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Subcutaneous Recombinant Interferon-β-1a (Rebif®)

A Review of its Use in Relapsing-Remitting Multiple Sclerosis

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Data Selection

Sources: Medical literature published in any language since 1980 on interferon-beta-1a, identified using MEDLINE and EMBASE, supplemented by AdisBase (a proprietary database of Adis International). Additional references were identified from the reference lists of published articles. Bibliographical information, including contributory unpublished data, was also requested from the company developing the drug.

Search strategy: MEDLINE search terms were 'interferon-beta-1a'. EMBASE search terms were 'interferon-beta-1a' or 'IFN-beta-1a'. AdisBase search terms were 'interferon-beta-1a' or 'IFN-beta-1a'. Searches were last updated 11 May 2005.

Selection: Studies in patients with multiple sclerosis who received interferon-β-1a. Inclusion of studies was based mainly on the methods section of the trials. When available, large, well controlled trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

Index terms: Interferon-β-1a, multiple sclerosis, pharmacodynamics, pharmacokinetics, therapeutic use, tolerability.

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Summary

Abstract

Subcutaneous recombinant interferon-β-1a (Rebif®) 22 or 44μg three times weekly is a valuable option in the first-line treatment in patients with relapsing-remitting multiple sclerosis (RRMS). It has shown benefits on outcome measures related to relapses, progression of disability and magnetic resonance imaging (MRI) in clinical trials. A significant efficacy advantage for subcutaneous interferon-β-1a three times weekly over intramuscular interferon-β-1a 30μg once weekly was shown at 24 and 48 weeks. The most common adverse events are generally mild and clinically manageable. Considering both direct and indirect comparative clinical trial data, an assessment suggests that subcutaneous interferon-β-1a 44μg three times weekly has the best benefit-to-risk values of the available disease-modifying drugs used to treat RRMS.

Pharmacological Properties

Glycosylated recombinant interferon-β-1a has the same primary structure and biological effects in the body as endogenous human interferon-β. Immunomodulatory activity, the principal pharmacodynamic property of interferon-β-1a, most likely results from interferon-stimulated gene products mediating biological activities. The long-term clinical significance of the development of neutralising antibodies (NABs) to interferon-β-1a is currently unclear; therefore, it is recommended that treatment decisions are based on clinical efficacy and not on the presence of NABs alone.

In healthy volunteers, subcutaneous interferon-β-1a has a long apparent elimination half-life and appears to accumulate after repeated doses.

Therapeutic Efficacy

In a randomised 2-year trial, subcutaneous interferon-β-1a 22 or 44μg three times weekly for 2 years was more effective than placebo as assessed by a number of clinical (e.g. relapse rate per patient, proportion of patients without clinical relapse and changes from baseline in Kurtzke Expanded Disability Status Scale [EDSS] scores) and MRI (total burden of disease and numbers of active lesions per patient per scan) endpoints. Significant dose-response effects in favour of the higher dosage were evident when the study period was extended for another 2 years. Extension data for a total follow-up period of 7–8 years in the original cohort showed sustained clinical benefits with subcutaneous interferon-β-1a therapy.

In a 48-week comparative trial, patients randomised to subcutaneous interferon-β-1a 44μg three times weekly were more likely to remain free of relapses and have significantly more favourable measures of MRI lesion activity at weeks 24 and 48 weeks, and a longer time to first relapse, than those randomised to intramuscular interferon-β-1a 30μg once weekly. In the crossover extension phase (median treatment duration 34 weeks), clinical and MRI outcomes improved in patients who crossed over from treatment with intramuscular interferon-β-1a 30μg once weekly to subcutaneous interferon-β-1a 44μg three times weekly.

Tolerability

In clinical trials of subcutaneous interferon-β-1a, the most commonly reported adverse events (e.g. injection-site reactions, headache and influenza-like symptoms) were generally mild, manageable and reversible. Mild, asymptomatic and reversible haematological disorders and alterations in liver function tests may occur. A few patients experience serious effects on liver function.

Subcutaneous interferon-β-1a 44μg three times weekly was associated with a significantly higher incidence of injection-site disorders and liver function or haematological abnormalities than intramuscular interferon-β-1a 30μg once weekly. No between-group differences were noted regarding the proportions of patients experiencing serious adverse events.

Pharmacoeconomic and Other Considerations

In an assessment that evaluated the four available RRMS disease-modifying treatments based on the numbers of patients needed to treat to obtain benefit or harm, subcutaneous interferon-β-1a 44μg three times weekly had the best benefit-to-risk values. Based on data from pivotal directly comparative trials, subcutaneous interferon-β-1a 44μg three times weekly had favourable benefit-to-risk values relative to subcutaneous interferon-β-1a 22μg three times weekly and intramuscular interferon-β-1a 30μg once weekly. Based on indirect comparative data from published clinical trials, subcutaneous interferon-β-1a appeared to have favourable efficacy values relative to interferon-β-1b every other day, and interferon-β formulations appeared to have favourable benefit-to-risk ratios relative to placebo and also subcutaneous glatiramer acetate 20μg once daily.

In pharmacoeconomic analyses from a healthcare payer perspective, subcutaneous interferon-β-1a 44μg three times weekly was predicted to be increasingly more cost effective than placebo over the mid- (10 years) and long- (20 years) term with regard to preventing EDSS-months of disability in the UK and France, and cost saving relative to intramuscular interferon-β-1a 30μg once weekly over 48 weeks in the US.

1. Introduction

Multiple sclerosis (MS), the most frequent cause of long-term neurological disability in young adults, has a prevalence of ≈1 in 1000 in temperate regions.[1,2] Principal symptoms include blurred vision, motor problems leading to difficulties in walking, bladder and sexual dysfunction, sensory problems and ataxia.[2-4] The condition has a mean age of onset of ≈30 years and affects fewer men than women.[2,5] A genetic predisposition, environment, geographical location and viral infections may also be important pathogenetic factors for MS.[1,2]

Histologically, MS is characterised by the presence of demyelinated, sclerotic lesions and axonal loss in the CNS resulting from inflammatory damage.[1,2] Demyelination subsequently interferes with nerve conduction, resulting in progressive neurological impairment.

MS is generally classified according to the clinical course of the disease.[2,4] The majority of patients (≈85%) present with relapsing-remitting MS (RRMS), which is characterised by episodes of acute worsening (relapses or exacerbations) followed by complete or partial recovery.[2-4] Between relapses, patients are neurologically and symptomatically stable. A large proportion of patients with untreated RRMS develop secondary progressive MS (SPMS), which is characterised by progressive deterioration of neurological function with or without superimposed relapses.[1,4]

Although no treatment is available that completely arrests the accumulation of disability in RRMS, major advances in recent years have led to the

introduction of several disease-modifying agents, including two forms of interferon-β-1a (subcutaneously administered Rebif® [1] and intramuscularly administered Avonex®), subcutaneous interferon-β-1b (Betaseron®, Betaferon®) and subcutaneous glatiramer acetate (Copaxone®), which reduce the frequency and severity of relapses and/or delay disease progression.[1-4,6-8] The marketing of natalizumab (Tysabri®), a recombinant humanised IgG4κ monoclonal antibody, was voluntarily suspended following reports of progressive multifocal leukoencephalopathy in clinical trials in MS.[9]

This review focuses on the role of subcutaneous recombinant interferon-β-1a in patients with RRMS.

2. Pharmacodynamic Properties

Recombinant interferon-β-1a, a glycosylated polypeptide with the same amino acid sequence and molecular weight as endogenous human interferon-β, exhibits similar biological effects in the body as the native molecule.[10-12] Subcutaneous interferon-β-1a 22 or 44μg equates to ≈6 or 12 MIU of antiviral activity.[10]

The complex mechanism of action of interferon-β-1a in MS is thought to be based primarily on immunomodulatory activity and may also involve antiproliferative and antiviral activity (table I). Interferon-β-1a is considered to control excessive immune responses in the inflamed lesions of MS, but without general immunosuppression.[13,14] Most of the putative immunomodulatory actions of interferon-β-1a are likely to result from mediation of some biological activities by interferon-stimulated gene products, including 2′,5′-oligoadenylate synthetase, β_2-microglobulin, neopterin and myxovirus resistance protein A.[10] Such products are thought to be generated via a signal cascade induced by interaction of interferon-β-1a with cell-surface receptors.[13,15] A detailed profile of its proposed mechanism of action in MS is provided in previous reviews.[13-15]

Studies in healthy volunteers indicated that the biological response to interferon-β-1a is sustained when administered three times weekly in preference to once weekly.[16]

Table I. Summary of the pharmacodynamic effects of interferon-β-1a that may be important to its mechanism of action in multiple sclerosis

Markers of interferon-β activity[11,12,16,17,19-22]
↑ intracellular and serum 2′,5′-oligoadenylate synthetase activity
↑ serum levels of neopterin, β_2-microglobulin or soluble vascular adhesion molecule-1
↑ PBMC levels of human myxovirus resistance protein A messenger RNA
Markers of disease activity[14,22-25]
↑ PMBC expression of TNF-related apoptosis-inducing ligand
↓ PMBC levels of matrix metalloproteinases messenger RNA
Immunomodulatory and/or antiproliferative activity[13-16,26,27]
↓ T-cell activation and proliferation
↓ production of IL-1β, IL-6, IL-12, interferon-γ, TNFα and TNFβ
Block interferon-γ-induced production of oxygen free radicals by mononuclear phagocytes
↑ expression of intercellular adhesion molecules in brain endothelial cells (thereby restoring the blood-brain barrier)
↑ serum and cerebrospinal fluid levels of IL-10
Augment suppressor function
Down-regulate cellular survivin expression by T cells
↓ interferon-β-induced expression of major histocompatibility complex class II molecules (thereby ↓ self-antigen presentation in the CNS)
↓ metalloproteases (potentially leading to ↓ in blood-brain barrier disruption, migration of T cells into the CNS and demyelination)
Antiviral activity[28]
Active against human herpesvirus-6

IL = interleukin; **PBMC** = peripheral blood mononuclear cell; **TNF** = tumour necrosis factor; ↓ indicates decrease; ↑ indicates increase.

