

Advances in the treatment of relapsing–remitting multiple sclerosis: the role of pegylated interferon β -1a

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Abstract: Multiple sclerosis (MS) is a progressive, neurodegenerative disease with unpredictable phases of relapse and remission. The cause of MS is unknown, but the pathology is characterized by infiltration of auto-reactive immune cells into the central nervous system (CNS) resulting in widespread neuroinflammation and neurodegeneration. Immunomodulatory-based therapies emerged in the 1990s and have been a cornerstone of disease management ever since. Interferon β (IFN β) was the first biologic approved after demonstrating decreased relapse rates, disease activity and progression of disability in clinical trials. However, frequent dosing schedules have limited patient acceptance for long-term therapy. Pegylation, the process by which molecules of polyethylene glycol are covalently linked to a compound, has been utilized to increase the half-life of IFN β and decrease the frequency of administration required. To date, there has been one clinical trial evaluating the efficacy of pegylated IFN. The purpose of this article is to provide an overview of the role of IFN in the treatment of MS and evaluate the available evidence for pegylated IFN therapy in MS.

Keywords: interferon, pegylation, multiple sclerosis, relapsing–remitting, disease-modifying therapy

Multiple sclerosis: an overview

Multiple sclerosis (MS) is a progressive, neurodegenerative disease affecting roughly 2.3 million people worldwide.¹ MS is characterized by infiltration of auto-reactive T cells, B cells and other immune mediators into the central nervous system (CNS), causing demyelinating lesions, axonal degeneration and formation of sclerotic plaques.² Neural damage may manifest symptomatically as optic neuritis, numbness or tingling in the extremities, muscle weakness, slurred speech and bowel/bladder dysfunction.^{3–5} There is also an increasing appreciation of “soft” or “hidden” symptoms such as fatigue,^{6–8} cognitive impairment^{8–10} and comorbidity with other psychiatric disorders.¹¹ Diagnosis typically occurs between 20 and 40 years of age but may occur at any stage in life, and women are affected two to three times more often than men.¹ The etiology of MS remains unknown; however, it is likely an interplay between genetics and environmental factors.^{2,3,12–15}

The first episode of neurological symptoms, characteristic of an inflammatory demyelinating event in the brain or spinal cord, is classified as a clinically isolated syndrome (CIS).¹⁶ This remains so until a definite diagnosis of MS, with “dissemination of demyelinating lesions in space and time”, is made based on clinical episodes, magnetic resonance imaging (MRI) and/or analysis of cerebrospinal fluid.^{17,18} There are three subtypes of MS based on the manifestation of clinical symptoms:

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relapsing–remitting MS (RRMS), secondary progressive MS (SPMS) and primary progressive MS (PPMS), which can be further classified as active- or non-active based on clinical or MRI criteria.¹⁶ The most common diagnosis is RRMS, which affects 80–85% of patients and is characterized by acute exacerbations followed by periods of remission.^{1,5,19} Exacerbations, referred to as attacks or relapses, are defined as new symptoms in the absence of fever reflecting decreased neurological function, lasting at least 24 h and separated from other new symptoms by at least 30 days.¹⁸ Remission from relapse may be partial or complete; neurologic recovery following a relapse tends to be better in early stages of the disease but becomes less complete with repeated relapses.^{3,5} Approximately 75% of patients presenting with RRMS will convert to SPMS within 35 years of the initial symptoms, which is marked by a decline in acute relapses with a steady increase in the progression of disability.⁵ PPMS is diagnosed in ~15% of cases and is characterized by a steady progression of disability from onset, which may occur with or without the presence of clinical relapses and/or MRI activity.^{1,5,19}

Current therapies for disease management

There are currently 11 disease-modifying therapies (DMTs) approved for MS in Canada (Table 1), with several emerging therapies in Phase II and III clinical trials. All currently approved DMTs modulate immune functions and are indicated for treatment of CIS, RRMS and/or SPMS with relapses. To date, there are no approved DMTs to mitigate neurodegenerative disease mechanisms for progressive forms of MS, although some experimental therapies are targeted toward neural repair mechanisms. First-line therapies in Canada include interferon beta-1b (IFN β -1b; Betaseron[®], Extavia[®]), IFN β -1a (Avonex[®], Rebif[®]), pegylated IFN β -1a (PEG-IFN β -1a; Plegridy[®]), glatiramer acetate (Copaxone[®]), teriflunomide (Aubagio[®]) and dimethyl fumarate (Tecfidera[®]). Second-line therapies available are fingolimod (Gilenya[®]), natalizumab (Tysabri[®]) and alemtuzumab (Lemtrada[®]). Given that there is no cure for MS, the goals of current therapeutic interventions are to reduce the number and severity of relapses, minimize long-term disability and improve overall quality of life. In clinical trials, outcomes typically examined include annualized relapse rates (ARRs), MRI parameters such as disease burden (T2 lesion volume) or disease activity (number of new/newly enlarging T2 lesions or gadolinium-enhancing T1 lesions) and disability progression (Expanded Disability Status Scale [EDSS]²⁰). The efficacy

and safety profiles of currently available DMTs are briefly summarized in Table 1.

Overall, treatment decisions are based on benefit/risk profile.²¹ First-line therapies have shown similar efficacy in placebo-controlled^{22–30} and head-to-head trials,^{27,31–35} which is supported by recent meta-analysis data.^{36–38} Second-line therapies show greater efficacy in reducing relapse rates and MRI activity but are also associated with more adverse side effects and potential toxicities.^{39–43} These second-line therapies are typically used only in patients who show disease activity while on first-line therapies, who cannot tolerate first-line therapies or who have extremely active RRMS from onset.²¹ Thus, the optimization of MS therapy ultimately depends on individual disease activity, response to treatment, tolerability and practitioner or patient preference. Proven efficacy and long-term safety information from numerous clinical trials make IFN β an attractive first-line therapy; however, an important drawback is patient adherence due to frequent dosing schedules. Thus, the development of pegylated IFN β (Plegridy[®]) has provided an alternative injectable agent that has similar efficacy and safety profiles as traditional IFN β therapies but significantly reduces the frequency of administration.^{44–50} In this review, we focus our discussion on placebo-controlled trials of subcutaneous IFN β -1a and head-to-head trials against other IFN β formulations to evaluate the role of PEG-IFN β -1a therapy in MS (Table 2).

