matrix metalloproteinase (MMP) diminishes the ability for lymphocyte penetration. Activation of IFNAR1/2 receptors results in phosphorylation of signal transducers and activators of transcription (STAT)1-STAT2 factors that further results in secretion of anti-inflammatory cytokine profiles. Activation of IFNAR1/2 also results in decrease of major histocompatibility complex II (MHC II) expression and diminishes lymphocyte activation. IFN- β also increases apoptotic markers like Annexin-V and active caspase-3 via Fas-receptor/transmembrane activator and CAML interactor (TACI) signaling, resulting in specific depletion of memory B cells. IL, Interleukin.

MECHANISM OF ACTION OF INTERFERON β IN MULTIPLE SCLEROSIS

The initial interest in IFN as a potential therapeutic option in MS was motivated primarily by the known antiviral activities of IFNs. Subsequently, the immunomodulatory and antiproliferative properties of IFNs were discovered. The exact MOA of IFN- β therapies in MS is not fully understood. Their beneficial treatment effect is considered to be related to several overlapping mechanisms such as the down-regulation of the major histocompatibility complex

(MHC) class II expression present on the antigen-presenting cells (i.e., dendritic cells, Langerhans cells, and B-cell lymphocytes), induction of T-cell production of interleukin 10 (IL-10), which shifts the balance toward the anti-inflammatory T helper (Th)-2 cells, and inhibition of T-cell migration as a result of blockade of metalloproteases and adhesion molecules (Dhib-Jalbut and Marks 2010) (a short synopsis of IFN MOA is shown in Fig. 1). These MOAs are mediated through transcriptional factors and subsequent gene regulation. The major route in which IFN- β produces its effect is by activating

the Janus kinase (JAK)-signal transducers and activators of transcription (STAT) pathway. IFN- β binding to the type I IFN receptor causes phosphorylation of STAT1 and STAT2 and the formation of STAT1-STAT2 heterodimers, which translocate to the nucleus, bind the IFN-stimulated response element (ISRE), and modulate the expression of ISRE-regulated genes (Ransohoff 1998). The cellular response to IFNs is complex and results in changes in the expression of more than 500 genes representing $\sim 0.5\%$ of the human genome (Weinstock-Guttman et al. 2003). More recently, up-regulation of mechanisms that require FAS-receptor/TACI (transmembrane activator and CAML interactor) signaling and production of apoptotic markers like Annexin-V and caspase-3 were shown as specific inducers of B-cell apoptosis. Because of the increasing evidence of the pivotal B-cell role in MS immunopathology, this IFN- β MOA becomes even more relevant (Rizzo et al. 2016).

There are two forms of recombinant IFN- β that are in use for treatment of MS. IFN- β -1b is produced in *Escherichia coli*, it is not glycosylated, and has subtle, but important amino acid differences from the naturally occurring IFN- β . These differences result in lower biological-specific activity, which requires larger doses and increases the risk of developing neutralizing antibodies. IFN- β -1b also shows strong and reversible binding to human serum albumin, which contributes to decrease the relative potency to 10% when compared to the equivalent IFN- β -1a formulation (Goodin 2005). IFN- β -1a is produced in the Chinese hamster ovary cell line and its amino acid sequence is identical to that of the native IFN.

CLINICAL EFFICACY OF INTERFERON- β IN RELAPSING REMITTING MULTIPLE SCLEROSIS (RRMS)

The IFN- β Multiple Sclerosis Study Group

The initial 2-year, double-blinded, placebo-controlled trial for IFN- β -1b that started enrollment in 1988 was the first study to report beneficial treatment effects in MS (The IFNB Multiple Sclerosis Study Group 1993). The study partic-

ipants were randomized into placebo, low-dose IFN- β (1.6 million international units [MIU]), and high-dose IFN- β (8 MIU) administered subcutaneously every other day (QOD). The relapse rate was less in the 8 MIU IFN- β group compared to the 1.6 MIU group and placebo (0.84 vs. 1.17 vs. 1.27, respectively). The 3-year extension of this trial failed to show statistical significance, although it indicated a trend in decreasing disability compared to placebo ($p = 0.161$). Additionally, 52 patients enrolled at the British Columbia site underwent frequent magnetic resonance imaging (MRI) exams (every 6 weeks for 3 years) for MRI analysis (Paty and Li 1993). For the first time, MRI analysis was used as a surrogate measure for MS disease activity in a clinical trial supporting the clinical findings. The 8 MIU dose group had a median of 80% reduction in the number of active scans and a 23% reduction in the MRI-detected burden of the disease. The lesion load in the 8 MIU group decreased by 6.2%, whereas in the 1.6 MIU and the placebo group it increased by 1.1% and 17.1%, respectively. In the 16-year follow-up analysis of the original treatment groups, mortality rates significantly differed from 18.3% in the placebo group, 9.3% in the 1.6 MIU dose group, to the lowest 5.6% in the 8 MIU group (Ebers et al. 2009; Reder et al. 2010). Out of the 113 people that reached the expanded disability status scale (EDSS) of 6.0, 45.6% were originally assigned to placebo, 38.8% of those assigned to IFN- β -1b 1.6 MIU, and 45.8% in IFN- β -1b 8 MIU. However, this analysis did not consider death as part of the disability outcome, skewing the results against the treatment arm. Similarly, in the longest 21-year follow-up analysis, IFN- β -1b showed a 46.8% reduction in the long-term all-cause mortality when compared to placebo (Goodin et al. 2012a). During the 16-year follow-up, substantial technological changes in terms of MRI usage prevented direct comparison with the initial results. The new analysis showed that higher EDSS scores were associated with a higher T2 lesion load, T1 hypointense lesions (black holes), lower brain volumes, and smaller cervical cord volumes (Li et al. 2006). Additionally, the long-term assessment used multiple cognitive outcome measures like the

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symbol digit modality task (SDMT), paced auditory serial addition test (PASAT), and California verbal learning test II (CVLT-II), among others. Baseline EDSS scores, T2 lesion load, and premorbid IQ were calculated as independent predictors of poorer cognitive performance after the 16-year follow-up (Langdon et al. 2007). Even though both trial groups showed comparably stable neurocognitive performance, the placebo-treated patients had higher decline in both immediate and delayed verbal memory functioning when compared to the treatment group ($p = 0.021$ and $p = 0.044$, respectively) (Lacy et al. 2013).