In healthy volunteers given a single intramuscular or intravenous dose of interferon-β-1a 22μg, statistically significant clinical changes were shown in heart rate, body temperature, mean leukocyte and erythrocyte counts, and haematocrit and haemoglobin levels.[11,12,16-18] These changes are typical of the influenza-like syndrome that often occurs in patients treated with interferon-β-1a (section 5).

2.1 Antibodies to Interferon-β-1a

Patients receiving interferon-β may develop antibodies that bind to the recombinant protein, includ-

1 The use of trade names is for product identification purposes only and does not imply endorsement.

ing neutralising antibodies (NABs) that cancel the biological activity of interferon-β[29] and reduce bioavailability.[30] The presence of antibodies to interferon-β-1a may depend on several factors, (e.g. pre-treatment disease severity, dosage, route of administration, duration of treatment and assay method used).[31] NABs to one interferon-β formulation are cross-reactive against others.[31-33]

In patients with RRMS, the immunogenicity of interferon-β-1a was less than that of interferon-β-1b.[34] The immunogenicity of interferon-β-1a increases with the frequency of administration (three times weekly vs once weekly) and route of administration (subcutaneous vs intramuscular).[34] In the EVIDENCE (EVidence of Interferon Dose-response: European-North American Comparative Efficacy) trial (section 4.2),[35] NABs developed in the serum of significantly more patients receiving subcutaneous interferon-β-1a 44μg three times weekly than in those receiving intramuscular interferon-β-1a 30μg once weekly (25% vs 2%; $p < 0.001$).

In most NAB-positive patients, serum antibodies tended to appear within the first 2 years of treatment with subcutaneous interferon-β, although approximately one-third of these patients revert to NAB-negative status during longer-term follow-up.[36]

Pivotal clinical trials of duration ≤2 years (PRISMS [Prevention of Relapses and disability by Interferon-β-1a Subcutaneously in Multiple Sclerosis][37] and EVIDENCE[35] and its crossover extension phase;[38] section 4) did not show conclusive results with regard to the effect of the presence of serum NABs (titre ≥20 neutralising units/mL at any time) on the long-term clinical efficacy of subcutaneous interferon-β. However, as the clinical effect of NABs is not seen until 12–18 months after start of interferon therapy, studies of ≤2 years are not suitable for evaluation of the clinical effect of NABs. Longer studies have suggested that the presence of serum NABs against interferon-β reduces the clinical effect of the drug.[39,40] Hence, whereas the 2-year PRISMS study did not show an influence of NABs on clinical relapse rate,[37] the 2-year extension of this trial (PRISMS-4) showed that the annualised relapse rate in recipients of subcutaneous interferon-β-1a 44μg three times weekly was significantly greater in those with NABs than in those without NABs (0.81 vs. 0.50; $p = 0.002$).[39] In observational data for up to 60 months in 541 patients with MS who had received any formulation of interferon-β, the odds ratio for having relapses was approximately 1.5 ($p < 0.03$) in NAB-positive periods relative to NAB-negative periods.[40]

A relationship was also identified between magnetic resonance imaging (MRI) measures of disease activity (section 4) and NABs in patients receiving subcutaneous interferon-β-1a 44μg three times weekly.[35,38,39] Patients with serum NABs had significantly ($p < 0.001$) greater mean numbers of T2-weighted (T2W) active lesions than those without NABs at week 48 of the EVIDENCE trial (1.6 vs 0.6 lesions),[35] and during the EVIDENCE crossover extension study (2 vs 0.6 lesions; median treatment duration 34 weeks)[38] and years 3 and 4 of the PRISMS-4 study (1.4 vs 0.3).[39] Moreover, MRI scans at 4 years in the PRISMS-4 study showed that the burden of disease increased by 17.6% from baseline in NAB-positive patients, but decreased by 8.5% in NAB-negative patients ($p < 0.001$).[39]

3. Pharmacokinetic Properties

The pharmacokinetic profile of subcutaneous interferon-β-1a has been reviewed previously[15] and a brief overview is provided here. The pharmacokinetics of subcutaneous interferon-β-1a at the approved dosage in patients with MS have not been investigated; therefore, data (estimated using ELISA) in healthy volunteers administered single or repeated doses of interferon-β-1a 66μg are reported (table II).[20] Interferon-β-1a appears to accumulate after repeated subcutaneous doses.[20] Subcutaneous interferon-β-1a 66μg administered on alternate days for 1 week increased the mean maximum serum concentration value by ≈2-fold (table II) and mean area under the serum concentration-time curve value by ≈2.5-fold.[20]

Interferon-β-1a has a long apparent elimination half-life.[20] After intravenous administration of interferon-β-1a 66μg, a pattern of tri-exponential decay was evident (half-lives of 3 minutes, 42 minutes

Table II. Pharmacokinetic parameters of subcutaneous interferon-β-1a 66μg (18 MIU) in healthy adult volunteers[20]

Parameter	Single dose (n = 11)		Multiple doses[a] (n = 8)	
	mean (± SD)	median (range)	mean (± SD)	median (range)
C_{max}[b] (IU/mL)	7.5 (2.4)	6.7 (4–12)	12.3 (3.9)	11.8 (7.5–17.8)
Time to C_{max} (h)	10 (15)	2 (0.5–48)	3.8 (2.4)	3.5 (1.5–8)
Area under the serum concentration-time curve (IU • h/mL)	95[c] (44)	95[c] (25–162)	211[d] (93)	197[d] (87–376)
Bioavailability (%)	28 (16)	27 (6–62)		
Absorption time (h)	6.8 (2.9)	6.4 (1.1–12.0)		
C_{max} accumulation ratio[e]			2.0 (0.3)	2.4 (2.1–3.1)

a Four doses on alternate days.

b Baseline serum interferon activity was subtracted from post dose values.

c From time 0 to 48h.

d From time 0 to 168h.

e C_{max} after fourth dose divided by C_{max} after first dose.

C$_{max}$ = maximum serum concentration.

and 21.5 hours).[20] For the subcutaneous and intramuscular route, absorption appears to be the rate-limiting step in the terminal phase. The estimated terminal elimination half-life of interferon-β-1a after repeated subcutaneous doses is 66 hours.[20]

Sex had no significant influence on interferon-β-1a pharmacokinetics.[19] The pharmacokinetic profile of interferon-β-1a has not been established in patients with renal or hepatic insufficiency, or in paediatric or elderly patients.

4. Therapeutic Efficacy

The efficacy of subcutaneous recombinant interferon-β-1a 22 or 44μg three times weekly in patients with RRMS relative to placebo (PRISMS; section 4.1)[37] or intramuscular interferon-β-1a 30μg once weekly (EVIDENCE; section 4.2)[35] has been assessed in two large randomised studies and their crossover extensions[38,39] (see table III for study design details). During the crossover phases, patients in the subcutaneous interferon-β-1a arms continued with their initial treatment,[38,39] patients in the placebo arm of the PRISMS trials crossed over to subcutaneous interferon-β-1a 22 or 44μg three times weekly[39] and patients in the intramuscular interferon-β-1a arm of the EVIDENCE trial crossed over to subcutaneous interferon-β-1a 44μg three times weekly.[39] In a long-term observational follow-up of the PRISMS trial,[36,41] 382 patients returned for assessment ≈7–8 years after the enrolment date; patients may have continued, stopped, changed or restarted therapy.