Interferon β

IFN β was the first biologic approved for MS therapy. IFNs are a family of cytokines involved in the regulation of innate and adapted immunity^{12,51–53} and are thus ideal candidates for immunomodulatory therapies in MS. Early attempts at IFN therapy in MS included the use of IFN γ , IFN α and IFN β .⁵⁴ Unexpectedly, administration of IFN γ resulted in activation of the immune system and increased the occurrence of relapses. Several different formulations of IFN α and IFN β were explored with promising results, but IFN β had a more acceptable patient safety profile. Both recombinant IFN β -1b produced in *Escherichia coli* and recombinant IFN β -1a produced in mammalian cells are approved for the treatment of MS (Table 1). Differences in post-translational modifications confer reduced biological activity of non-glycosylated IFN β -1b compared to glycosylated IFN β -1a,⁵⁵ which is reflected in their dosages. Clinical trials with IFN β have demonstrated a reduction in relapse rates and MRI activity.^{22–24} Delays in disease progression, as measured with EDSS, have also been reported over the 1- to 2-year clinical

Table 1 Disease Modifying Therapies approved by Health Canada for the treatment of Multiple Sclerosis^a

| DMT: Trademark | Indication | Dosage | Clinical Trial | Efficacy ^b | Safety ^{c,d} | Mechanism of Action ^e |
|--|--------------------------------------|--|---|------------------------------------|---|---|
| First line | | | | | | |
| Interferonβ-Ib Betaseron [®] Extavia [®] | CIS, RRMS, SPMS w/ relapses | 250 μ g SC; QAD 250 μ g SC; QAD | IFN β MSSG ²² | 34% | <i>Common to all interferonβ</i> – injection site rxn – flu-like symptoms – decreased blood cell counts – increased LFT | <i>Common to all interferonβ</i> – decrease in pro-inflammatory and increase anti-inflammatory cytokine profiles – inhibition of Th1 cell proliferation – downregulation of antigen presentation by B cells and glial cells in CNS – reduce entry of immune cells into the CNS, most likely through inhibition of MMPs – increase expression of neurotrophic factors |
| Interferonβ-Ia Avonex [®] Rebif [®] | CIS, RRMS, SPMS w/ relapses | 30 μ g IM; QW 22 μ g SC; TIW 44 μ g SC; TIW | MSSRG ²³ PRISMS ²⁴ PRISMS ²⁴ | 18% 27% 33% | | |
| PEG-Interferonβ Plegridy [®] | RRMS | 125 μ g SC; Q2W | ADVANCE ²⁵ | 36% | | |
| Glatiramer acetate Copaxone [®] | CIS, RRMS | 20 mg SC; QD | CMSSG ²⁶ CONFIRM ²⁷ | 29% 29% | – injection site rxn – post-injection rxn (flushing, chest pain, dyspnea) | – shifts from pro-inflammatory Th1/Th17 to anti-inflammatory Th2 response – regulation of monocytes, dendritic & B cells – increase expression of neurotrophic factors |
| Teriflunomide Aubagio [®] | RRMS | 14 mg PO; QD | TEMSo ³⁰ TOWER ²⁹ | 32% 36% | – GI symptoms – decreased blood cell counts – increased LFT | – dihydroorotate dehydrogenase inhibitor; reduces synthesis of pyrimidine nucleotides – reduced proliferation of activated T cells – shifts from pro-inflammatory Th1/Th17 to anti-inflammatory Th2 response |
| Dimethyl fumarate Tecfidera [®] | RRMS | 240 mg PO; BD | DEFINE ²⁸ CONFIRM ²⁷ | 53% 44% | – flushing – GI symptoms – decreased blood cell counts – strong allergic rxn, including anaphylaxis ^d – PML ^d | – shifts from pro-inflammatory Th1/Th17 to anti-inflammatory Th2 response – cytoprotective effects through Nrf2 – modulation of NF- κ B activity |
| Second line | | | | | | |
| Fingolimod Gilenya [®] | RRMS | 0.5 mg PO; QD | FREEDOMS ⁴⁰ FREEDOMS-II ³⁹ | 54% 48% | – bradycardia – decreased blood cell counts – infection – skin cancer ^d – PML ^d | – SIP receptor agonist; internalization and degradation – inhibits egress of activated lymphocytes from lymph node – modulate astrocyte function |
| Natalizumab Tysabri [®] | RRMS | 300 mg IV; Q4W | AFFIRM ⁴¹ | 68% | – infusion rxn – PML | – humanized mAb that binds α 4 integrin – blocks interaction with VCAM-1 preventing migration of activated lymphocytes into CNS |
| Alemtuzumab Lemtrada [®] | RRMS | 0.5 mg IV; 5 consecutive days in year 1, then 3 consecutive days in year 2 | CARE MS-I ⁴² CARE MS-II ⁴² | 55% 49% (vs IFN β -Ia) | – infusion rxn – infection – thyroid disorders – secondary autoimmunity | – humanized mAb that binds CD52 – depletion of CD52-expressing lymphocytes through antibody-mediated cytotoxicity |

Notes: ^aan additional DMT, daclizumab (humanized mAb that binds CD25) marketed as Zinbryta[®], was approved by Health Canada for treatment of RRMS in December 2016 while manuscript was in print; ^befficacy reported as % reduction in relapse rate compared to placebo, except for alemtuzumab (compared to IFN β -Ia), in Phase III clinical trials; ^creported in Phase III clinical trials, except indicated as ^drecently reported by Health Canada (<http://www.hc-sc.gc.ca>; accessed January 14, 2017); ^eproposed mechanisms based on known pharmacology and/or current evidence from clinical trials and animal models.⁵³

Abbreviations: BD, twice daily; CIS, clinically isolated syndrome; CNS, central nervous system; DMT, disease modifying therapy; GI, gastrointestinal; IFN, interferon; IM intramuscular; IV, intravenous; LFT, liver function tests; mAb, monoclonal antibody; MMP, matrix metalloproteinase; MS, multiple sclerosis; NF- κ B, nuclear factor-kappa B; Nrf2, nuclear factor-erythroid 2-related factor 2; PEG, polyethylene glycol; PO, per oral; PML, progressive multifocal leukoencephalopathy; QAD, once every other day; QD, once daily; QW, once weekly; Q2W, once every 2 weeks; Q4W, once every 4 weeks; RRMS, relapsing-remitting MS; rxn, reaction; SIP, sphingosine-1-phosphate; SC, subcutaneous; SPMS, secondary progressive MS; TIW, three times weekly; VCAM-1, vascular cell adhesion molecule 1.