Multiple Sclerosis Collaborative Research Group (MSCRG) Interferon β -1a

IFN- β -1a (Avonex) is an IM IFN- β -1a product that is administered once a week. This treatment was tested on 301 RRMS patients in a double-blind, placebo-controlled, randomized trial (Jacobs et al. 1996). In comparison to IFN- β -1b (Betaseron), the primary outcome of this trial was disability progression over the 104-week study period measured as a sustained increase of 1.0 EDSS unit from baseline and sustained for 6 months (confirmed disability progression [CDP]). The IFN- β -1a treatment group showed a 37% reduction in probability of CDP versus placebo. The study was discontinued early, as the primary outcome was already reached at 18 months (before all patients completed the 2-year follow-up). The annual relapse rate (ARR) in the treatment arm decreased to 0.67 when compared to 0.82 for the placebo patients (reduction of 18.3% and $p = 0.04$). Twofold more placebo patients had at least three exacerbations when compared to the IFN- β -1a-treated patients and the median time to initial exacerbation was delayed by 11.2 weeks. Even though the presence of gadolinium-enhancing lesions (GdELs) at study baseline strongly correlated with additional development of new lesions in both groups, a significant reduction in the number of new lesions ($p = 0.006$), enlarging lesions ($p = 0.024$), or a composite of both ($p = 0.002$) were seen in the IFN- β -1a-treated group when compared to placebo (Simon et al. 1998). With

all subjects analyzed, the IFN- β -1a group had median T2 lesion volume increase of 628 mm³ versus 1410 mm³ seen in the placebo arm (not reaching significance, $p = 0.22$). However, the treatment effect was seen in patients with baseline GdEL⁺ at their baseline scan, indicating that the beneficial effect of IFN- β -1a is strongest in highly active inflammatory disease. Therefore, the placebo patients with a presence of MRI activity captured at baseline MRI scan had higher T2 lesion volume accumulation when compared to their IFN- β -1a GdEL⁺ counterparts ($p = 0.022$). Moreover, the treatment with IFN- β -1a resulted in a reduction of brain atrophy during the second year of the trial (mean % brain parenchymal fraction [BPF] change of -0.233 in the IFN- β -1a arm versus -0.521 in the placebo arm, $p = 0.03$) (Rudick et al. 1999). This MRI post hoc analysis revealed that brain atrophy progression worsened yearly without correlations with clinical manifestations. Unfortunately, the treatment effects seen at year 2 on preventing brain atrophy measured as a mean percent change in BPF was not significant at the 8-year follow-up (-2.5% vs. -3.0% , IFN- β -1a vs. initial placebo, respectively). Patients randomized into the treatment arm were significantly less likely to progress to EDSS of 4.0 or greater at the 8-year follow-up as compared to the initial placebo group. The sustained EDSS increase of 1.0 unit during the initial pivotal study has shown to be the strongest predictor of reaching clinically significant disability (EDSS of 4 and 6) after 8 years (Rudick et al. 2010). Other early predictors of limited response to IFN- β -1a therapy at year 8 were two or more clinical relapses during the study period and greater baseline T2 lesion volume. Furthermore, the Assessment of Drug Utilization, Early Treatment and Clinical Outcomes (ASSURANCE) 15-year long-term follow-up study showed that patients that remained on the IM IFN- β -1a had less disability and progression to meaningful EDSS milestones compared to placebo patients (Bermel et al. 2010). Breakthrough disease activity as measured with cumulative GdEL⁺ lesions found at year 1 and year 2 scans while on therapy strongly correlated with severe disability (the highest rate of GdEL⁺ was seen in the highest

quartile group containing patients with Δ -EDSS of 4.50–8.50, $p = 0.0047$) after 15 years (Bermel et al. 2013).

Prevention of Relapses and Disability by Interferon β -1a Subcutaneously in Multiple Sclerosis

As a result of the unresolved clinical benefits and dose dependency seen in the previously mentioned pivotal trials of IM and SC IFN- β -1b, an additional placebo-controlled SC IFN- β -1a given three times per week (TIW) (Rebif) with larger doses and more frequent treatment regimen was initiated. Prevention of relapses and disability by IFN- β -1a subcutaneously in MS (PRISMS) study recruited 560 RRMS patients and randomized them into three groups: 22 μ g IFN- β -1a, 44 μ g IFN- β -1 given TIW, and placebo (PRISMS Study Group 1998). The treatment groups showed a reduction of 27% and 33%, respectively, in ARR compared to placebo, as well as decrease in sustained disability progression (decrease of 22% and 30%, respectively, as compared to placebo). The MRI analysis showed a reduction in accumulation of T2 active lesion (67% and 78%, respectively, decrease as compared to placebo) that confirmed the effectiveness and the dose dependency of SC IFN- β -1a. The extension of this study (PRISMS-4) evaluated the long-term efficacy of SC IFN β -1a TIW (PRISMS Study Group and the University of British Columbia 2001). Although the initial placebo-assigned patients from the original PRISMS crossed over into one of the treatment arms, the efficacy measures remained favorable to the original IFN- β -1a 44 μ g and IFN- β -1a 22 μ g groups. This extension study, similar to the previous IFN extension studies, supported the importance of early treatment initiation, which will be more broadly discussed in the clinically isolated syndrome (CIS) section of this article. The prevention of disability conclusively shows the superiority of the 44 μ g dose when compared to the IFN- β -1a 22 μ g dose. Patients in the 44 μ g dose displayed fewer confirmed EDSS changes over 4 years (0.17/patient/year) when compared to the crossover groups (0.24/patient/year) and to the 22 μ g dose group