Treatment groups in individual trials and long-term follow-up were well balanced for baseline characteristics (e.g. age, sex, duration of illness, neurological disability and number of relapses in the previous 2 years). Primary analysis was in the intention-to-treat population. Data from the long-term observational follow-up are available only in abstract form.[36,41]

Standard clinical outcome measures for assessing the efficacy of treatments in MS include:[35,37]

- relapse rate (primary endpoint in the PRISMS trials[37,39] and EVIDENCE crossover phase[38]), relapse severity or proportion of relapse-free patients (primary endpoint in the EVIDENCE trial[35]);
- Kurtzke Expanded Disability Status Scale (EDSS) scores, which provide a subjective global rating of neurological impairment resulting from MS and the progression of the disease (a score of 0 indicates normal neurological examination, 5 indicates disability severe enough to impair daily activities and limited ambulation without aid, and 10 indicates death due to MS);
- MRI results, which provide an objective measure to quantify changes in lesion load in the CNS using gadolinium-enhanced T1-weighted (T1W; indicates current disease activity and acute in-

flammation) and proton-density T2W (represents the total disease burden) lesions. MRI outcome measures are not currently adequately validated for use as primary endpoints.

4.1 Compared with Placebo

In the PRISMS trial,[37] subcutaneous interferon-β-1a 22 or 44μg three times weekly was more effective than placebo as assessed by a number of clinical (e.g. relapse rate per patient, proportion of patients without clinical relapse and changes from baseline in EDSS scores) and MRI (total burden of disease and numbers of active lesions per patient per MRI scan) endpoints (table IV). Significant dose-response effects in favour of the higher dosage were evident for relapse frequency and MRI outcomes (table IV) and also measures of disability when the study period was extended in the PRISMS-4 study.[39]

The mean clinical relapse rate per patient was significantly lower with subcutaneous interferon-β-1a 22 or 44μg than with placebo (relative difference 29% and 32%; $p < 0.005$) after 2 years in the PRISMS trial.[37] In the PRISMS-4 extension, patients who crossed over from placebo therapy to subcutaneous interferon-β-1a 22 or 44μg three times weekly (crossover groups) had 50% and 46% reductions in annual relapse counts relative to the number of annual relapses during placebo treatment ($p < 0.001$).[39] Patients who had received active treatment with interferon-β-1a 22 or 44 μg throughout the PRISMS-4 trial (interferon-β-1a groups) had significantly fewer relapses per year than the crossover groups (table IV).[39] Although the between-group difference was not significant, there was a tendency for a smaller number of annual relapses per patient to occur with interferon-β-1a 44μg compared with interferon-β-1a 22μg ($p = 0.069$). Indeed, during years 3 and 4 of the PRISMS-4 trial, the interferon-β-1a 44μg group had a lower risk of relapse than the interferon-β-1a 22μg group ($p = 0.014$) or the group who crossed over to interferon-β-1a 44μg ($p = 0.014$).[39]

Extension data for a total follow-up period of 7–8 years in the original cohort showed a mean annualised relapse rate that was significantly lower in the

Table III. Study design details of two key multicentre clinical trials of subcutaneous (SC) interferon-β-1a (IFNβ-1a) three times weekly (tiw) in patients (pts) with relapsing-remitting multiple sclerosis (RRMS) and their crossover extension phases

Randomised trials	**PRISMS**[37]	**EVIDENCE**[35]
Pt inclusion criteria	Age >18y with RRMS for ≥1y with ≥2 relapses during the previous 2y and EDSS scores ≤5[37] or 5.5[35]	
Pt exclusion criteria	Interferon, radiation, cyclophosphamide or other immunomodulatory or immunosuppressive treatments during the previous 12mo	
Trial design (no. of enrolled pts)	Randomised, double-blind, placebo-controlled (560)	Randomised, open-label, evaluator-blinded, active-comparator-controlled (677)
Treatment arms (duration)	SC IFNβ-1a 22 or 44μg tiw vs placebo (2y)	SC IFNβ-1a 44μg tiw vs IM IFNβ-1a 30μg once weekly (48wk)
Primary endpoint	No. of clinical relapses[a] per pt over 2 years	Odds ratio for remaining relapse[a] free at 24wk
Crossover extensions (duration)	**PRISMS-4**[39] **(2y controlled assessment)**	**EVIDENCE crossover (median 34wk)**[38]
Study design (no. of pts)	Placebo group re-randomised to SC IFNβ-1a 22 or 44μg tiw (172) and pts in the active treatment groups continued blinded active treatment at their initial dosage (334)	IM group crossed over to SC IFNβ-1a 44μg tiw (223); SC group continued initial therapy (272)
Primary endpoint	No. of clinical relapses[a] per pt over 4y	Annualised relapse rate comparing the within-pt changes from wk 24–48 pre-crossover with the crossover phase

a Defined as a new symptom appearing, or an old symptom worsening, over ≥24h and without fever, and which could be attributed to disease activity; the symptomatic change had to be preceded by improvement or stability for ≥30d.

EDSS = Kurtzke Expanded Disability Status Scale; **EVIDENCE** = EVidence of Interferon Dose-response: European-North American Comparative Efficacy; **IM** = intramuscular; **PRISMS** = Prevention of Relapses and disability by Interferon-β-1a Subcutaneously in Multiple Sclerosis.

Table IV. Efficacy of subcutaneous (SC) interferon-β-1a (IFNβ-1a) 22 or 44μg three times weekly compared with placebo (PL) in patients (pts) with relapsing-remitting multiple sclerosis. Summary of intention-to-treat results from the 2-year randomised, double-blind PRISMS trial and its controlled 2-year crossover extension (PRISMS-4). In PRISMS-4, pts in the PL group were re-randomised and crossed over to SC IFNβ-1a 22 (PL/SC IFNβ1a 22μg) or 44μg tiw (PL/SC IFNβ-1a 44μg) and pts in the active treatment groups continued blinded active treatment at their initial dosage for an additional 2 years

Outcome	PRISMS[37,42]			PRISMS-4[39]			
	SC IFNβ-1a 22μg (n = 189)	SC IFNβ-1a 44μg (n = 184)	PL (n = 187)	SC IFNβ-1a 22μg (n = 167)	SC IFNβ-1a 44μg (n = 167)	PL/SC IFNβ-1a 22μg (n = 85)	PL/SC IFNβ-1a 44μg (n = 87)
Relapse- and disability-related outcomes (mean rate per pt unless otherwise indicated)							
Relapse rate[a]	1.82/2y**	1.73/2y**	2.56/2y	0.80/y††	0.72/y††	0.99/y	1.06/y
Relapse-free pts (%)	27*	32**	16	14.4†	19.0††	NR[b]	NR[b]
Moderate or severe relapse rate	0.71/2y**	0.62/2y**	0.99/2y				
Hospitalisations for MS	0.38/2y	0.25/2y**	0.48/2y				
Corticosteroid courses	0.97/2y*	0.75/2y**	1.392/2y	0.5/y	0.4/y‡	NR	NR
Change in EDSS score	0.23/2y*	0.24/2y*	0.48/2y				
Magnetic resonance imaging outcomes (median)[c] [no. of pts]							
T2W lesions per pt per scan	0.75*** [171]	0.5***‡‡ [171]	2.25 [172]	1.3†† [180]	0.5†††‡‡ [180]	2.0 [90]	2.7 [92]
Change from baseline in burden of disease (%)[d]	−1.2*** [185]	−3.8*** [182]	10.9 [184]	3.4 [NR]	−6.2†‡ [NR]	9.7 [NR]	7.2 [NR]
CU active lesions per pt per scan	0.17*** [64]	0.11*** [68]	0.88 [66]				

a Primary endpoint.

b Rate in combined crossover groups was 6.7%.

c Proton-density T2W scans were performed every 6mo in PRISMS and annually in PRISMS-4; T2W and gadolinium-enhanced T1W scans were performed once monthly in some pts.

d Total area of T2W lesions.

CU = combined unique (T1W + T2W); **EDSS** = Kurtzke Expanded Disability Status Scale; **NR** = not reported; **PRISMS** = Prevention of Relapses and disability by Interferon-β-1a Subcutaneously in Multiple Sclerosis; **T1W** = T1-weighted; **T2W** = T2-weighted; * $p \leq 0.05$, ** $p < 0.005$, *** $p \leq 0.0001$ vs PL; † $p < 0.05$, †† $p < 0.001$ vs corresponding crossover group; ‡ $p < 0.05$, ‡‡ $p < 0.001$ vs SC IFNβ-1a 22μg.

interferon-β-1a 22 (n = 136) or 44μg (n = 123) groups than in the combined interferon-β-1a 22 or 44μg crossover groups (n = 123), even though patients in the crossover groups may have received active therapy for up to 6 years (0.61 and 0.64 vs 0.78 relapses [values estimated from a figure]; $p < 0.05$).[36]

Subcutaneous interferon-β-1a also prolonged the time to first relapse.[37,39] In the first 2 years, subcutaneous interferon-β-1a 22μg delayed the median time to first relapse by 3 months relative to placebo, whereas the delay with 44μg therapy was 5 months (statistical significance not reported).[37] In PRISMS-4, subcutaneous interferon-β-1a 22 or 44μg prolonged the median time to second relapse by 8.3 ($p = 0.006$) and 16.9 months ($p < 0.001$) relative to the combined crossover groups.[39] The median time to second relapse was significantly ($p = 0.046$) longer for the 44μg group than for the 22μg group.