Table 2 Summary of PRISMS, INCOMIN, EVIDENCE and ADVANCE trials**PRISMS²⁴ – Prevention of Relapses and Disability by Interferon beta-1a Subcutaneously in Multiple Sclerosis**

| | |
|--------------------|--|
| Inclusion criteria | Clinically definite RRMS for ≥ 1 year; ≥ 2 relapses in preceding 2 years, and baseline EDSS scores of 0–5 |
| Exclusion criteria | Previous systemic treatment with IFNs, lymphoid irradiation or cyclophosphamide or with other immunomodulatory or immunosuppressive therapy in previous 12 months |
| Intervention | IFN β -1a (Rebif [®]) 22 or 44 μ g SC TIW or placebo |
| Primary outcome | Relapse rate over the course of 2-year study |
| Summary of results | Relapse rates were reduced by 27% in the 22 μ g IFN β -1a intervention and 33% in the 44 μ g IFN β -1a intervention group compared to placebo group. IFN β -1a interventions were also associated with an increased proportion of patients remaining relapse free, decreased change in EDSS scores and decreased time to first progression. MRI end points showed a decrease in total burden of disease (Δ T2 lesion volume), number of new/newly enlarging T2 lesions and number of T1 Gd-enhancing lesions with IFN β -1a treatment compared to placebo. High-dose treatment (44 μ g) showed more favorable outcomes compared to low-dose treatment (22 μ g) |

INCOMIN³¹ – Independent Comparison of Interferon

| | |
|--------------------|--|
| Inclusion criteria | Clinically definite RRMS; ≥ 2 clinically documented relapses during the preceding 2 years with no relapse (and no corticosteroid treatment) for at least 30 days before study entry and baseline EDSS score of 1–3.5 |
| Exclusion criteria | Previous systemic treatment with IFN β or treatment with other immunosuppressive or immunomodulatory drugs (except corticosteroids) |
| Intervention | IFN β -1b (Betaseron [®]) 250 μ g SC QAD or IFN β -1a (Avonex [®]) 30 μ g IM QW |
| Primary outcome | Proportion of patients who remained relapse free over the course of 2-year study |
| Summary of results | In the IFN β -1b SC intervention group, 49% of patients remained relapse free compared to 33% in the IFN β -1a IM intervention group. IFN β -1b treatment was also associated with a decrease in ARR and 6-month sustained progression in EDSS. MRI end points showed an increase in the proportion of patients remaining free from new T2 lesions, remaining free from T1 Gd-enhancing lesions and showing no MRI activity with IFN β -1b SC compared to IFN β -1a IM treatment |

EVIDENCE³² – Evidence of Interferon Dose-response-European North American Comparative Efficacy

| | |
|--------------------|---|
| Inclusion criteria | Clinically confirmed RRMS; ≥ 2 relapses in previous 2 years and baseline EDSS score of 0–5.5 |
| Exclusion criteria | Previous treatment with IFN β |
| Intervention | IFN β -1a (Rebif [®]) 44 μ g SC TIW or IFN β -1a (Avonex [®]) 30 μ g IM QW |
| Primary outcome | Proportion of patients who remained relapse free at ≥ 48 weeks |
| Summary of results | In the IFN β -1a SC TIW intervention group, 56% of patients remained relapse free compared to 48% in the IFN β -1a IM QW intervention group. IFN β -1a SC TIW was also associated with a decrease in ARR and time to first relapse, but no difference was observed in EDSS progression. MRI end points showed a decrease in the number of new or enlarging T2 lesions in the IFN β -1a SC TIW compared to the IFN β -1a IM QW treatment |

ADVANCE²⁵ – Pegylated Interferon beta-1a for Relapsing–Remitting Multiple Sclerosis

| | |
|--------------------|--|
| Inclusion criteria | RRMS; ≥ 2 relapses in previous 3 years with at least one relapse in previous 12 months and baseline EDSS score of 0–5 |
| Exclusion criteria | Progressive MS, previous treatment with IFN β for >4 weeks or discontinuation <6 months before baseline |
| Intervention | PEG-IFN β -1a Plegridy [®] 125 μ g SC Q2W or Q4W or placebo |
| Primary outcome | ARR at 48 weeks |
| Summary of results | ARR were reduced by 36% in the PEG-IFN Q2W and 28% in the PEG-IFN Q4W intervention groups compared to the placebo group. PEG-IFN β interventions were also associated with an increased proportion of patients remaining relapse free and a decreased proportion of patients showing 12-week sustained EDSS progression. MRI end points showed a decrease in total burden of disease (Δ T2 lesion volume), number of new/newly enlarging T2 lesions and number of T1 Gd-enhancing lesions with PEG-IFN β treatment compared to placebo. More frequent injections (Q2W) showed more favorable outcomes compared to low-frequency injections (Q4W) |

Abbreviations: ARR, annualized relapse rate; EDSS, expanded disability status scale; IFN β , interferon beta; IM, intramuscular; MS, multiple sclerosis; PEG, polyethylene glycol; QAD, once every other day; QW, once weekly; Q2W, once every 2 weeks; Q4W, once every 4 weeks; RRMS, relapsing–remitting MS; MRI, magnetic resonance imaging; SC, subcutaneous; TIW, three times weekly.

trial periods,^{23,24} and long-term benefits have been associated with continued IFN β treatment in follow-up studies.^{56,57} However, a large retrospective study by Shirani et al⁵⁸ reported no link between IFN β treatment and the long-term disability progression, which has renewed debate around this issue.^{59–61}

Dosage and administration

IFN treatment is currently indicated for the treatment of CIS, RRMS and SPMS with relapses. Commercially available formulations of IFN β -1b include Betaseron[®] and Extavia[®],

which are administered subcutaneously (SC) every other day (QAD) at a dose of 250 μ g. IFN β -1a is marketed as Avonex[®] administered intramuscularly (IM) once weekly (QW) at a dose of 30 μ g or Rebif[®] administered SC three times weekly (TIW) at a dose of 22 or 44 μ g.

Mechanisms of action

The precise mechanisms of action of IFN β in MS therapy are unknown but have been attributed to its antiproliferative, antiviral and immunomodulatory abilities.⁵² Systemic

administration of IFN β is believed to primarily modulate immune cell function in the periphery.⁶² In general, IFN β appears to oppose the pathogenic processes associated with MS disease progression by shifting from a pro-inflammatory to an anti-inflammatory immune profile (Figure 1). A key player in MS pathology are auto-reactive T cells that migrate across the blood–brain barrier (BBB), initiating inflammatory cascades in the CNS inflicting damage on axons, neurons and myelin sheaths.^{2,63} IFN β therapy is associated with a decrease in the expansion of pro-inflammatory Th1 and Th17 subtypes and promotes the expansion of anti-inflammatory Th2 subtype.^{64–68} IFN β has also been shown to modulate the function of regulatory T cells,⁶⁹ B cells,^{70,71} natural killer cells⁷² and dendritic cells.⁷³ The complexity of immune cell

signaling networks makes it difficult to delineate the direct and indirect effects of IFN β on each cell type.⁵² Effects of IFN β on T cell function are mostly likely mediated indirectly through up-regulation of anti-inflammatory mediators, such as interleukin (IL)-10,^{66,74–78} and down-regulation of pro-inflammatory cytokines, such as IL-17, osteopontin and tumor necrosis factor α (TNF α),^{64,73,74,78,79} secreted from other types of immune cells.