(0.22/patient/year) (PRISMS Study Group and the University of British Columbia 2001). Three hundred eighty-two out of the original 560 enrolled patients continued into the long-term, open-label, follow-up study (Kappos et al. 2006b). When compared to the other groups, the original IFN- β -1a 44 μ g group showed the longest time to reach confirmed progression and a clinically relevant progression EDSS of 4.0. Additionally, the medication effect that successfully decreased the inflammatory component translated into reduction of brain volume loss over the 8 years. The trend of better performance by the original IFN- β -1a 44 μ g group was shown by the reduction in brain atrophy when compared to the low-dose 22 μ g formulation. Additional post hoc analysis highlighted the long-term adherence as a factor associated with better clinical outcomes. The group labeled as “max dose, max time” had lower ARRs, lower secondary progressive MS (SPMS) conversion rates, and lower T2 burden of disease (Uitdehaag et al. 2011). A pilot placebo-controlled study of patients using 44 μ g IFN- β -1a showed accelerated brain atrophy within the first 6 months, correlating with a decrease of T-cell expression and active inflammatory cytokine reduction (Dwyer et al. 2015). This supported the immunological basis of the pseudoatrophy seen after IFN treatment initiation (Dwyer et al. 2015). In the same study, increased magnetization transfer ratio (MTR) signal within the white matter suggested that the medication may provide active remyelination (Zivadinov et al. 2014).

Pegylated Interferon β -1a (ADVANCE Trial)

In the pivotal phase III trial of PEG-IFN- β -1a (Plegridy) 1512 patients were randomized into 1:1:1 ratio (placebo, PEG-IFN- β -1a 125 μ m every 2 weeks, and PEG-IFN- β -1a 125 μ m every 4 weeks, respectively) (Calabresi et al. 2014). At week 48, relapses were significantly lower in patients taking the active medication when compared to placebo. The ARR was 0.256 in the every-2-week group compared to 0.397 in the placebo group ($p = 0.0007$). Patients randomized to the 4-week interval dosing had an ARR of 0.288 (nonsignificant when compared to pla-

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cebo, $p = 0.0114$). Additionally, multiple MRI-derived end points were statistically favoring the 2-week interval group. PEG-IFN- β -1a once every 2 weeks showed inflammatory suppression when compared to placebo as assessed by GdEL⁺ lesion number (-0.26 vs. 0.77), new T2 lesions (3.7 vs. 11.2), and T1 hypointense lesions (1.8 vs. 3.8). Although still significantly improved, the effect of PEG-IFN on the sustained disability progression was less apparent (0.62 hazard ratio [HR], $p = 0.038$). Advanced brain imaging like MTR also showed treatment improvement when compared to placebo, whereas whole brain atrophy failed to do so (supplementary data of Calabresi et al. 2014). Similarly to the PRISMS trial crossover design, after the initial first year of the trial, the placebo group was randomized into the active treatment arm, whereas the original PEG-IFN- β -1a groups remained on their preassigned doses (Kieseier et al. 2015). This extension study further provided evidence into the efficacy of PEG-IFN- β -1a, where patients originally assigned to the treatment arm outperformed those who were switched after year 1 (Kieseier et al. 2015). No evidence of disease activity (NEDA), a measure composite of no clinical relapse, disease progression, and MRI activity, was achieved in 33.9% of PEG-IFN- β -1a q2-week groups versus 15.1% and 21.5% for placebo and q4-week groups, respectively (Arnold et al. 2014). Patients continued participating in ATTAIN, a long-term, dose-frequency, blinded extension, which showed significant increase in NEDA over 3 years of treatment (30.5% vs. 19.8% 2-week vs. 4-week groups, respectively) (Arnold et al. 2015).

Dose Comparison Trials and IFN- β Outcomes

As the initial pivotal trials left certain doubts about the dose dependency and bioactivity of the different preparation, several randomized head-to-head trials were initiated. Both EVIDENCE (comparing SC IFN β -1a TIW vs. weekly IM IFN- β -1a) and INCOMIN (comparing SC IFN- β -1b QOD to IM IFN- β -1a) studies showed superiority of higher-dose and more frequent administration regimens (Durelli et al. 2002; Panitch et al. 2002). However, differences in efficacy seen in EVIDENCE only persisted in

the first 24 weeks into the trial and was not maintained later on (Panitch et al. 2005). Similarly, INCOMIN trial used groups that were not well matched with regard to baseline clinical characteristics favoring the younger and healthier IFN- β -1b arm (Vartanian 2003). The inconsistency of the results was further complicated by negative results of several open-label dose-comparative studies (Clanet et al. 2002; Trojano et al. 2003; Minagar et al. 2008). The European IFN- β -1a comparison trial showed that there are neither clinical nor MRI differences between 30 μ g and 60 μ g IM doses. Even though it was not the primary purpose of this trial, the study provided invaluable information regarding the clinical efficacy as well. It showed that the nonlinear trajectory of brain atrophy seen in the first 4 months reflected the anti-edematous changes induced by the IFN treatment (Zivadinov et al. 2008). With an initial pretreatment relative annualized atrophy rate of -1.06% , baseline to month 4 rate of -1.49% , and -0.33% from month 4 to year 3 showed that IFN- β significantly reduces the atrophy rate, which corroborates the findings seen from initial Multiple Sclerosis Collaborative Research Group (MSCRG) trial (Hardmeier et al. 2005).

OBSERVATIONAL OPEN-LABEL IFN STUDIES

Assessing the slowly accumulating disability in MS can be a challenge, with an average 15-year gap in the natural history of progression from no disability to impaired walking (EDSS 6.0) (Weinshenker et al. 1989). In pooled analysis of 31 placebo-randomized trials, detection of clinical efficacy in short-term interventional trials by using the existing definitions of disease progression could not be validated (Ebers et al. 2008). In addition, considerable variations in disability and function within the first years of enrollment failed to translate into predicting future long-term disability (Goodin et al. 2012b). However, because of the high study costs and ethical concerns regarding placebo-controlled trials, they are conducted only up to 3 years (Table 1). Therefore, the most reliable long-term efficacy data for IFN- β comes from open-label extensions and observational studies both hav-

Table 1. Clinical and magnetic resonance imaging (MRI) outcomes for the four pivotal relapse-remitting multiple sclerosis trials