Significant differences were noted for subcutaneous interferon-β-1a 22 or 44μg versus placebo regarding mean increases in EDSS score over 2 years (table IV) and time to sustained progression of disability (defined as an increase in EDSS score of 1 point from baseline sustained over ≥3 months) for the first quartile of patients (18.5 and 21.3 vs 11.9 months; $p < 0.05$).[37] In the PRISMS-4 extension, the fortieth percentile times to first confirmed EDSS progression were 35.9, 42.1 and 24.2 months for the subcutaneous interferon-β-1a 22, 44μg and combined crossover groups; the between-group difference was significant only for the 44μg group versus the crossover group ($p = 0.047$).[39] Over 4 years, significantly less disability progression was associated with the higher dose of subcutaneous interferon-β-1a 44μg than with the lower dose (0.17 vs 0.22 one-point EDSS changes per patient per year; $p \leq 0.03$); the difference between the higher-dosage

group and the combined crossover group was also significant (0.17 vs 0.24; $p \leq 0.03$).[39] In 7- to 8-year observational data, the overall median time to disability progression was 5.4 years (between-group differences were not significant).[36]

The total MRI burden of disease and median numbers of T2W active lesions and combined unique active lesions per patient per MRI scan were significantly less with subcutaneous interferon-β-1a 22 or 44μg three times weekly than with placebo after 2 years (table IV).[42] A dose-dependent clinical response was evident over 2 years:[42] interferon-β-1a 44μg reduced the median number of new or newly enlarged T2W active lesions by 78% relative to placebo ($p < 0.0001$); the corresponding decrease with interferon-β-1a 22μg was 67% ($p < 0.0001$ vs placebo; $p = 0.0003$ vs the higher dosage). The proportion of patients with no T2W activity was significantly higher with interferon-β-1a 22 or 44μg than with placebo (19% and 31% vs 8%; $p = 0.001$); the difference between the two active treatment groups was also significant ($p = 0.009$).[42]

In PRISMS-4, both subcutaneous interferon-β-1a groups had significantly fewer new T2W lesions per patient per scan than the corresponding crossover groups, and the change in the burden of disease was significantly lower in the subcutaneous interferon-β-1a 44μg group than in the corresponding crossover group (table IV). The 44μg dosage of subcutaneous interferon-β-1a was superior to the 22μg dosage with regard to the number or new T2W lesions and change in burden of disease.[39]

In the 7- to 8-year observational follow-up,[41] the median increase in total lesion burden was lower in the group receiving subcutaneous interferon-β-1a 44μg than in the subcutaneous interferon-β-1a 22μg group or the combined crossover group (5% vs 17.4% and 24.5%; p-value not reported).

4.2 Compared with Intramuscular Interferon-β-1a

In the EVIDENCE trial, patients receiving subcutaneous interferon-β-1a 44μg three times weekly were more likely to remain free of relapses at 24 and 48 weeks than those receiving intramuscular interferon-β-1a 30μg once weekly (table V).[35] At 24 and 48 weeks, the odds ratios for remaining relapse free were 1.9 (95% CI 1.3, 2.6) and 1.5 (95% CI 1.1, 2.1) in favour of subcutaneous interferon-β-1a 44μg three times weekly. In the crossover extension phase (median treatment duration 34 weeks), ≈80% of patients treated with subcutaneous interferon-β-1a 44μg were relapse free, regardless of whether they were continuing on subcutaneous interferon-β-1a 44μg three times weekly treatment or had crossed over from intramuscular interferon-β-1a 30μg once weekly (table V).[38]

Subcutaneous interferon-β-1a 44μg three times weekly significantly prolonged the time to first relapse relative to intramuscular interferon-β-1a 30μg once weekly.[35] Patients treated with subcutaneous rather than intramuscular interferon-β-1a were 32% less likely to have a relapse during the first 24 weeks of treatment; at 48 weeks, the relative risk reduction was 21% (overall hazard ratio 0.70 [95% CI 0.55, 0.88]; $p = 0.003$).[35]

The difference in relapse rates between subcutaneous interferon-β-1a 44μg three times weekly and intramuscular interferon-β-1a 30μg once weekly was more pronounced during the first 24-week period (relative difference 27%; $p = 0.022$) than in the second 24-week period (relative difference 16%; not significant) [table V].[35] The number of patients with mild, moderate or severe relapses was lower at each severity level with subcutaneous interferon-β-1a than with intramuscular interferon-β-1a; however, the proportion of relapses in each severity level were similar in each treatment group. At the end of the crossover phase, patients who had converted from intramuscular to subcutaneous therapy had a significant 50% decrease in mean annualised relapse rate relative to the 24- to 48-week period in the EVIDENCE trial (table V).[38] A significant 26% decrease in this parameter was also noted in patients who continued to receive their initial subcutaneous therapy during the crossover phase; the change in annualised relapse rate was significantly greater in the treatment-crossover group than in the group that continued subcutaneous therapy ($p < 0.05$).

Table V. Efficacy of subcutaneous (SC) interferon-β-1a (IFNβ-1a) 44μg three times weekly (tiw) versus intramuscular (IM) IFNβ-1a 30μg once weekly (qw) in patients (pts) with relapsing-remitting multiple sclerosis. Summary of intention-to-treat results from the 48-week randomised, open-label, evaluator-blinded EVIDENCE trial and its crossover extension (median duration 34 weeks).[38] In the crossover phase, the IM IFNβ-1a 30μg group crossed over to SC IFNβ-1a 44μg tiw; within-pt changes from week 24–48 of EVIDENCE trial (pre-crossover) were compared with those in the crossover phase

Outcomes	EVIDENCE[35]				EVIDENCE crossover phase[38]			
	SC 44μg tiw (n = 339)	IM 30μg qw (n = 338)	SC 44μg tiw (n = 339)	IM 30μg qw (n = 338)	SC 44μg tiw (n = 272)		IM 30μg qw/SC 44μg tiw (n = 223)	
	24wk	24wk	48wk	48wk	pre-crossover	crossover	pre-crossover	crossover
Relapse- and disability-related outcomes (mean rate per pt unless otherwise indicated)								
Relapse-free pts (%)[a]	75***	63	62**	52		82		81
Relapse rate	0.29*	0.40	0.54	0.64				
Annualised relapse rate[b]					0.46	0.34†	0.64	0.32††
Corticosteroid courses			0.12*	0.19				
Magnetic resonance imaging outcomes[c] (mean no. per pt per scan unless otherwise indicated)								
CU active lesions	0.8***	1.2						
T1W active lesions	0.6***	1.0						
T2W active lesion	0.3***	0.6	0.9***	1.4	0.8	1.1	0.9	0.7†
T2W active scans per pt (%)	15***	27	27***	43	22	24	37	26††
No T2W active scans (% of pts)	60***	43	63***	45	74	71	60	61

a Primary endpoint in EVIDENCE trial.

b Primary endpoint in EVIDENCE crossover phase.

c Proton-density T2W and/or gadolinium-enhanced T1W scans were performed every 4 weeks up to week 24 and T2W scans were preformed at week 48.

CU = combined unique (T1W + T2W); **EVIDENCE** = EVidence of Interferon Dose-response: European-North American Comparative Efficacy; **T1W** = T1-weighted; **T2W** = T2-weighted; * $p \leq 0.05$, ** $p < 0.01$, *** $p < 0.001$ vs IM IFNβ-1a; † $p < 0.05$, †† $p < 0.001$ vs pre-crossover in the same pt cohort.

Disease progression (a one-point increase from baseline in EDSS scores) was shown in similar numbers of patients in the subcutaneous interferon-β-1a 44μg three times weekly group and the intramuscular interferon-β-1a 30μg once weekly group (43 vs 49 patients confirmed at 3 months; 20 vs 28 patients confirmed at 6 months).[35] Although the between-group difference showed a trend towards reduction of progression risk in subcutaneous interferon-β-1a group, no conclusions can be made regarding the effects of treatment on the accumulation of physical disabilities, due to the short duration of the study and the small number of patients.

Patients treated with subcutaneous interferon-β-1a 44 μg three times weekly rather than intramuscular interferon-β-1a 30μg once weekly had significantly more favourable measures of MRI lesion activity at weeks 24 and 48 (table V).[35] Follow-up data in the crossover phase revealed no major changes in MRI findings for patients remaining on subcutaneous therapy relative to the 24–48 week pre-crossover period in the EVIDENCE trial.[38] However, in patients crossing over from intramuscular to subcutaneous therapy, there was a 22% decrease in the mean number of T2W active lesions per patient per scan and a 30% decrease in the mean percentage of active scans per patient (table V).[38]

5. Tolerability

The tolerability of subcutaneous interferon-β-1a was evaluated in the PRISMS (section 5.1) and EVIDENCE (section 5.4) trials and their crossover extensions discussed in section 4, and in retrospective evaluations of hepatic (section 5.2)[43-46] and haematological (section 5.3)[47] effects from clinical trials and postmarketing surveillance.