IFN β has also been implicated in acting at the BBB, impeding migration of leukocytes into the CNS. Matrix metalloproteinases (MMPs), more specifically MMP-9 and tissue inhibitor of metalloproteinase-1 (TIMP-1), are involved in the degradation and remodeling of the extracellular matrix.⁸⁰ IFN β has been shown to decrease serum levels

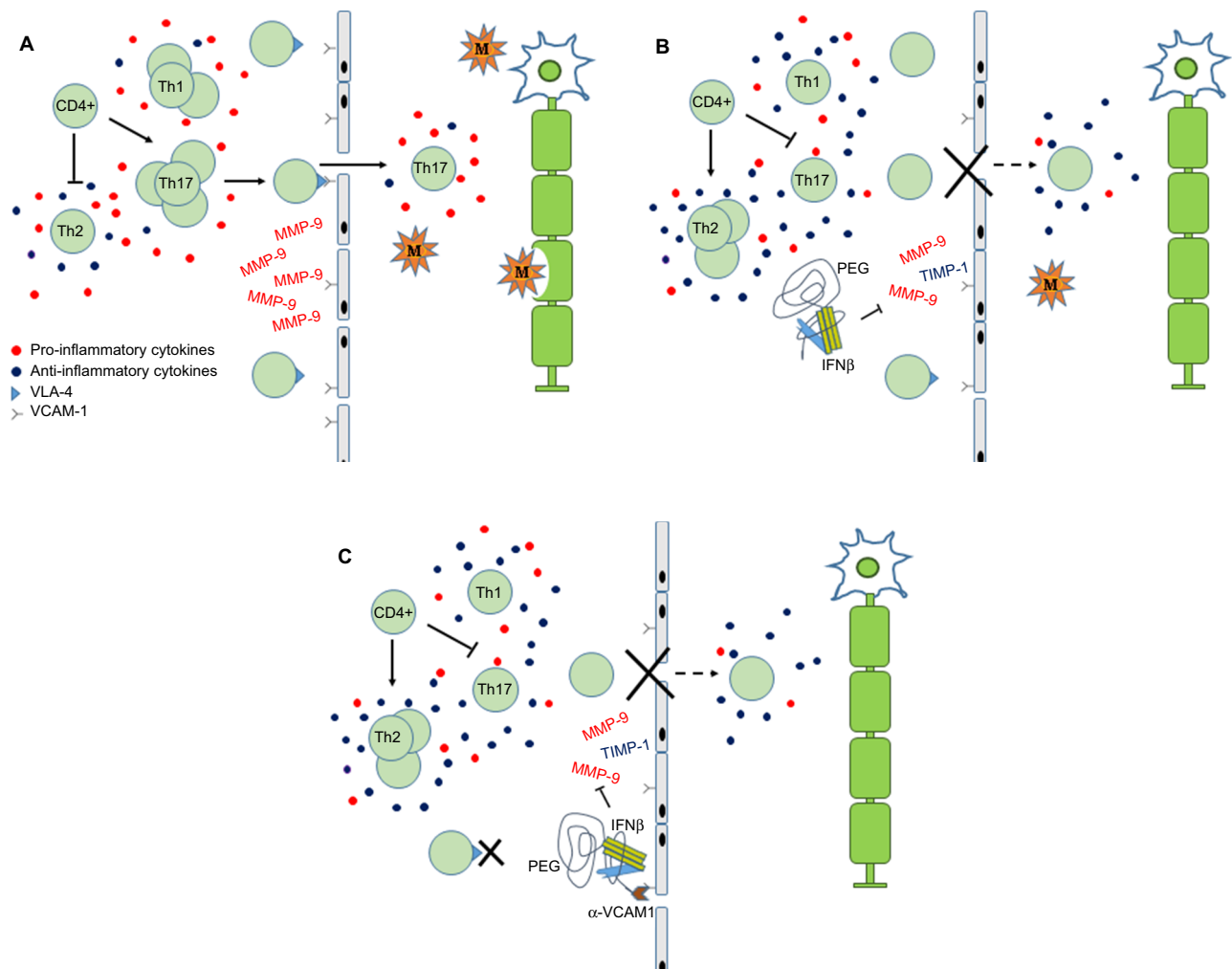


Figure 1 Schematic depicting the role of PEG-IFN β therapy in MS.

Notes: (A) In MS, pro-inflammatory cytokines stimulate CD4+ cells to proliferate and differentiate into Th1 and Th17 effector cells. Activated T cells express VLA-4, which interacts with VCAM-1 on endothelial cells, to facilitate crossing the BBB. In the CNS, auto-reactive T cells and macrophages result in damage to the myelin sheath, axons and neurons. Inflammatory demyelinating lesions result in the clinical presentation of MS. (B) IFN β is conjugated to PEG to increase the molecule's serum concentration and half-life. Proposed actions of IFN β include modulating cytokine milieu to favor anti-inflammatory pathways, which inhibits expansion of Th1/Th17 and promotes expansion of Th2 cells. Down-regulation of VLA-4 and inhibition of MMP-9 reduce migration of activated T cells into CNS. (C) Linking of anti-VCAM-1 antibodies to the PEG tail may enhance IFN β anti-inflammatory actions by 1) blocking interaction of leukocytes expressing VLA-4 with VCAM-1 and 2) increasing local concentration of PEG-IFN β at BBB. **Abbreviations:** BBB, blood–brain barrier; CNS, central nervous system; IFN β , interferon beta; M, macrophage; MMP, matrix metalloproteinase; MS, multiple sclerosis; PEG, polyethylene glycol; PEG-IFN β , pegylated interferon β ; TIMP-1, tissue inhibitor of metalloproteinase-1; VCAM-1, vascular cell adhesion molecule 1; VLA-4, very late activation antigen-4.

of MMP-9 and modulate MMP-9:TIMP-1 ratio, and this was associated with a decrease in the number of new and/or active MRI lesions.^{81,82} To facilitate crossing the BBB, activated T cells up-regulate adhesion molecules, such as very late activation antigen-4 (VLA-4), which interact with vascular cell adhesion molecule 1 (VCAM-1) receptor expressed by endothelial cells (Figure 1). Evidence suggests that administration of IFN β down-regulates expression of VLA-4/ α -4 integrin, thereby inhibiting lymphocyte migration into the CNS.^{83–85} Together, these mechanisms reduce the number of pro-inflammatory immune cells in circulation and suppress the ability of activated leukocytes to enter the CNS. In addition to immunomodulatory effects, IFN β treatment has been associated with increased expression of neurotrophic factors,^{86–88} which may convey cytoprotective effects.