Clinical and MRI outcomes	Subgroups	Study name					
		IFN- β study group		MSCRG ^a		PRISMS	
		1.6 MIU	8 MIU	30 μ g	22 μ g	44 μ g	ADVANCE ^b
ARR	IFN- β	1.04	0.85	0.61	1.82	1.73	q2 wk
	Placebo	1.18		0.90		2.56	0.288
	<i>p</i> -value	0.030^c		0.002		<0.005^c	0.397
Proportion of patients with disease progression	IFN- β	47%	35%	21.20%	18.5/23% ^e	21.3/31% ^e	0.0007^d
	Placebo	46%		33.30%		11.9 ^e	6.05%
	<i>p</i> -value	0.096		0.02		<0.05^e	10%
GdEL ⁺ lesion number	IFN- β	1.8 $\pm$ 0.4	2.0 $\pm$ 0.7	0.8 $\pm$ 0.22	1.4 (0–6.7)	1.3 (0–4)	0.038
	Placebo	4.9 $\pm$ 1.3		1.65 $\pm$ 0.48	8.0 (2.7–27)		1.4 $\pm$ 0.17
	<i>p</i> -value	0.0089		0.05		<0.0001	<0.0001
T2-lesion volume change in %	IFN- β	10.50%	–0.10%	6.50%	–1.20%	–3.80%	7.3 (35%) ^f
	Placebo	20.00%		13.20%		10.90%	11.2 ^f
	<i>p</i> -value	<0.001		0.36		<0.0001	<0.0001^f
Whole brain volume change	IFN- β	N/A	N/A	–0.233 $\pm$ 0.74	N/A	N/A	–0.67 $\pm$ 0.83
	Placebo	N/A		–0.521 $\pm$ 0.8		N/A	–0.62 $\pm$ 0.89
	<i>p</i> -value	N/A		0.03^g		N/A	0.084

Interferon β (IFN- β) study group—Betaseron pivotal trial; MSCRG—Multiple Sclerosis Collaborative Research Group pivotal trial for Avonex; PRISMS—Prevention of Relapses and Disability by IFN- β 1a Subcutaneously in Multiple Sclerosis pivotal trial for Rebif; ADVANCE—pegylated interferon (PEG-IFN)- β 1a for relapsing remitting multiple sclerosis pivotal trial for Plegriid. Alpha level of 0.05 was considered as significant and is shown in bold.

MIU, Million international units; q4 wk, every 4 weeks; q2 wk, every 2 weeks; ARR, annualized relapse rate; GdEL, gadolinium-enhancing lesion; N/A, not available.

^a104 weeks study period.

^bResults at 48 weeks follow-up.

^cRelapse rate.

^dBased on negative binomial regression; adjusted for baseline expanded disability status scale (EDSS) (<4 vs. $\geq$ 4), baseline relapse rate, and age (<40 vs. $\geq$ 40).

^eTime in months for EDSS progression <1/reduction in disease progression.

^fAdjusted mean number of lesions (percentage reduction vs. placebo).

^gMean % brain parenchyma fraction change post hoc analysis of Avonex trial.

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ing unfortunately specific limitations (Freedman 2011; Signori et al. 2016). Real-world studies provide data on the effectiveness among different IFN- β formulations, while controlling for factors like comorbidities, other medication use, and adherence, which may play a substantial role in the varying disease outcomes. Meta-analysis on observational IFN- β -based studies included 32,026 patients and showed that there are no differences among the different IFN- β treatment effects (Einarson et al. 2017).

Long-term follow-up data enabled the identification of early clinical and MRI-derived IFN- β efficacy markers, which led to the development of scores that can predict treatment outcomes. For example, the measurement of MRI-derived disease activity just after 1 year of IFN- β initiation was able to identify patients that will continue to accumulate disability over the following year (Rio et al. 2008). Additionally, an analysis within the large MRI in MS (MAGNIMS) network database showed that while on IFN- β therapy, substantial MRI activity (≥ 3 new T2 lesions) in the presence of at least one relapse is associated with a high risk of disability worsening over the following 2–3 years (Sormani et al. 2016). This can help clinicians in detecting short-term treatment failure and influence their decision on switching IFN- β as their first-line therapy. In an independent analysis of the PRISMS trial, the combination of 1-year MRI lesion activity and occurrence of relapses explained 100% of the treatment effect on disability progression over 2 years (Sormani et al. 2011). After adjusting for these scores, the differences between the treatment arms disappeared and no residual effect of IFN on EDSS was observed. Although persistent clinical activity during the early IFN- β treatment remained associated with poor long-term prognosis, some MRI activity failed to translate in long-term EDSS change (Rio et al. 2017). The emergence of new disease-modifying therapies (DMTs) offers clinicians new therapeutic options; however, they do not lack toxicity and are not risk-free treatments. Therefore, there is growing emphasis on the need for developing tools that will better capture patients at risk for long-term disability. Composite measure of clinical disability

progression, relapses, and MRI activity termed NEDA or routine brain atrophy measurement may help contribute to the understanding of the unpredictability of long-term IFN- β treatment outcomes (Zivadinov et al. 2016; Uher et al. 2017).

BIOMARKERS FOR ASSESSMENT OF IFN CLINICAL EFFICACY

The effects of IFN- β activity can be assessed by measuring the up-regulation of IFN- β -induced messenger RNAs (mRNAs) such as human myxovirus resistance protein I (MxA), IL-10, $\beta 2$ -microglobulin, and tumor necrosis-related apoptosis inducing ligand (TRAIL) via the activation of the JAK-STAT pathway (Weinstock-Guttman et al. 2008). However, the timing of blood draw is a critical factor because the peak of MxA mRNA in the plasma occurs 6–12 h after the IFN- β injection (Pachner et al. 2005). Furthermore, the lack of significance seen between MxA expression and with the clinical and MRI phenotypes limited their clinical use and meaningfulness (Weinstock-Guttman et al. 2007). IFN-driven up-regulation of genes involved in the sterol synthesis pathways enabled use of differential cholesterol profiles as a potential biomarker for treatment efficacy. Early decreases in cholesterol markers, mainly high-density lipoprotein (HDL) cholesterol, were shown to be associated with short- to midterm brain atrophy outcomes (Uher et al. 2016). Similarly, the Dicer protein, which cleaves the double-stranded RNA and pre-microRNA, has been shown to be a potential marker of IFN- β response (Magner et al. 2016). Along with these examples, cluster analysis on levels of monocyte-derived IFNAR1, IFNAR2, and pSTAT1-2 were able to determine the phenotype associated with good IFN- β response (Hurtado-Guerrero et al. 2017). In a comparative study of three IFN- β formulations, IFN- β -1b showed higher bioactivity as measured by levels of MxA and vascular cell adhesion molecules when compared to the two IFN- β -1a preparations (Deisenhammer et al. 2000). One of the possible reasons for the heterogeneity of IFN- β activity is the heightened expression of circulating “interferon-inhibitory

activity" (IIA) and free-soluble IFN- α/β receptors (sIFNRs) (Chadha et al. 2006). Elevated levels of IIA in patients resulted in partial response to the IFN treatment and were significantly linked with the T2 lesion volume. Although multiple biomarkers have tried to effectively measure the treatment response to IFN- β , not one has yet been identified as clinically meaningful.