5.1 General Profile

Adverse events associated with subcutaneous interferon-β-1a are generally mild and manageable.[37,39] Injection-site reactions, headache, influenza-like symptoms, fatigue, myalgia, fever, elevation of liver enzymes and haematological abnormalities were the most commonly reported adverse events with subcutaneous interferon-β-1a during the first 3 months of the PRISMS trial (figure 1).[37] During the 2-year extension, adverse events were mild and similar to those noted during the initial 2-year phase and generally resolved as treatment continued.[39] Seven- to 8-year follow-up data also revealed a generally manageable tolerability profile for subcutaneous interferon-β-1a.[36] The dropout rate for adverse events in interferon-β-1a recipients was <6% in the PRISMS[37] and PRISMS-4[39] studies.

Injection-site reactions are common with subcutaneous interferon-β-1a, but most are mild and reversible.[37,39] Skin necrosis at the site of injection may occur (3% of patients receiving subcutaneous interferon-β-1a 44μg during the PRISMS-4 trial;[39] equivalent to 1 occurrence per 9300 injections or ≈1 per 60 patients per year) and usually resolves spontaneously.

Interferon-β-1a was not associated with an increase in depressive symptomatology.[48] Psychiatric disorders were the most frequently reported severe adverse event in both the subcutaneous interferon-β-1a and placebo groups in the PRISMS trial; the proportion of patients with clinical depression was strongly associated with depression at baseline.[48]

5.2 Effects on Hepatic Function

Elevations in hepatic aminotransferase levels are associated with treatment with interferons.[43-46] Rare cases of severe liver injury, including hepatic failure requiring liver transplantation, have been reported.[43]

In a review of pooled data from six randomised, controlled trials of subcutaneous or intramuscular interferon-β-1a in patients primarily with RRMS,[43] asymptomatic elevation of hepatic aminotransferase (particularly ALT) levels was common during the

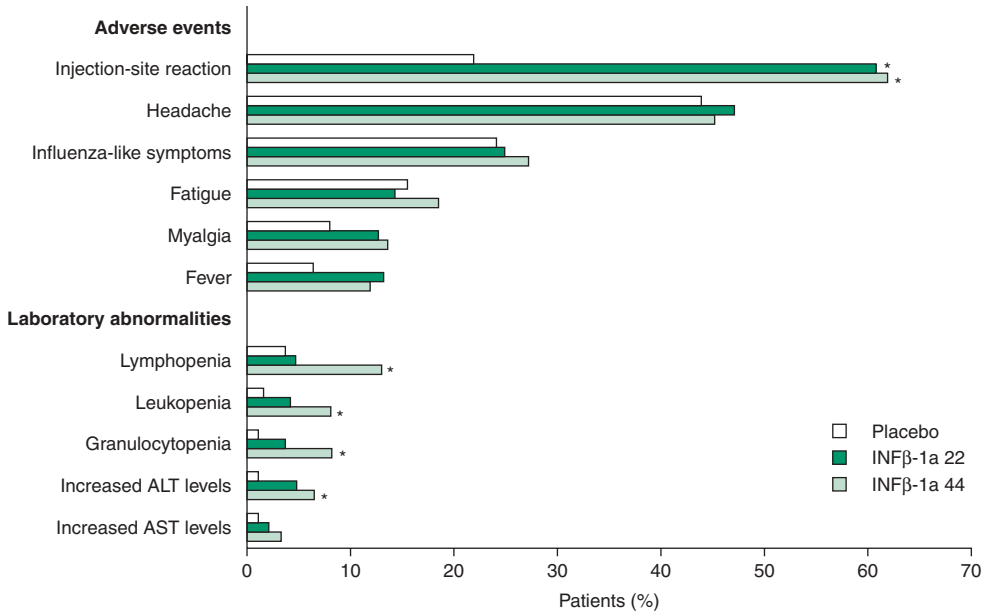

Fig. 1. Tolerability of interferon-β-1a (IFNβ-1a) in patients with relapsing-remitting multiple sclerosis. Incidence of treatment-emergent adverse events or laboratory abnormalities reported in patients receiving three-times-weekly IFNβ-1a 22μg (n = 189), IFNβ-1a 44 μg (n = 184) or placebo (n = 187) during the first 3 months of therapy in the PRISMS (Prevention of Relapses and disability by Interferon-β-1a Subcutaneously in Multiple Sclerosis) trial.[37] * $p \leq 0.05$ vs placebo.

first 12 months of treatment (elevated ALT levels occurred in up to 59% of patients receiving subcutaneous interferon-β-1a 44μg three times weekly and ≈40% of those receiving intramuscular interferon-β-1a 30μg once weekly). Most elevations in liver enzyme levels occurred during the first 3–6 months of treatment. After 2 years, 11% of patients treated with subcutaneous interferon-β-1a 44μg three times weekly and 6% of placebo recipients had elevated ALT levels; these values were similar to the baseline rate of ALT elevation (7–10%).[43] Elevations in levels of liver enzymes were dose related and resolved spontaneously or with dosage adjustment. Only 0.4% of patients given either subcutaneous or intramuscular interferon-β-1a stopped treatment because of hepatic enzyme elevations.[43]

In clinical practice, interferon-β has been associated with greater elevations of liver enzyme levels than in pivotal clinical trials.[44-46] In a 6-year retrospective chart review of 835 patients with MS prescribed subcutaneous or intramuscular interferon-β-1a or -1b in Canada, 34% of patients developed *de novo* elevated aminotransferase levels.[44] The majority (84%) of patients continued with treatment despite the elevated levels; aminotransferase levels returned to normal levels in two-thirds of patients. The risk of developing liver test abnormalities is greatest in the first year of interferon-β treatment and increases with more frequent administration and higher dosages of interferon-β.[45] The effect on aminotransferases is greater with subcutaneous administration of interferon-β-1a or -1b than with intramuscular administration of interferon-β-1a.[45]

In postmarketing surveillance data for interferon-β-1a in ≈70 000 patients with MS treated during a 5-year period (130 000 patient-years) revealed 30 instances of serious, symptomatic hepatic dysfunction (i.e. 1 instance per 4000 patient-years).[43] Two of these patients (including one exposed to the potentially hepatotoxic agent nefazodone) required liver transplantation.[43]

5.3 Haematological Effects

Mild, asymptomatic and reversible haematological disorders have been reported with subcutaneous interferon-β-1a.[47] In a review of pooled data from several controlled studies of subcutaneous interferon-β-1a in patients with MS,[47] dose-related haematological abnormalities occurred more frequently with subcutaneous interferon-β-1a than with placebo. A greater proportion of patients receiving interferon-β-1a experienced asymptomatic decreases in white blood cell, neutrophil, lymphocyte and platelet counts during the first 6 months of treatment ($p < 0.002$). Most events were mild, transient and had little effect on adherence to therapy.[47]

Postmarketing surveillance data for subcutaneous interferon-β-1a from 1998 to 2003 revealed 117 adverse events attributed to white blood cell, red blood cell or platelet abnormalities.[47] This equates to 8.3% of all reported events associated with interferon-β-1a. Only 12.8% of these abnormalities were considered serious; most of these reports were confounded by underlying conditions or the use of potentially haematotoxic agents (e.g. mitoxantrone).

5.4 Compared with Intramuscular Interferon-β-1a

In the EVIDENCE trial,[35] subcutaneous interferon-β-1a 44μg three times weekly was associated with a higher incidence of treatment-emergent adverse effects per patient than intramuscular interferon-β-1a 30μg once weekly (9.1 vs 7.9 events; $p = 0.007$).[49] This was predominantly due to a higher incidence of injection-site reactions with three-times-weekly subcutaneous administration (83% vs 28% of patients; $p < 0.001$).[35] A similar proportion of patients in each treatment group experienced serious adverse events (6% vs 5%) or withdrew from treatment because of adverse events (4.7% vs 4.2%).[35]

Patients receiving subcutaneous interferon-β-1a had higher incidences of liver function abnormalities or ALT level elevations than those receiving intramuscular interferon-β-1a (18% vs 9% and 12% vs 5%; both $p = 0.002$).[35] The incidences of lymphopenia and white blood cell abnormalities were also significantly higher with subcutaneous interferon-β-1a than with intramuscular interferon-β-1a (4% vs <1% and 11% vs 5%; both $p < 0.01$).[35]

In the EVIDENCE crossover extension, almost all adverse events were mild or moderate in patients who converted from intramuscular to subcutaneous interferon-β-1a.[38] Relative to during the 24–48 week pre-crossover period, the crossover group had increases in the incidence of injection-site reactions (from 33% to 51%), elevated ALT levels (from 5% to 11%) and white blood cell abnormalities (from 5% to 10%) during the crossover phase.

6. Pharmacoeconomic and Other Considerations

6.1 Comparative Benefits and Risks of Disease-Modifying Therapies

Both efficacy and tolerability should be considered when evaluating disease-modifying therapies in RRMS. Due to the current lack of data from trials directly comparing first-line treatments for RRMS, it is difficult to assess the relative advantages or disadvantages of each product. Based on clinical trial data, an assessment evaluated each disease-modifying treatment based on the number of patients needed to treat to obtain benefit (NNT) on various outcome measures and the number of patients needed to treat to cause an adverse event leading to treatment discontinuation (NNH).[50] NNT and NNH values are generally rounded up to the next integer (values <5.0 are taken to one decimal place to allow discrimination between regimens). For NNT, better outcomes are indicated by lower rather than higher values; conversely, higher NNH values are better than lower values.