Clinical trials

The Prevention of Relapses and Disability by Interferon beta-1a Subcutaneously in Multiple Sclerosis (PRISMS) study^{23,89,90} was pivotal multi-centered, randomized, double-blind, placebo-controlled clinical trial investigating the benefit of SC IFN β -1a administration TIW for RRMS (Table 2). Participants were randomized to either 22 or 44 μ g or placebo groups with a primary outcome of number of relapses during the 2-year study period.²³ The number of relapses was lower in both intervention groups compared to placebo: 27% (95% confidence interval [95% CI] 14–39) reduction for the 22 μ g dose (1.82 vs 2.56) and 33% (95% CI 21–44) reduction for the 44 μ g dose (1.73 vs 2.56) (Table 3). This included a delay in the time to relapse and a decreased number of severe relapses, steroid courses and hospitalizations with IFN β -1a treatment. Monitoring of disease activity with MRI⁸⁹ showed a corresponding decrease in the number of Gd-enhancing T1 lesions, number of active T2 lesions and reduction in burden of disease (T2-weighted). Participants receiving placebo showed a 10.9% increase in total lesion volume compared to a 1.2% decrease for the 22 μ g intervention and 3.8% decrease for the 44 μ g intervention. After 4 years, IFN β -1a treatment continued to reduce ARR (0.90 in year 1 vs 0.44 in year 4 for high-dose group) and improve MRI outcomes.⁹⁰ Furthermore, both 4-year treatment groups showed favorable outcomes compared to the delay-treatment, crossover groups. Follow-up analyses at both 8⁹¹ and 15 years⁵⁶ are indicative of long-term benefit of IFN β -1a therapy on disease course, favoring early treatment intervention, higher dosages and longer exposure times.

Following the PRISMS study, head-to-head trials further investigated the efficacy of different IFN β formulations and dosage in the Independent Comparison of Interferon

(INCOMIN) study³¹ and Evidence of Interferon Dose-response-European North American Comparative Efficacy (EVIDENCE) study.³² The INCOMIN trial³¹ compared 250 μ g IFN β -1b SC injections QAD with 30 μ g IFN β -1a IM injections QW over 2 years (Table 2). The primary outcome of the proportion of patients remaining relapse free favored IFN β -1b therapy (49%) over IFN β -1a therapy (33%); this was also reflected by a 29% reduction in the ARR (0.5 for IFN β -1b vs 0.7 for IFN β -1a). For MRI outcomes, IFN β -1b SC therapy increased the proportion of patients who remained free from Gd-enhancing T1 lesions or new T2 lesions compared to IFN β -1a. The burden of disease for participants receiving IFN β -1b decreased 2.8% whereas IFN β -1a increased 11.7%. However, due to multiple variables in treatment regimen, it is difficult to ascertain whether improved outcome relates to difference in formulation, dosage, frequency or route of administration.

The EVIDENCE trial³² compared IFN β -1a treatment at a dosage of 44 μ g administered by SC injections TIW (TIW) with a dosage of 30 μ g administered by IM injections QW over 1 year (Table 2). The primary outcome was the proportion of patients remaining relapse free, which favored 44 μ g SC TIW therapy (56%) over 30 μ g IM QW therapy (48%). There was a 17% reduction in ARR in the 44 μ g SC TIW group (0.54) compared to the 30 μ g IM QW group (0.65), and the mean number of active T2 lesions was also reduced by 36%. Thus, both the IFN β -1b SC (cumulative dose 28 MIU/week) in the INCOMIN study and the IFN β -1a SC (cumulative dose 36 MIU/week) in the EVIDENCE trial showed greater efficacy than IFN β -1a IM (cumulative dose 6 MIU/week). Pharmacokinetic studies indicate that the bioavailability of IFN β does not appear to differ substantially between SC and IM administration.⁶² Taken together, data from the PRISMS, INCOMIN and EVIDENCE trials demonstrated that higher, more frequent dosing of IFN β improve patient outcomes.

Therapeutic considerations

Safety profile

IFNs are naturally occurring cytokines and generally well tolerated. The PRISMS study²³ reported common adverse events of IFN β -1a treatment to include injection-site reactions (redness, swelling), flu-like symptoms, fever, headache and myalgia. However, flu-like symptoms were also commonly reported in placebo group (24% vs 25% and 27% in 22 and 44 μ g treatment groups, respectively). Most injection-site reactions were mild, with only eight incidences of skin necrosis (>150,000 injections). Less common, but serious, adverse events include decreased numbers of white blood cells and platelets and elevated liver enzymes. Similar safety

Table 3 Comparison of currently available data on interferon β -1a and pegylated interferon β -1a