Antibody formation as immunogenic response toward molecules with any genetically modified properties is expected. However, the mechanism of IFN- β antibody occurrence is not because of the classical immunological immune induction, but rather the slow and continuous breakdown of immunogenic tolerance (Schellekens 2002). Based on the antibody ability to inhibit the effect of IFN- β , both common binding (BAb) and rare neutralizing (NAb) antibodies have been characterized (Bendtzen 2003). The current consensus is that BAb are used for initial screening, whereas NAb are confirmatory tests of IFN-inhibiting antibodies (Sorensen et al. 2005a). Furthermore, BAb titer larger than 1:2400 had 98.5% specificity and 74.7% sensitivity in predicting NAb formation and strengthen the notion of use of BAb as an antibody-screening tool (Hegen et al. 2014). The development of NAb toward IFN- β largely depends on the specific preparation in terms of differences in molecular structure, application site, dosage, and frequency. The direct IFN- β comparison trial (EVIDENCE) showed substantially lower immunogenicity of IM IFN- β -1a over SC IFN- β -1a (2% vs. 25% in ≥ 20 neutralizing units/mL, respectively). Similarly, an open-label comparison corroborated the results showing 2-year NAb positivity in 42% patients in the 22 μ g Rebif group, 34% for Betaferon 8 MIU, and finally, only 8% for 30 μ g Avonex-treated patients (Sorensen et al. 2003). This immunogenicity difference was also confirmed in a large dataset of 42,555 samples from six European countries. Moreover, an observed prescribing switch toward the less immunogenic preparation of IM IFN- β -1a was noted (Link et al. 2017). Several studies have shown that after prolonged use of, especially, IFN- β -1b, there is noted reduction in the antibody presence. It has been hypothesized that disappearance of an im-

mune reaction toward the medication could be because of reconstitution of the immune tolerance or epitope maturation (Sorensen et al. 2005b). Additionally, it has been shown that the persistency of the antibodies is a multifactorial process determined by the antibody titer, affinity maturation, and IgG subclass switching. Patients with transient appearance of IFN- β showed predominantly IgG₁ and IgG₃ subclass, whereas, the predominance of IgG₂ and IgG₄ contributed toward their persistence (Dujmovic et al. 2017). The inhibiting effects of NAb has been shown in both original pivotal trials of Betaferon and Rebif, where NAb attenuated the treatment effect, which returned the relapse rate, and the MRI response back to placebo levels (The IFNB Multiple Sclerosis Study Group and the University of British Columbia MS/MRI Analysis Group 1996). In the PRISMS trial, it was shown that NAb⁺ patients had significantly higher ARR when compared to NAb patients (0.85 vs. 0.52, $p < 0.05$) (Francis et al. 2005). In addition to the effect seen on increasing relapse rates and MRI-derived activity, IFN- β NAb also directly correlated to the quantification of the biological response as measured by MxA assays (Santos et al. 2006). Both European Federation of Neurological Societies (EFNS) (see Table 3) and the Neutralizing Antibodies on Interferon β in Multiple Sclerosis (NABINMS) consortium have published guidelines and recommendations regarding the clinical use of IFN- β NAb (Sorensen et al. 2005a; Polman et al. 2010). In their conclusion, apart from deducting clinical and practical NAb cutoff titers, a consideration of switching patients with sustained high NAb⁺ titer and/or lack in MxA bioactivity to non-IFN- β therapy was suggested. The presence of NAb remains the only biomarkers known to be associated with decrease in clinical benefit.

CLINICAL EFFICACY OF INTERFERON β IN CLINICALLY ISOLATED SYNDROME

CIS is a disease phenotype with first clinical neurological presentation and features that resemble inflammatory MS demyelination; however, it does not fully fulfill the McDonald criteria for dissemination in time. Based on three positive

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Table 2. Major interferon β (IFN- β) trials in clinically isolated syndromes

Study	Therapy	Time from symptom onset	CDMS		<i>p</i> -value
			IFN- β	Placebo	
CHAMPS	IM IFN- β -1a	≤ 1 month	20%	38%	<0.001
ETOMS	SC IFN- β -1a	≤ 3 months	34%	45%	0.047
BENEFIT	SC IFN- β -1b	≤ 2 months	28%	45%	<0.001
REFLEX	SC IFN- β -1a	≤ 2 months	21%/22% ^a	38%	$<0.001/0.002^a$

Data modified from Freedman et al. (2014).

Clinically defined multiple sclerosis (CDMS) at 2 years follow-up (defined as two attacks with clinical evidence of two separate lesions, with at least one of the lesions producing objective central nervous system [CNS] dysfunction and with paraclinical evidence of demyelinating lesions by brain magnetic resonance imaging [MRI] examination).

IM, Intramuscular; SC, subcutaneous.

^aREFLEX study had two treatment arms, IFN- β -1a 44 μ g three times a week and IFN- β -1a 44 μ g once weekly.

CIS trials, IFN- β today is routinely prescribed for this subset of patients. All studies (Betaferon/Betaseron in Newly Emerging MS for Initial Treatment [BENEFIT], Controlled High-Risk Subjects Avonex Multiple Sclerosis Prevention Study [CHAMPS], and Early Treatment of Multiple Sclerosis Study [ETOMS]; Table 2) testify to the importance of early initiation of therapy, even before the official diagnosis of clinically defined MS (CDMS). With the early IFN- β use, the rate of CDMS conversion has been reduced by 44%–50% when compared to placebo after long-term follow-up periods (Freedman et al. 2014).