The assessment suggests that, relative to other disease-modifying RRMS treatments, subcutaneous interferon-β-1a 44μg three times weekly has the best benefit-to-risk values.[50]

Based on directly comparative data from the PRISMS trial and its extension (PRISMS-4), subcutaneous interferon-β-1a 44μg three times weekly had favourable benefit-to-risk values relative to 22μg three times weekly (table VI).[50] Relative to treatment with placebo, one to two patients need to be treated with subcutaneous interferon-β-1a for 2 years to prevent one relapse, six patients need to be treated for one patient to remain free of relapses, and

Table VI. Evaluation of the risks and benefits of treating multiple sclerosis with subcutaneous (SC) interferon (IFN)-β-1a 44μg three times weekly (tiw) relative to SC IFNβ-1a 22μg tiw or intramuscular (IM) IFNβ-1a 30μg once weekly (qw). Assessment of number of patients (pts) needed to treat to receive benefit (NNT) or harm (NNH; number of pts needed to treat for an adverse outcome leading to treatment discontinuation).[50] NNT and NNH values are derived from efficacy and tolerability data in the PRISMS,[37] PRISMS-4[39]and EVIDENCE[35] trials (see sections 4 and 5 for details). Unless otherwise indicated, outcome measures are mean values per pt

Outcomes	SC IFNβ-1a 44μg tiw vs SC IFNβ-1a 22μg tiw (PRISMS)				SC IFNβ-1a 44μg tiw vs IM IFNβ-1a 30μg qw (EVIDENCE)	
	2y		4y		48wk	
Efficacy outcome measures	**Results**	**NNT**	**Results**	**NNT**	**Results**	**NNT**
Relapse count	1.74 vs 1.82	12	0.72 vs 0.80	13	0.54 vs 0.64	10
Annualised 4y relapse rate			2.84 vs 3.20	2.8		
Relapse-free (%)	32 vs 25	15	19 vs 14	20	62 vs 52	10
Progression-free (%)	73 vs 70	34	56 vs 51	20		
Rate of EDSS progression			0.17 vs 0.22	20		
Annualised 4y EDSS progression rate			0.68 vs 0.88	5		
Pts with no T1-weighted active scans (%)	44 vs 39[a]	3.7			55 vs 38[b]	6
Pts with no T2-weighted active scans (%)	31 vs 19	9			63 vs 45	6
Discontinuation due to an adverse event	**Results**	**NNH**	**Results**	**NNH**	**Results**	**NNH**
All events	4.9 vs 3.2	59	9.8 vs 4.3	19	5.6 vs 5.3	334
IFNβ-specific events	2.2 vs 0.5	59	5.4 vs 2.1	31	4.1 vs 3.0	91

a 9mo data on subset of pts with frequent scans.

b 24-wk data.

EDSS = Kurtzke Expanded Disability Status Scale; **EVIDENCE** = EVidence of Interferon Dose-response: European-North American Comparative Efficacy; **PRISMS** = Prevention of Relapses and disability by Interferon-β-1a Subcutaneously in Multiple Sclerosis.

ten patients need to be treated to have one patient remain progression free.[50] With regard to adverse events, compared with placebo, 27 patients need to be treated with subcutaneous interferon-β-1a for 2 years to have one patient stop therapy due to any adverse event and 46 patients to have one patient stop therapy due to an interferon-specific adverse event.

Subcutaneous interferon-β-1a 44μg three times weekly had favourable benefit-to-risk values relative to intramuscular interferon-β-1a 30μg once weekly. Based on direct comparative data from the EVIDENCE trial (section 4.2), NNT values for all outcome measures were better with subcutaneous interferon-β-1a than with intramuscular interferon-β-1a (table VI).[50] The difference between treatment groups for discontinuation for overall or interferon-specific adverse events was small (table VI).

Indirect comparative data from published clinical trials was used to evaluate the relative benefits and risks of disease-modifying treatments for RRMS; however, the assessment is limited by differences in design, patient populations, endpoints, definition of endpoints and methods of statistical analysis between clinical trials.[50] The analysis demonstrated that interferon-β products had substantially lower NNT than NNH values and, therefore, favourable benefit-to-risk values relative to placebo. Based on comparisons of NNT and/or NNH values across studies, the assessment also suggested that interferon-β products were likely to have favourable benefit-to-risk values relative to subcutaneous glatiramer acetate 20μg once daily and that subcutaneous interferon-β-1a 22 or 44 μg three times weekly is more effective than subcutaneous interferon-β-1b 250μg every other day.

6.2 Pharmacoeconomic Considerations

In recent pharmacoeconomic analyses from a healthcare payer perspective based on data from the PRISMS and EVIDENCE trials (section 4), subcutaneous interferon-β-1a 44μg three times weekly was predicted to be increasingly more cost effective than placebo over 10 and 20 years[51] and cost saving relative to intramuscular interferon-β-1a 30μg once weekly over 48 weeks.[52]

Subcutaneous interferon-β-1a 44μg three times weekly was predicted to be more cost effective than placebo with regard to preventing EDSS-months of disability in the long-term treatment of patients with RRMS in the UK and France (table VII).[51] An econometric time-series regression model used PRISMS-4 data[39] (section 4.1) to determine the cost

Table VII. Cost effectiveness of subcutaneous interferon-β-1a 44μg three times weekly (IFNβ-1a) relative to placebo (PL) in relapsing-remitting multiple sclerosis from a healthcare payer perspective in the UK and France. Summary of data from an econometric time-series regression model over a time horizon of 10 and 20 years (year of costing 2000; cost discount rate 6%).[51] The model was based on data from the PRISMS-4 trial[39] in 184 pts receiving IFNβ-1a for 4y and 187 pts receiving PL for 2y

Parameter	UK				France			
	10y		20y		10y		20y	
	IFNβ-1a	PL	IFNβ-1a	PL	IFNβ-1a	PL	IFNβ-1a	PL
Efficacy								
EDSS-months of disability	484	605	1266	1587	484	605	1266	1587
EDSS-months of disability prevented	121		321		121			321
Costs (€)								
Standard care[a]	246 260	304 223	496 442	609 938	82 636	114 803	179 604	244 599
IFNβ-1a[b]	146 814		228 738		118 702		184 985	
Total	393 074	304 223	725 180	609 938	201 338	114 803	364 589	244 599
Incremental cost per EDSS-month of disability prevented (€)	732		359		712		374	

a Determined per EDSS level (≤3.5, 4–6 and >6 points) and based on published regional data.

b Based on the manufacturer's price list (assumes full treatment compliance).

EDSS = Kurtzke Expanded Disability Status Scale; **PRISMS** = Prevention of Relapses and disability by Interferon-β-1a Subcutaneously in Multiple Sclerosis.

effectiveness of subcutaneous interferon-β-1a 44μg three times weekly relative to placebo over a time horizon of 10 and 20 years (year of costing 2000). Transient and permanent changes in disability were measured by the area under the EDSS score-time curve. The analysis did not model progression of patients from RRMS to SPMS. Comparing the cost per EDSS-month of disability prevented at 10 and 20 years, treatment became increasingly cost effective over time. The cost of standard care was lower in the subcutaneous interferon-β-1a group, because of the mean 48% reduction in the number of hospitalisations associated with active treatment relative to placebo treatment over 2 years in the PRISMS trial (table VII). Secondary analyses substantiated the dose dependence of interferon-β-1a; interferon-β-1a 44μg relative to interferon-β-1a 22μg therapy saved an additional 15 EDSS-months of disability over 10 years at a cost per EDSS-month prevented of €1396 in France and €2316 in the UK.[51]

Over 48 weeks, subcutaneous interferon-β-1a 44μg three times weekly was predicted to be cost saving relative to intramuscular interferon-β-1a 30μg once weekly in a US pharmacoeconomic analysis (available as an abstract/poster).[52] The analysis used EVIDENCE efficacy data[35] (section 4.2) and direct medical costs estimated from published US data (year of costing 2002).[52] Although the drug cost of subcutaneous interferon-β-1a was higher than that of intramuscular interferon-β-1a ($US12 800 vs $US9800), the subcutaneous formulation was associated with fewer relapses and, therefore, lower costs incurred in the management of relapses. The subcutaneous formulation was predicted to have a more favourable costs : costs-avoided ratio after 48 weeks (21.6 vs 30.5) and a lower cost per time to first relapse over 24 weeks ($US1100 vs $US1400 per month) than the intramuscular formulation.[52] With subcutaneous interferon-β-1a 44μg three times weekly, the cost per patient to avoid one relapse was $US12 460 (based on a NNT of 10.39).