| | IFN β -1a *PRISMS: 2-year study ²⁴ | | | PEG-IFN β -1a *ADVANCE: 1-year study ²⁵ | | |
|--|--|-----------------------|-----------------------|---|---|---|
| | Placebo SC; TIW | 22 μ g SC; TIW | 44 μ g SC; TIW | Placebo SC; Q2W | 125 μ g SC; Q2W | 125 μ g SC; Q2W |
| Administration | | | | | | |
| Number of patients enrolled | 187 (170) | 189 (167) | 184 (165) | 500 (456) | 512 (438) | 500 (438) |
| % Completed treatment | 91 | 88 | 90 | 91 | 86 | 88 |
| Clinical outcomes | | | | | | |
| Relapse rate ^b | 2.56 | 1.82 | 1.73 | 0.40 | 0.26 | 0.29 |
| % reduction of relapse rate vs placebo | – | 27 | 33 | – | 36 | 28 |
| % relapse free (1 year) | 22 | 37 | 45 | 71 | 81 | 78 |
| Disability progression ^c | 0.48 | 0.23 | 0.24 | 0.105 | 0.068 | 0.068 |
| MRI outcomes | | | | | | |
| Burden of disease ^d | 10.9% | –1.2% | –3.8% | 0.77 cm ³ | –0.26 cm ³ | 0.06 cm ³ |
| T2 new/enlarging lesions | 4.5 | 1.3 | 0 | 10.9 | 3.6 | 7.9 |
| T1 Gd-enhancing lesions | 8.0 | 1.4 | 1.3 | 1.4 | 0.2 | 0.9 |
| New active lesions ^e | 10.6 | 2.1 | 1.3 | 11.2 | 3.7 | 7.3 |
| NABs | – | Anti-IFN: 23.8% | Anti-IFN: 12.5% | – | Anti-IFN: <1% ^f anti-PEG: 6% ^f | Anti-IFN: <1% ^f anti-PEG: 8% ^f |
| Adverse events (%) ^g | | | | | | |
| Injection-site reactions | 22 | 61 | 62 | 7 | 62 | 56 |
| Influenza-like illness | 24 | 25 | 27 | 13 | 47 | 47 |
| Headache | 44 | 47 | 45 | 33 | 44 | 41 |
| Fatigue | 16 | 14 | 19 | 10 | 10 | 11 |
| Myalgia | 8 | 13 | 14 | 6 | 19 | 19 |
| Fever | 6 | 13 | 12 | 15 | 45 | 44 |
| Abnormal blood cell counts | | | | | | |
| Leukopenia | 2 | 4 | 8 | 1 | 7 | 4 |
| Lymphopenia | 4 | 5 | 13 | 3 | 5 | 4 |
| Elevated liver enzymes | | | | | | |
| Alanine aminotransferase | 1 | 5 | 7 | 1 | 2 | 2 |
| Aspartate aminotransferase | 1 | 2 | 3 | 1 | 1 | 1 |
| Adverse events resulting in discontinuation | 1 | 3 | 5 | 1 | 5 | 5 |
| Pharmacokinetics ⁶² | | | | | | |
| AUC ^h | – | 12 IU·h/mL | 71.6 IU·h/mL | – | 24.5 ng·h/mL | 23.5 ng·h/mL |
| C _{max} | – | 1.3 IU/mL | 12.8 IU/mL | – | 221 pg/mL | 202 pg/mL |
| T _{max} (h) | – | 1–2 | 0.25 | – | 35.9 | 35.1 |
| half-life (h) | – | n.a. | 12.8 | – | 62.8 | 56.8 |

Notes: *Comparison of placebo-controlled studies; no head-to-head trials have directly compared IFN β -1a to PEG-IFN β -1a. ^bDefined as number of relapses over 2-year study period (PRISMS) or ARR at 48 weeks (ADVANCE). ^cDefined as change in EDSS over duration of study (PRISMS) or proportion of patients with 12-week sustained progression in EDSS \geq 1.0 (ADVANCE). ^dDefined as change in total in T2 lesion volume from baseline (PRISMS, mm²; ADVANCE, cm³). ^eDefined as the sum of T1 Gd-enhancing and new or newly enlarging T2 lesions (PRISMS, clinically unique; ADVANCE new active). ^fReported at 2 years.¹²² ^gPRISMS reported adverse events in first 3 months of therapy and ADVANCE reported adverse events over the full 48 weeks. ^hMeasured over 8 h for 22 μ g IFN β -1a and measured over 168 h for 44 μ g IFN β -1a and 125 μ g PEG-IFN β -1a. C_{max}, maximum serum concentration; T_{max}, time to reach C_{max}.

Abbreviations: ARR, annualized relapse rate; AUC, area under curve; EDSS, Expanded Disability Status Scale; IFN, interferon; Q2W, once every 2 weeks; MRI, magnetic resonance imaging; n.a., not available; NABs, neutralizing antibodies; PEG, polyethylene glycol; SC, subcutaneous; TIW, three times weekly.

profiles were reported in 4-year follow-up studies. Over 4 years, there were three deaths reported none of which were related to the treatment.^{90,92}

There were initially reports of IFN β therapy causing an increase in the incidence of depression. Given the neurologic pathology of MS and its chronic progressive nature, the estimated lifetime prevalence of major depression in MS is as high as 50%.^{93,94} With such a high comorbidity rate of

depression among MS patients,¹¹ it is difficult to definitively link IFN β therapy with an increased risk of depression. There was no significant difference among treatment groups in the PRISMS trial; depression was reported by 28% of patients receiving placebo, 21% of patients receiving 22 μ g of IFN β and 24% of patients receiving 44 μ g of IFN β .²³ During the study, one patient in the placebo group committed suicide and three patients in each group reported attempting suicide or

suicidal ideation. Furthermore, no difference in the incidence of depression has been found between patients receiving IFN β and glatiramer acetate therapy.⁹⁵

Neutralizing antibodies

Another concern associated with IFN β -1a therapy is the production of neutralizing antibodies (NAbs). In the PRISMS study, 23.8% of participants receiving the 22 μ g dose and 12.5% of participants receiving the 44 μ g dose were positive for NAbs but concluded that NAbs had no impact on the mean relapse count in either intervention.²³ The INCOMIN study reported more frequent production of NAbs with IFN β -1b (30%) than with IFN β -1a (7%) therapy, but again this did not appear to negatively impact treatment efficacy.³¹ In contrast, the EVIDENCE study with IFN β -1a reported a higher prevalence of NAbs within the 44 μ g SC TIW (26%) compared to the 30 μ g IM QW (3%) intervention and noted that NAbs developed earlier among the high-dose intervention.³² Disease activity was significantly greater in participants receiving 44 μ g SC TIW who were positive for NAbs compared to those who were negative for NAbs; however, NAb^{+ve} and NAb^{-ve} participants had less MRI activity than their 30 μ g IM QW counterparts.

The clinical implications of NAbs in IFN β therapy remain unclear. High titers of NAbs appear to be related to the formulation, dosing regimen and route of administration.^{31,32,96–98} NAb levels often peak within 6–12 months of starting therapy and then decline, with ~10% of patients developing persistent NAbs.⁹⁸ At persistently high titers, NAbs can reduce biological activity^{99,100} and negatively impact long-term drug therapy.^{97,99,101–103} The most recent treatment recommendations provide little consensus on how to approach this issue:²¹ current practices include periodic testing of NAb levels, testing for NAbs only when considering switching therapies or opting to base treatment decisions solely on clinical outcomes.