Controlled High-Risk Subjects Avonex Multiple Sclerosis Prevention Study

The first randomized placebo-controlled trial (CHAMPS) recruited 383 patients who had their first demyelinating event (Jacobs et al.

2000). After the initial corticosteroid therapy, they were randomized into two groups of IM IFN- β -1a and IM injections of placebo. At the 3-year follow-up, the cumulative probability of transition into CDMS was reduced by half when compared to placebo (rate ratio of 0.56, 95% CI 0.38–0.81). The IFN- β -1a group had a transition probability of 35%, whereas the placebo had a 50% chance of converting into CDMS. The beneficial effects were seen on the MRI analysis as well. The IFN- β -1a group had 42% fewer GdEL⁺ lesions at 6 months, 55% fewer at 12 months, and 67% fewer at 18 months. In addition, the IFN- β -1a group had a median increase of only 1% of lesion volume from baseline to 18 months when compared to a 16% increase seen in the placebo group. The trial was stopped after pre-planned interim analysis and patients from the placebo arm were switched to IFN- β -1a. The median time of the late initiation of IFN- β -1a was 29 months after the CHAMPS placebo ran-

Table 3. Guidelines on the use of anti-interferon β (IFN- β) antibody testing in multiple sclerosis

Recommendations by the European Federation of Neurological Societies (EFNS)	Level of recommendation
BAb assays can be used for screening of IFN- β antibodies	Level A
NAb testing should be performed in specialized laboratories	Level A
Nab should be performed with validated CPE or MxA assays using serial dilution test	Level A
NAb should be tested within first 24 months of therapy	Level A
NAb measurement is not needed in NAb patients after 24 months of IFN therapy	Level B
Patients with NAb should be retested every 3–6 months	Level A
Therapy should be discontinued in patients with high titer NABs and retested in 3–6 months	Level A

Data modified from Sorensen et al. (2005a).

BAb, Binding antibodies; Nab, neutralizing antibodies; CPE, cytopathic effect; MxA, myxovirus resistance protein 1.

domization. The immediate therapy group had lower probability of developing CDMS at 5-year follow-up when compared to the delayed therapy group (36% vs. 49%, HR of 0.65) (Kinkel et al. 2006). Similarly, at the 10-year follow-up, the immediate group had a lower CDMS conversion rate (HR of 0.65); however, early IFN- β -1a initiation did not improve disability measures when compared to late initiators (Kinkel et al. 2012). This highlighted the progressive nature of the later stages of the disease, despite the reduced relapse rates over 10 years of treatment. In the MRI post hoc analysis, 86% of CIS patients that had low T2 burden (two to eight lesions) at baseline showed additional activity, had fewer new brain lesions, lower brain volume loss, and less disability accumulation compared to the “high” T2 burden group (Simon et al. 2015).

Early Treatment of Multiple Sclerosis Study

In a similar study, patients after their initial demyelinating attack were randomized into 22 μ g IFN- β -1b or placebo every week and were followed for 2 years (Comi et al. 1995). The follow-up analysis showed that 34% of 22 μ g IFN- β -1b and 45% of placebo patients converted to CDMS (odds ratio [OR] 0.61, 95% CI 0.37–0.99) (Comi et al. 2001). Additionally, the second relapse was substantially delayed in the IFN- β -1b group (569 days for IFN- β -1b vs. 252 days for placebo, $p = 0.023$). Even though the treatment group had significantly more GdEL⁺ lesions at baseline, the follow-up MRI data showed fewer new T2 lesions compared to placebo ($p < 0.001$). Several explanations can be used to understand the lower efficacy seen in ETOMS when compared to CHAMPS. One explanation can be that to lessen the attack, mandatory high dose steroid was used in the CHAMPS study, whereas only 70% of CIS patients in ETOMS did receive variable doses of steroids (Beck et al. 1992). In addition, the long interval and the low dose of the weekly 22 μ g IFN- β -1b used were probably subtherapeutic and not sufficient to create satisfactory disease suppression. Finally, the ETOMS study recruited CIS patients that had multifocal symptoms, whereas CHAMPS had only patients with a unifocal attack.

Because of the mentioned low-dose formulation used in ETOMS, an additional Rebif Flexible Dosing in Early MS (REFLEX) study was initiated (Comi et al. 2012). The patients were randomized into three groups of IFN- β -1b 44 μ g TIW, IFN- β -1b once a week, and placebo. Both treatment regimens showed a 2-year cumulative lowering the probability for establishing the MS McDonald criteria and CDMS when compared to placebo, with rates of conversion of 20.6% versus 21.6% and 37.5% (IFN- β -1b 44 μ g TIW, once a week, and placebo, respectively). Both treatment arms showed reduction of unique active lesions (81% for TIW and 63% once a week when compared to placebo) (De Stefano et al. 2014). REFLEXION, an open-label extension study of REFLEX, has already published its 3- and 5-year results (Comi et al. 2017). Patients that did not reach CDMS continued with their initial randomization regimen, whereas patients on placebo and CDMS patients switched to the IFN- β -1b 44 μ g TIW protocol. Two major conclusions were reached from the extension study. Over the period of 5 years, early initiation of IFN- β -1b (within 2 months of the focal neurological attack) significantly delayed the time of conversion to CDMS up to 2 years. Second, based on MRI outcomes, the IFN- β -1b 44 μ g TIW regimen did outperform the weekly dosage.