7. Dosage and Administration

Subcutaneous interferon-β-1a 22 or 44μg three times weekly is indicated in the treatment of patients with relapsing forms of MS.[10] Treatment for the first 2 weeks should be at 20% of the total dosage, increasing to 50% of the total dosage during weeks 3–4 and to the full dosage by week 5.[10] Rotation of the injection site can help prevent severe injection-site reactions, and influenza-like symptoms may be ameliorated by concurrent use of analgesics and/or antipyretics on treatment days. Formal drug interaction studies have not been conducted with subcutaneous interferon-β-1a.

Refer to the manufacturer's local prescribing information for comprehensive information regarding monitoring requirements, precautions, contraindications, dosage and administration.

8. Place of Subcutaneous Recombinant Interferon-β-1a in the Management of Relapsing-Remitting Multiple Sclerosis

Although MS cannot be cured, disease-modifying agents can reduce relapse frequency and severity and may delay disease progression.[3,8] First-line disease-modifying therapies comprise subcutaneous and intramuscular interferon-β-1a, subcutaneous interferon-β-1b and subcutaneous glatiramer acetate, all of which have shown beneficial effects on relapses and MRI measures of disease activity in large, randomised, placebo-controlled clinical trials.[1,3,4,8,53] Unlike interferon-β-1a, glatiramer acetate has not definitively been shown to delay disease progression.[50,53] The choice of disease-modifying therapy for patients with RRMS should consider both efficacy and tolerability.

Subcutaneous interferon-β-1a 22 or 44μg three times weekly has a beneficial effect on the course of RRMS, with statistically significant effects compared with placebo in the three key measures of treatment effectiveness: reducing relapses, delaying disability progression and reducing MRI assessments of disease activity (section 4.1). Dose-response effects in favour of the higher dosage were evident (section 4.1). Treatment with subcutaneous interferon-β-1a should be initiated early in the

course of the disease and continued long term (section 4.1).

Adverse events associated with subcutaneous interferon-β-1a have generally been mild and transient, with the principal event being injection-site reactions (section 5.1). Management of adverse events (e.g. by educating the patient on realistic treatment outcomes and adverse effects, using prophylactic and symptomatic measures for adverse events and providing adequate medical support) may increase patient adherence to therapy, resulting in long-term therapeutic benefits. Interferon-β products are all associated with a risk of hepatotoxicity, which increases with higher dosages and more frequent administration (section 5.2). An increased length of time between injections may allow recovery of damaged hepatocytes.[45] Glatiramer acetate, which does not appear to be hepatotoxic, should be considered in patients with elevated liver enzymes twice the upper level of normal.[44]

Using direct comparative data from the EVIDENCE trial, subcutaneous interferon-β-1a 44μg three times weekly had more favourable benefit-to-risk values than intramuscular interferon-β-1a 30μg once weekly (section 6.1). Subcutaneous interferon-β-1a was superior to intramuscular interferon-β-1a over 24 and 48 weeks with regard to relapse-related and MRI outcomes, although no conclusions can be made regarding the effects of treatment on the disease progression (section 4.2). The between-group difference in relapse rates was significant during the first 24-week period, but not in the second 24-week period. Subcutaneous interferon-β-1a was associated with a significantly higher incidence of injection-site disorders, liver function abnormalities and haematological abnormalities than the intramuscular formulation (section 5.4). This study had a relatively short duration (i.e. not long enough to assess the effect of NABs on clinical outcomes) and lacked patient-blinding (due to differences in method and frequency of injection). It is impossible to determine which differing aspect (formulation, frequency of administration, route of administration or total weekly dose) of the two treatment regimens led to the clinical benefits.

Due to differences in study design between clinical trials, it is difficult to assess the relative advantages or disadvantages of the four first-line disease-modifying therapies based on results from placebo-controlled trials of the individual drugs. Nevertheless, the assessment of the benefits and risks of disease-modifying drugs using indirect comparative data from published clinical trials suggests that interferon-β has better NNT and NNH values than subcutaneous glatiramer acetate 20μg once daily, and subcutaneous interferon-β-1a 22 or 44μg three times weekly has better NNT values than subcutaneous interferon-β-1b 250μg every other day (section 6.1). Considering both direct and indirect comparative clinical trial data, the assessment suggests that subcutaneous interferon-β-1a 44μg three times weekly has the best NNT and NNH values relative to the other disease-modifying RRMS treatments.

As the efficacy of interferon-β is reduced over time by the presence of NABs (section 2.1), the potential development of NABs should be considered when treating RRMS.[34] Interferon-β-1a is less immunogenic than interferon-β-1b, but the immunogenicity of interferon-β-1a is increased by the frequency and the route (subcutaneous vs intramuscular) of administration. NABs to interferon-β-1a and interferon-β-1b are cross-reactive; therefore, switching NAB-positive patients from one interferon-β formulation to another is unlikely to affect the antibody status of a given patient. A decision about whether to continue or withdraw interferon-β treatment should be based on clinical measures or biological response to interferon-β and not on the presence of NABs alone. Long-term studies are required to access the effect of NABs on the relative clinical efficacy of interferon-β products.[34]

Reducing the number of relapses and delaying disease progression in patients with RRMS may reduce many direct medical and indirect costs. Cost-effectiveness analyses from a healthcare perspective have shown subcutaneous interferon-β-1a 44μg three times weekly to be cost effective relative to placebo in the UK and France and cost saving relative to intramuscular interferon-β-1a 30μg once

weekly in the US (section 6.2). Pharmacoeconomic analyses from a societal perspective (i.e. including costs due to lost productivity of patients and their informal caregivers) based on long-term data and modelling the effect of progression to SPMS would give a clearer picture of the potential cost effectiveness of treatment. Data from direct comparative trials are required to further determine the relative cost effectiveness of the available disease-modifying therapies.

In conclusion, subcutaneous interferon-β-1a 22 or 44μg three times weekly is a valuable option in the first-line treatment in patients with RRMS. It has shown benefits on outcome measures related to relapses, progression of disability and MRI in clinical trials. A significant efficacy advantage for subcutaneous interferon-β-1a 44μg three times weekly over intramuscular interferon-β-1a 30μg once weekly was shown at 24 and 48 weeks. The most common adverse events are generally mild and clinically manageable. Considering both direct and indirect comparative clinical trial data, an assessment suggests that subcutaneous interferon-β-1a 44μg three times weekly has the best benefit-to-risk values of the available disease-modifying drugs used to treat RRMS.

References

1. Khan O, Zabad R, Caon C, et al. Comparative assessment of immunomodulating therapies for relapsing-remitting multiple sclerosis. CNS Drugs 2002; 16 (8): 563-78
2. O'Connor P. Key issues in the diagnosis and treatment of multiple sclerosis: an overview. Neurology 2002 Sep 24; 59 (6 Suppl. 3): S1-33
3. Goodin DS, Frohman EM, Garmany Jr GP, et al. Disease modifying therapies in multiple sclerosis: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and the MS Council for Clinical Practice Guidelines. Neurology 2002 Jan 22; 58 (2): 169-78
4. Corboy JR, Goodin DS, Frohman EM. Disease-modifying therapies for multiple sclerosis. Curr Treat Options Neurol 2003 Jan; 5 (1): 35-54
5. Beta interferon and glatiramer acetate for the treatment of multiple sclerosis. Technology Appraisal Guidance No. 32. London: National Institute for Clinical Excellence, 2002 Jan
6. Polman CH, Uitdehaag BMJ. Drug treatment of multiple sclerosis. BMJ 2000 Aug 19; 321: 490-4
7. Fernandez O. Interferons in relapsing-remitting multiple sclerosis: are there benefits from long-term use? CNS Drugs 2004; 18 (15): 1057-70
8. Freedman MS, Blumhardt LD, Brochet B, et al. International consensus statement on the use of disease-modifying agents in multiple sclerosis. Mult Scler 2002 Feb; 8 (1): 19-23
9. Biogen Idec Inc., Elan Pharmaceuticals. Important drug warning: voluntary suspension of Tysabri (natalizumab) marketing [online]. Available from URL: http://www.tysabri.com [Accessed 2005 Mar 22]
10. Serono, Inc. Rebif (interferon-beta-1a) sc injection: prescribing information. Rockland (MA): Serono, Inc., 2004
11. Liberati AM, Horisberger MA, Palmisano L, et al. Double-blind randomized phase I study on the clinical tolerance and biological effects of natural and recombinant interferon-β. J Interferon Res 1992; 12 (5): 329-36
12. Liberati AM, Garofani P, De Angelis V, et al. Double-blind randomized phase I study on the clinical tolerance and pharmacodynamics of natural and recombinant interferon-β given intravenously. J Interferon Res 1994; 14 (2): 61-9
13. Dhib-Jalbut S. Mechanisms of action of interferons and glatiramer acetate in multiple sclerosis. Neurology 2002 Apr 23; 58 (8 Suppl. 4): S3-9
14. Zhang J, Hutton G, Zang Y. A comparison of the mechanisms of action of interferon beta and glatiramer acetate in the treatment of multiple sclerosis. Clin Ther 2002 Dec; 24 (12): 1998-2021
15. Wagstaff AJ, Goa KL. Recombinant interferon-β-1a: a review of its therapeutic efficacy in relapsing-remitting multiple sclerosis. Biodrugs 1998; 10 (6): 471-94
16. Rothuizen LE, Buclin T, Spertini F, et al. Influence of interferon β-1a dose frequency on PBMC cytokine secretion and biological effect markers. J Neuroimmunol 1999 Sep 1; 99 (1): 131-41
17. Buraglio M, Trinchard-Lugan I, Munafo A, et al. Recombinant human interferon-β-1a (Rebif) vs recombinant interferon-β-1b (Betaseron) in healthy volunteers: a pharmacodynamic and tolerability study. Clin Drug Invest 1999; 18 (1): 27-34
18. Salmon P, Le Cotonnec JY, Galazka A, et al. Pharmacokinetics and pharmacodynamics of recombinant human interferon-β in healthy male volunteers. J Interferon Cytokine Res 1996 Oct; 16 (10): 759-64
19. Munafo A, Trinchard-Lugan I, Nguyen TX, et al. Comparative pharmacokinetics and pharmacodynamics of recombinant human interferon beta-1a after intramuscular and subcutaneous administration. Eur J Neurol 1998 Mar; 5 (2): 187-93
20. Buchwalder PA, Buclin T, Trinchard I, et al. Pharmacokinetics and pharmacodynamics of IFN-β1a in healthy volunteers. J Interferon Cytokine Res 2000 Oct; 20 (10): 857-66
21. Bertolotto A, Gilli F, Sala A, et al. Evaluation of bioavailability of three types of IFNβ in multiple sclerosis patients by a new quantitative-competitive-PCR method for MxA quantification. J Immunol Methods 2001 Oct 1; 256 (1-2): 141-52
22. Deisenhammer F, Mayringer I, Harvey J, et al. A comparative study of the relative bioavailability of different interferon beta preparations. Neurology 2000 Jun 13; 54 (11): 2055-60
23. Galboiz Y, Shapiro S, Lahat N, et al. Matrix metalloproteinases and their tissue inhibitors as markers of disease subtype and response to interferon-β therapy in relapsing and secondary-progressive multiple sclerosis patients. Ann Neurol 2001 Oct; 50 (4): 443-51
24. Brescia Morra V, Coppola G, Orefice G, et al. Interferon-β treatment decreased cholesterol plasma levels in multiple sclerosis patients. Neurology 2004 Mar; 62 Pt 1: 829-30
25. Wandinger KP, Lunemann JD, Wengert O, et al. TNF-related apoptosis inducing ligand (TRAIL) as a potential response