Adherence

Frequent IFN β administration has been shown more effective for managing RRMS;^{31,32} however, given that the disease is chronic and progressive, this dosing regimen may not be amenable for many patients. Overall, adherence rates of injectable DMTs requiring frequent administration (i.e., \geq QW) have been estimated at 27–76%,^{104–110} with decreased adherence associated with an increased risk of relapse.^{105,106} The most commonly reported reasons for discontinuation were lack of efficacy, tolerability (i.e., adverse effects such as flu-like symptoms and injection-site reactions) and patients' decision (i.e., both practical issues and mental exhaustion).^{111–115} Discontinuation due to adverse effects typically occurs within

the first year of treatment,^{114,115} but this can be mitigated by dose titration, prophylactic treatment of flu-like symptoms and injection-site reactions, increased patient education and the use of autoinjectors.^{116,117} Another viable approach has been drug modification to increase pharmacokinetic profile and prolong bioavailability to reduce frequency of administration, such as the pegylation of IFN β -1a.⁴⁴

Pegylated interferon β

Pegylation is the process by which molecules of polyethylene glycol (PEG) are chemically conjugated to a biological product. The addition of PEG increases the size of a macromolecule, generally increasing its solubility, stability and mobility in solution.^{118,119} Pegylation decreases the rate of renal clearance and may also reduce receptor- or antibody-mediated clearance and proteolytic degradation.^{44,118} This results in increased exposure, half-life and serum concentrations of the therapeutic agent. Other potential benefits of pegylation are reduced antigenicity and immunogenicity, as PEG could potentially mask recognition of epitopes.^{44,118} Addition of large PEG molecules can often decrease binding to target through steric hindrance,¹¹⁹ yet the overall goal is to balance pharmacodynamic and pharmacokinetic properties to improve treatment efficacy.¹¹⁸ These attributes are ideal for a biomolecule such as IFNs, which are rapidly cleared without any modifications.⁶² For example, pegylated forms of IFN α -2a (Pegasys[®]; Hoffman La Roche) and IFN α -2b (PegIntron[®]; Schering-Plough) have been used in the management of chronic hepatitis C for over a decade.^{119,120} The development of PEG-IFN β -1a, a 20 kDa linear methoxy PEG molecule conjugated to the alpha amino group of the N terminal amino acid residue of IFN β , demonstrated a desirable pharmacokinetic and pharmacodynamic profile to decrease the frequency of administration for the management of MS.⁴⁴

Dosage and administration

PEG-IFN β -1a is marketed as Plegridy[®] and currently indicated for the treatment of RRMS. PEG-IFN β -1a is administered SC every 2 weeks (Q2W) at a dose of 125 μ g.

Mechanisms of action

The mechanisms of action of PEG-IFN β -1a are presumably similar to its parent compound. The N-terminus of IFN β , which is known not to be critical for its activity, was chosen for the site of attachment.⁴⁴ Although predicted not to affect ligand-binding interactions, a size-dependent decrease in antiviral activity was observed with increasing size of PEG molecules. As smaller PEG molecules did not convey the desired pharmacokinetic properties, 20 kDa was

chosen for the pegylation of IFN β -1a.⁴⁴ In healthy controls, PEG-IFN β -1a and IFN β -1a administration resulted in similar changes in cytokine gene expression favoring an anti-inflammatory profile.¹²¹ To our knowledge, the anti-inflammatory properties of PEG-IFN β -1a have not yet been directly investigated or reported in clinical trials or animal models of MS.

Clinical trials

To date, there has been one randomized, double-blind, placebo-controlled clinical trial investigating PEG-IFN β -1a in RRMS. The ADVANCE trial^{25,122,123} was a 2-year study, consisting of a 48-week placebo-controlled phase and 48-week crossover phase, comparing the efficacy of 125 μ g PEG-IFN β -1a administered by SC injection Q2W or every 4 weeks (Q4W; Table 2). At 48 weeks, the primary outcome of ARR showed a benefit for both PEG-IFN β therapy regimens compared to placebo.²⁵ The ARRs were 0.256 (95% CI 0.206–0.318) for the Q2W intervention and 0.288 (95% CI 0.234–0.355) for the Q4W intervention compared to 0.397 for placebo (95% CI 0.328–0.481), corresponding to a 36% and 28% reduction in the Q2W and Q4W, respectively. MRI outcomes^{25,123} showed a decrease in the number of new or newly enlarging T2 lesions in both PEG-IFN β treatment groups but only a significant decrease in the number of Gd-enhancing and T1 hypointense lesions in the Q2W group compared to placebo. Total T2 lesion volume increased in the placebo group by 0.77 cm³ and Q4W treatment group by 0.06 cm³ and decreased in the Q2W treatment group by 0.26 cm³. The proportion of patients achieving “no evidence of disease activity” (NEDA), defined as absence of both clinical and MRI disease activity, was 33.9% in the PEG-IFN β Q2W, 21.5% in the PEG-IFN β Q4W and 15.1% in the placebo group.¹²³ These data demonstrate a benefit of both PEG-IFN β treatments but suggest an advantage of a more frequent dosing regimen to minimize disease activity.

Upon completion of the first year, participants receiving placebo were re-randomized to one of the treatment interventions and participants already receiving drug intervention remained on the same dosing regimen.¹²² Both continuous intervention groups showed a reduction in the ARR compared to the corresponding delayed-treatment groups, 37% reduction and 17% reduction in the Q2W and Q4W dosing, respectively. The ARR decreased among participants receiving continuous PEG-IFN β Q2W from 0.230 (95% CI 0.183–0.291) to 0.178 (95% CI 0.136–0.233), while the ARR was roughly maintained among participants receiving continuous PEG-IFN β Q4W (0.286 [95% CI 0.231–0.355] and 0.291 [95% CI 0.231–0.368]). Also, the number of new or

newly enlarging T2 lesions continued to decline for both the continuous Q2W and Q4W groups. When directly comparing the two dosing regimens, there was a 24% reduction in ARR and 60% reduction in the number of new or newly enlarging T2 lesions in the Q2W compared to the Q4W. Subgroup analysis indicated that the efficacy of PEG-IFN β was similar across different populations of RRMS patients.¹²⁴ A recent preliminary report from the ATTAIN study, an extension of the ADVANCE trial, indicates that the efficacy of each treatment was maintained over 3 years.⁴⁵ This suggests, similar to other IFN β formulations, that early intervention, higher cumulative dosage and increased exposure time are advantageous.