IFN- β -1b (Betaferon/Betaseron) in Newly Emerging MS for Initial Treatment

The IFN- β -1b (Betaferon/Betaseron) in Newly Emerging MS for Initial Treatment (BENEFIT) trial randomized 487 patients into a 2:1 ratio of IFN- β -1b 8 MIU or placebo accordingly (Kappos et al. 2006a). The study confirmed the two previous CIS trials showed its effectiveness as early as a few months into the trial. At the end of the 2-year scheduled period, the probability of not developing McDonald MS criteria was twice as high in the IFN- β -1b group (31%) when compared to placebo. Also, when CDMS criteria was used, only 28% of IFN- β -1b-treated CIS patients had a second neurological attack, whereas 45% of the placebo patients did. The risk reduction calculated through HR favored IFN- β -1b versus

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placebo, with a 50% decrease in probability (HR 0.50, 95% CI 0.36–0.70). Interestingly, when the Barkhof criteria for dissemination in space at baseline was used, the 3-year predictive value of conversion to CDMS was not affected by treatment intervention (Moraal et al. 2009). The patients enrolled in this trial were extensively followed in a longitudinal manner, which resulted in cross-sectional summaries at 3 years (Kappos et al. 2007), 5 years (Kappos et al. 2009), 8 years (Edan et al. 2014), and 11 years of follow-up (Kappos et al. 2016). All of them provide conclusive data that although the delay in treatment of only 2 years was relatively short, the early use of IFN- β -1b prolongs the time to reach CDMS. Even 11 years after the trial entry, the IFN- β -1b group had 33% reduced risk of conversion into CDMS. In terms of neuropsychological measures, the early treatment arm had better PASAT-3 scores when compared to the later switched placebo group ($p = 0.007$). Having long-term data, this study also reported important patient-related outcome measures like employment, ability to care for themselves, and new hospitalizations. Both groups had similar resource utilizations with a high rate of employment (73.4% when compared to 81.3% at baseline), 97.5% of the patients were still living independently, and 91.4% were not hospitalized because of MS-related reasons (Kappos et al. 2016).

CLINICAL EFFICACY OF INTERFERON β IN PROGRESSIVE MULTIPLE SCLEROSIS

In most cases, after a certain disease course of acute relapses followed by complete or partial recovery, patients continue to evolve into a phase of gradual progression called SPMS. Moreover, the greater extent of brain volume loss, formation of T1-hypointensities, and greater T2 lesion load display already developed pathology, which may prove as a potential limiting factor in IFN- β use. Even though SPMS features clinical and MRI differences when compared to RRMS, the immunological processes are mostly overlapping. Therefore, these similarities provided rationale for consideration of IFN trials for the SPMS population. The partially understood pathophysiology of the secondary progressive

course and issues with the responsiveness of the available measurement scales contributed to discrepancies within the SPMS phase III trials. The initial positive results coming from the European Study Group on Interferon- β -1b in SPMS (EUSPMS) were not confirmed by later trials. Several meta-analyses showed the inability to prevent further disability progression, despite the treatment-related reduced risk of relapses (La Mantia et al. 2012). With recent new developments in the MS therapeutic field, further large IFN- β trials will most probably not take place.

European IFN- β Study in Secondary Progressive Multiple Sclerosis

The EUSPMS trial randomized 718 patients into eight MIU IFN- β -1b or placebo groups with 1:1 ratio (European Study Group on Interferon- β -1b in Secondary Progressive MS 1998). The eligibility for the study included baseline EDSS between 3.0 and 6.5, clinical progression defined as clinical deterioration (EDSS increase of ≥ 1.0 point for baseline EDSS of 3.0–6.0 or increase of ≥ 0.5 over baseline EDSS of 6.0–6.5) independent of relapses, and a record of two or more relapses with an increase of at least 1.0 in the EDSS within the last 2 years. The primary outcome of the trial was met, where the time to reach CDP was significantly delayed in favor of IFN- β -1b ($p = 0.0008$). Furthermore, 38.9% patients taking IFN- β -1b and 49.8% of placebo reached CDP (European Study Group on Interferon- β -1b in Secondary Progressive MS 1998). The treatment arm also showed significant reduction in the total T2 lesion volume ($p < 0.0001$). The sustained effect of IFN- β -1b on the inflammatory disease was shown by the differences in the longitudinal total lesion volume. Placebo-assigned patients had year-to-year lesion volume accumulation with mean increase of 16% by year 3 from baseline. On the other hand, the treatment arm showed reduction of 4% by year 1, 5% by year 2, and, finally, 2% reduction at year 3 (Miller et al. 1999). Additional analysis examining brain atrophy and T1 hypointense lesion load were acquired to assess neurodegenerative processes presumed to be seen in SPMS patients (Barkhof et al. 2001).

The IFN- β -1b treated group showed a decrease in the black-hole volumes by 7.7% per year, whereas the placebo-treated patients accumulated additional black-hole lesion volume by 14% per year. This treatment significance was not seen in terms of reducing the brain atrophy loss. IFN- β patients had a mean 2.9% loss when compared to 3.9% in placebo ($p = 0.34$) (Molyneux et al. 2000). Further post hoc analysis concluded that 30% more IFN- β -1b patients remained both disability progression and relapse free. Additionally, patients that had substantially more active disease before entering the study, benefited with noticeably larger treatment effect (Kappos et al. 2001). Despite the initial short-term effect, the 10-year follow-up reevaluation of the patient cohort did not provide confirmation of favorable IFN- β outcomes (Kuhle et al. 2016).

North American IFN- β Study in Secondary Progressive Multiple Sclerosis

Similar to the EUSPMS study, an additional 3-year multicenter IFN- β -1b trial took place in 35 centers in both the United States and Canada (Panitch et al. 2004). Using inclusion criteria that matched the European predecessor, it recruited 939 SPMS patients that were randomized into placebo, IFN- β -1b 8 MIU (250 μ g) or 5 MIU/m² (160 μ g/m²). Results did not show a dose-dependent effect; however, the group randomized to 5 MIU/m² equalized to the mean dose of 9.6 MIU, which was not considerably different from the established 8 MIU. Even though the treatment arm had a significant decrease in ARR, the primary outcome of time to CDP was not reached. Contrary to the EUSPMS that was terminated early because of futility, the NASPMS-planned interim analysis showed ineffectiveness and was concluded early as a negative trial. Because of the conflicting results, a pooled analysis of both trials was conducted (Kappos et al. 2004). The conclusion from this comparative investigation showed that the EUSPMS trial recruited younger patients with lower average disease duration, higher relapse rates, and higher inflammatory MRI activity, characteristics that still support an early inflam-

matory stage of the disease rather than the advanced progressive stage characterized by a different underlying pathobiology (Weiner 2009).