marker for interferon-beta treatment in multiple sclerosis. Lancet 2003 Jun 14; 361: 2036-43

26. Sharief MK, Semra YK. Down-regulation of survivin expression in T lymphocytes after interferon beta-1a treatment in patients with multiple sclerosis. Arch Neurol 2002 Jul; 59 (7): 1115-21
27. Harzheim M, Stepien-Mering M, Schroder R, et al. The expression of microfilament-associated cell-cell contacts in brain endothelial cells is modified by IFN-β1a (Rebif). J Interferon Cytokine Res 2004 Dec; 24 (12): 711-6
28. Hong J, Tejada-Simon MV, Rivera VM, et al. Anti-viral properties of interferon beta treatment in patients with multiple sclerosis. Mult Scler 2002 May; 8 (3): 237-42
29. Rice G. The significance of neutralizing antibodies in patients with multiple sclerosis treated with interferon beta. Arch Neurol 2001 Aug; 58 (8): 1297-8
30. Bertolotto A, Gilli F, Sala A, et al. Persistent neutralizing antibodies abolish the interferon β bioavailability in MS patients. Neurology 2003 Feb 25; 60 (4): 634-9
31. Ross C, Clemmesen KM, Svenson M, et al. Immunogenicity of interferon-β in multiple sclerosis patients: influence of preparation, dosage, dose frequency, and route of administration. Danish Multiple Sclerosis Study Group. Ann Neurol 2000 Nov; 48 (5): 706-12
32. Bertolotto A, Deisenhammer F, Gallo P, et al. Immunogenicity of interferon beta: differences among products. J Neurol 2004 Jun; 251 Suppl. 2: ll/15-24
33. Perini P, Facchinetti A, Bulian P, et al. Interferon-beta (INF-β) antibodies in interferon-β1a- and interferon-β1b-treated multiple sclerosis patients: prevalence, kinetics, cross-reactivity, and factors enhancing interferon-β immunogenicity *in vivo*. Eur Cytokine Netw 2001 Mar; 12 (1): 56-61
34. Vartanian TK, Zamvil SS, Fox E, et al. Neutralizing antibodies to disease-modifying agents in the treatment of multiple sclerosis. Neurology 2004 Dec 14; 63 (11 Suppl. 5): S42-9
35. Panitch H, Goodin DS, Francis G, et al. Randomized, comparative study of interferon β-1a treatment regimens in MS: the EVIDENCE Trial. Neurology 2002 Nov 26; 59 (10): 1496-506
36. Paty D. Long-term observational efficacy and safety follow-up of the PRISMS cohort [abstract no. P555 plus poster]. 19th Congress of the European Committee for Treatment and Research in Multiple Sclerosis; 2003 Sep 17-20; Milan
37. Randomised double-blind placebo-controlled study of interferon β-1a in relapsing/remitting multiple sclerosis: PRISMS (Prevention of Relapses and Disability by Interferon β-1a Subcutaneously in Multiple Sclerosis) Study Group. Lancet 1998; 352 (9139): 1498-504
38. Schwid SR, Thorpe J, Sharief M, et al. Enhanced benefit of increasing interferon beta-1a dose and frequency in relapsing MS: the EVIDENCE study. Arch Neurol 2005 May; 62 (5): 785-92
39. PRISMS-4: long-term efficacy of interferon-β-1a in relapsing MS. Neurology 2001 Jun 26; 56 (12): 1628-36
40. Sorensen PS, Ross C, Clemmesen KJ, et al. Clinical importance of neutralising antibodies against interferon beta in patients with relapsing-remitting multiple sclerosis. Lancet 2003 Oct 11; 362 (9391): 1184-91
41. Li D, Abdalla JA. Long-term observational follow-up of the PRISMS cohort: analyses of MRI BOD shows benefit of high dose, high frequency IFNbeta-1a (Rebif) [abstract no. P02.118]. Neurology 2004 Apr; 62 (7 Suppl. 5): A153-4
42. Li DK, Paty DW. Magnetic resonance imaging results of the PRISMS trial: a randomized, double-blind, placebo-controlled study of interferon-β1a in relapsing-remitting multiple sclerosis. Ann Neurol 1999 Aug; 46 (2): 197-206
43. Francis GS, Grumser Y, Alteri E, et al. Heptatic reactions during treatment of multiple sclerosis with inteferon-β-1a: incidence and clinical significance. Drug Saf 2003; 26 (11): 815-27
44. Tremlett HL, Oger J. Elevated aminotransferases during treatment with interferon-beta for multiple sclerosis: actions and outcomes. Mult Scler 2004 Jun; 10 (3): 298-301
45. Tremlett HL, Yoshida EM, Oger J. Liver injury associated with the β-interferons for MS: a comparison between the three products. Neurology 2004 Feb 24; 62 (4): 628-31
46. Tremlett H, Oger J. Hepatic injury, liver monitoring and the beta-interferons for multiple sclerosis. J Neurol 2004 Nov; 251 (11): 1297-303
47. Rieckmann P, O'Connor P, Francis GS, et al. Haematological effects of interferon-β-1a (Rebif) therapy in multiple sclerosis. Drug Saf 2004; 27 (10): 745-56
48. Patten SB, Metz LM. Interferon β-1a and depression in relapsing-remitting multiple sclerosis: an analysis of depression data from the PRISMS clinical trial. Mult Scler 2001 Aug; 7 (4): 243-8
49. Sandberg-Wollheim M, Bever C, Carter J, et al. Comparative tolerance of IFN beta-1a regimens in patients with relapsing multiple sclerosis: the EVIDENCE study. J Neurol 2005 Jan; 252 (1): 8-13
50. Francis GS. Importance of benefit-to-risk assessment for disease-modifying drugs used to treat MS. J Neurol 2004 Sep; 251 Suppl. 5: v/42-9
51. Lepen C, Coyle P, Vollmer T, et al. Long-term cost effectiveness of interferon-β-1a in the treatment of relapsing-remitting multiple sclerosis: an econometric model. Clin Drug Invest 2003; 23 (9): 571-81
52. Beresniak A., Coyle P, Vollmer T, et al. Cost-benefit and cost-effectiveness analyses of interferon beta-1a therapies for multiple sclerosis [abstract no. P414 plus poster]. 13th Annual Meeting of the European Neurological Society; 2003 Jun 14-18; Istanbul
53. Galetta SL, Markowitz C, Lee AG. Immunomodulatory agents for the treatment of relapsing multiple sclerosis: a systematic review. Arch Intern Med 2002 Oct 28; 162 (19): 2161-9

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