Therapeutic considerations

Safety profile

Reported side effects of PEG-IFN β were similar to those previously reported for both SC and IM injections of IFN β . These included mild-to-moderate adverse events such as injection-site reactions, influenza-like illness, fever, chills, headache and myalgia. In year 1, the incidence of discontinuation of the study due to adverse events was 6% in both treatment groups and 1% in the placebo group, the most commonly reported reason being influenza-like illness. The rate of severe adverse events was similar among the three study groups: 11% in the placebo, 18% for the every 2-week intervention and 16% for the every 4-week intervention.²⁵ Participants in both intervention groups had decreased number of blood cells and elevated liver enzymes, but neither was determined to be clinically significant and the majority returned to normal ranges within 2 years. The incidence of abnormal white blood cell counts remained low (\leq 10% of participants) across both intervention groups.^{25,122} Over the 2-year study, nine deaths occurred; however, an independent safety-monitoring board reported that these events were not likely related to the study drug and did not change the risk–benefit profile of PEG-IFN.¹²² A 3-year follow-up from the ATTAIN study indicates that PEG-IFN continues to show a similar safety profile.¹²⁵ As with other pegylated pharmaceuticals, adverse side effects are associated primarily with the active drug not the PEG moiety.¹¹⁹

Neutralizing antibodies

As stated previously, traditional SC IFN β -1a therapy can result in persistently high levels of NABs (\sim 10% of patients), which may negatively impact the treatment efficacy. Development of IFN β antibodies was $<$ 1% in both interventions, whereas development of antibodies against PEG was reported at 6% in Q2W and 8% in Q4W interventions.¹²² The appearance of NABs was determined not to impact efficacy or safety

of treatment, but due to low rate of incidence in this study, data should be interpreted with caution.¹²⁶

Adherence

The use of PEG-IFN β -1a has been estimated to reduce the number of injections by >90% compared to other first-line therapies.³⁷ In the ADVANCE study, 88% of the participants completed the first year²⁵ and 90% of continuing patients completed the second year.¹²² Tolerability and adverse events, such as flu-like symptoms and injection-site reactions, were still major factors leading to discontinuation; however, management strategies similar to standard IFN therapies can be used to mitigate impact.¹²⁷ Adherence to treatment, defined by the number of doses received divided by the number of doses expected to receive, was >99% in each group.²⁵ It should be noted though that adherence in controlled trials is usually greater than in a clinical setting.¹¹⁶ While reduced frequency of administration is expected to increase adherence,^{44,45,47,49} this will need to be further evaluated as PEG-IFN therapy is integrated into clinical practice.

Interferon β versus pegylated interferon β

A comparison of the efficacy, safety profile and pharmacokinetics data for PEG-IFN β -1a and its parent compound IFN β -1a is reported in Table 3. A considerable amount of data are available regarding the pharmacokinetic properties of different IFN β formulations, dosages and routes of administration; the only factor that substantially alters the pharmacokinetic profile is pegylation.⁶² PEG-IFN β -1a administration by IM injection showed a fourfold increase in drug exposure, assessed by the area under the curve (AUC), compared to an equal dosage of IFN β -1a.¹²¹ PEG-IFN β and IFN β administration both resulted in altered cytokine expression profiles, but the pharmacological response with PEG-IFN β had a more rapid onset and was sustained for a longer period.¹²¹ Only one study has done a direct comparison between standard therapeutic doses of IFN β -1a and PEG-IFN β -1a administered by SC injection over the course of 2 weeks.¹²⁸ When healthy participants were evaluated for accumulative drug exposure with six doses of 44 μ g IFN β -1a SC compared to a single dose of 125 μ g PEG-IFN β -1a, the AUC was found to be 60% higher for the PEG-IFN β dosage regime. This corresponds to approximately fourfold increase in C_{max} , approximately sixfold increase in T_{max} and approximately twofold increase in half-life. Thus, pegylation of the IFN β -1a molecule results in an increased serum concentration and greater drug exposure compared to the traditional IFN β -1a therapy. The tolerability of PEG-IFN β was favorable with a lower incidence of adverse

events compared to the IFN β dosing regimen.¹²⁸ This was presumably due to the need for less frequent injections with PEG-IFN β .

To date, there are no published head-to-head clinical trials comparing PEG-IFN β to the alternative formulations of IFN β or any other DMT. In the PRISMS study²³ and the ADVANCE study,²⁵ similar efficacy was observed between IFN β -1a and PEG-IFN β -1a interventions when comparing % relative reduction in relapse rate. Both studies also reported favorable MRI outcomes, including a decrease in disease activity (T1- and/or T2-weighted) and burden of disease (total lesion volume) with treatment. However, due to different methodology and reporting measures, direct comparisons of study outcomes are difficult. Although meta-analysis of efficacy and safety profiles³⁷ and cost-effectiveness analysis¹²⁹ tend to favor PEG-IFN β -1a, these are relatively premature. Full results from the ATTAIn study will provide further data on the long-term efficacy on safety of PEG-IFN β therapy. In addition to clinical trial data, longitudinal studies with IFN β -1a treatment also suggest positive effects on cognitive function¹³⁰⁻¹³² and long-term benefits of disease progression,^{55,90} but these types of data sets are not yet available for PEG-IFN β -1a. Ultimately, head-to-head clinical trials and observational studies from clinical practice will continue to inform us about the role of PEG-IFN β in MS disease management.

What are future therapeutic possibilities for PEG-IFN?

The conjugation of PEG to IFN β -1a has expanded the therapeutic options for the management of MS. By prolonging the half-life of IFN β -1a, increasing its exposure and decreasing its elimination,^{44,62} this novel formulation provides a safe and effective first-line therapy with a decreased frequency of administration. This new PEG-IFN β formulation has also created a platform upon which other immunomodulatory molecules may be added (Figure 1). This may serve to enhance the efficacy of IFN β by 1) providing opportunity to develop combination therapies and 2) targeting the IFN β to specific locations within the body. For example, by specifically targeting VCAM-1, expressed on activated endothelial cells, the anti-VCAM-PEG-IFN molecule could more effectively block activated T cells from crossing the BBB. Theoretically, this would also increase the local concentration of IFN β to the BBB possibly directing its immunomodulatory effects to this compartment and reduce non-specific systemic effects. Whether these hypothetical modifications would enhance IFN activity has yet to be determined. However, if successful it may lead to targeted delivery of IFN β with

potentially greater efficacy and a reduction in frequency of side effects.

Conclusion

IFN β , a naturally occurring cytokine, was the first DMT approved for MS therapy. Clinical evidence has consistently demonstrated a decrease in relapse rates and MRI activity; however, the inherent physical properties require it to be frequently administered in order to maintain therapeutic concentrations. The conjugation of PEG molecules to IFN β alters the pharmacokinetic properties of the parent drug, thereby decreasing the frequency of administration. This also provides a novel platform for combination therapy approach.

ADVANCE is currently the only clinical trial with published results on the efficacy of PEG-IFN β -1a compared to placebo in the treatment of RRMS; to date, there are no head-to-head trials comparing PEG-IFN β -1a to other approved DMTs. Furthermore, there are no treatment guidelines for practitioners that include initiating or switching to PEG-IFN β therapy. Here, we have made an effort to compile currently available information regarding IFN β therapy options with respect to various formulations. All available data suggest that the efficacy and safety profile of PEG-IFN β -1a is comparable to other IFN β therapies, with the added benefit of a decreased dosing schedule. This provides patients and practitioners with a viable alternate first-line therapy in the treatment of MS.

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Disclosure

The authors report no conflicts of interest in this work.

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