SPECTRIMS AND IMPACT TRIALS

Two additional SPMS trials were conducted in which SC IFN- β -1b (SPECTRIMS) and IM IFN- β -1a (IMPACT) were used (Secondary Progressive Efficacy Clinical Trial of Recombinant Interferon- β -1a in MSSG 2001; Cohen et al. 2002). The SPECTRIMS trial used the high 44 μ g IFN- β -1b dose and showed lack of efficacy in prolonging the time to CDP, whereas the IMPACT study used high-dose 60 μ g IFN- β -1a evaluated with the MS functional composite (MSFC) score that included a timed 25-foot walk (T25FW) test, 9-hole peg test (9HPT), and PASAT as primary outcomes (Cohen et al. 2001). Because of the difficulties in detecting meaningful change in the later stages of the disease using EDSS, this trial was the first to use MSFC as the primary outcome measure. As the study showed significant 40.4% reduction in MSFC z-scores between treatment groups ($p = 0.033$), EDSS failed to observe this benefit. In further composite deconstruction, the skewed noticeable benefit was driven by the 9HPT ($p = 0.024$) and PASAT ($p = 0.061$) versus the nonsignificant T25FW ($p = 0.378$). A common pattern of ARR reduction ($p = 0.008$), T2-hyperintense lesion, and GdEL⁺ lesion reduction (both $p < 0.001$) was detected. One of the explanations of this discrepancy is that the temporal order of different function deterioration is not simultaneous. As walking ability starts to worsen early in the secondary progressive stage, potentially higher disease burden would be needed to produce worsening of the hand and cognitive function (Giovannoni et al. 2017). In addition, the noticeable worsening in T25FW in both groups over 2 years failed to respond to IFN- β treatment.

COMPARATIVE HEAD-TO-HEAD STUDIES

Because of their established efficacy in reducing MS inflammation, IFN- β formulations played the role as an active comparator in many new pivotal trials. The additional data from the IM

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IFN- β -1a use in the fingolimod trial (Cohen et al. 2010) and from the SC IFN- β -1a TIW use in both the alemtuzumab and ocrelizumab trials (Cohen et al. 2012; Hauser et al. 2016) further testify to the beneficial effect of IFN- β in the management of MS. Even though in terms of efficacy the newly approved DMTs outperformed the β IFNs, and a higher rate of adverse effects was noted. Until further long-term safety data regarding the second-line DMTs emerges, the desirable risk–benefit ratio of IFN- β remains clinically relevant.

SAFETY AND ADHERENCE TO TREATMENT

Although all MS therapeutics carry inherited risk of potential adverse effects, IFN- β is usually well tolerated (Reder et al. 2014). Most common IFN- β reported side effects are “flu-like” symptoms of fever, chills and headache, injection-site reactions, myalgia, depression, and increase of liver enzymes. Most of these effects are a result of the transient increases in cytokines like IL-6 and tumor necrosis factor α (TNF- α); therefore, the symptoms appear a few hours after the administration and dissipate after 12 to 24 h (Langer-Gould et al. 2004). However, because of persistent “flu-like” side effects, a small number of patients (20%) do require continuous use of complementary anti-inflammatory therapy after the initial 2–3 months of treatment. The differences in application and formulation cause some discrepancies in site reactions reported. For example, in a direct comparison of both medications (EVIDENCE trial), the more frequent and higher dose of SC 44 μ g IFN- β -1b noted 83% site reactions versus only 28% in IFN- β -1a (Panitch et al. 2002). All IFN-based medications have some intrinsic associated risk with hepatotoxicity and increase liver aminotransferases (Chan et al. 2011). In a retrospective analysis of the three IFN products, there were elevations of AST and ALT in IFN- β patients when compared to placebo ($p < 0.005$). The pattern of liver enzyme changes varied among formulations, where de novo abnormalities were seen in SC IFN- β -1a and SC IFN- β -1b, but not in IM IFN- β -1a. In addition, the temporal peak ranged within the first 6

months in SC IFN- β -1a and SC IFN- β -1b and between 6 and 12 months for IM IFN- β -1a (Tremlett et al. 2004). This increase of liver markers usually is asymptomatic and transient; however, threefold or greater increase calls for dose reduction or discontinuation of the medication. Therefore, heightened vigilance in terms of liver function monitoring, especially in the first year of treatment initiation is advised (Francis et al. 2003).

As MS is affecting women at their childbearing age, the choice of a safe DMT is crucial. Even though all DMTs currently used in MS do carry potential risk to pregnancy outcomes, recent studies indicate that IFN- β can be continued during the first trimester of the childbearing period (Thiel et al. 2016). Exposure of IFN- β within the first 4 weeks was shown not to be associated with increased risk of spontaneous abortion and significant fetal complications (Amato et al. 2010). Combined with the increased risk of disease breakthrough occurring immediately postpartum and the pregnancy-related acceleration of SPMS transition, personalized decision-making of IFN- β therapy continuation will be needed until conception is confirmed (Pozzilli et al. 2015; Alroughani et al. 2016).

Both adherence (percentage of doses taken as prescribed over a set period) and persistence (total number of days taking the medication) are crucial in acquiring better clinical outcomes. In a large retrospective analysis of 2446 patients, the adherent groups showed a decrease in clinical relapses, MS-related hospitalizations, and medical costs (Tan et al. 2011). Based on the data from all prospective studies, the adherence in different IFN- β agents ranged from 83.9% in IM IFN- β -1a to 72.0% in SC IFN- β -1a and to 64.7% in IFN- β -1b (Menzin et al. 2013). Addressing factors like adverse events, ability to self-inject, treatment complexity, and cognitive barriers will potentially increase the adherence and benefit for the MS-prescribed therapies (Mohr et al. 2001; Devonshire et al. 2011).

CONCLUSION

Numerous long-term data testify for the significant contribution of IFN- β in improving the

care of MS patients. IFN- β still holds an important role in the treatment options for RRMS, CIS, and in SPMS patients that still experience highly active disease. Even though IFN- β produces only partial long-term responsiveness when compared to the newly developed DMTs, the well-known risk-benefit ratio offers certain reassurance in its everyday use. Better understanding of the drug MOA and developing specific IFN- β activity biomarkers will allow further stratification of patient responders.

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Interferon β for Multiple Sclerosis

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