The interferon beta therapies for treatment of relapsing–remitting multiple sclerosis: are they equally efficacious? A comparative review of open-label studies evaluating the efficacy, safety, or dosing of different interferon beta formulations alone or in combination

Volker Limmroth, Norman Putzki and Norman J. Kachuck

Abstract: Interferon beta preparations are the most widely used initial therapies prescribed for patients with relapsing–remitting multiple sclerosis. Phase III studies have demonstrated comparable efficacy on clinical measures of disease activity, variable benefits on radiological measures, and good overall tolerability. Subsequent clinical studies have attempted to compare directly the three available interferon beta preparations, reporting both safety and efficacy data. We review the literature on studies evaluating interferon beta therapy for patients with relapsing–remitting multiple sclerosis, discuss reasons for discrepant findings, and assess the utility of interferon beta-based combination regimens as the focus of future studies in the increasingly complex multiple sclerosis therapy landscape.

Keywords: interferon beta, efficacy, multiple sclerosis, safety

Introduction

For more than 15 years, interferon beta (IFN β) therapy has been a first-line treatment for relapsing–remitting multiple sclerosis (RRMS). During this time, clinicians' experience and evidence-based clinical data have indicated that patients are benefiting from these treatment regimens. Recent advances in our understanding of the underlying disease heterogeneity of multiple sclerosis (MS), the variable responses of patients to different treatments, and the introduction of new classes of pharmacotherapies have raised new questions regarding the optimal treatment regimen for patients with MS. As more therapeutic options for inflammatory forms of MS become available, treatment decisions for a given patient will become increasingly complex. On the cusp of these revolutions in MS therapy, we have reviewed the literature to date, comparing the three currently available IFN β formulations at different doses and as proven platforms for new optimal therapeutic combinations.

Three IFN β formulations are currently approved for the treatment of RRMS: subcutaneous (SC) IFN β -1b (Betaferon[®]/Betaseron[®], Extavia[®]), intramuscular (IM) IFN β -1a (Avonex[®]), and SC IFN β -1a (Rebif[®]; available in both 22 μ g and 44 μ g formulations). Although they used different primary endpoints, the respective pivotal phase III studies of each IFN β therapy over a 2-year period demonstrated comparable efficacy with respect to relapse-related measures and varying degrees of benefit with respect to inflammatory measures, such as gadolinium enhancement [PRISMS Study Group, 1998; Jacobs *et al.* 1996; IFNB Multiple Sclerosis Study Group, 1993]. Both IFN β -1a products also have been shown to slow disability progression as assessed by sustained change on the Expanded Disability Status Scale (EDSS) [PRISMS Study Group, 1998; Jacobs *et al.* 1996. These benefits were maintained in blinded studies of patients observed for up to 4 years [Clanet *et al.* 2002; PRISMS Study Group and

Ther Adv Neurol Disord

(2011) 4(5) 281–296

DOI: 10.1177/

1756285611413825

© The Author(s), 2011.
Reprints and permissions:
[http://www.sagepub.co.uk/
journalsPermissions.nav](http://www.sagepub.co.uk/journalsPermissions.nav)

Correspondence to:

Volker Limmroth, MD, PhD

Department of Neurology,
Cologne City Hospitals
(Merheim), Ostmerheimer
Strasse 200, 51109
Cologne, Germany,
limmrothv@kliniken-koeln.de

Norman Putzki

Department of Neurology,
University Hospital Essen,
Essen, Germany and
Director, Medical
Research, Biogen Idec,
Wellesley, MA, USA

Norman J. Kachuck

Department of Neurology,
Keck School of Medicine,
University of Southern
California, Los Angeles,
CA, USA

University of British Columbia MS/MRI Analysis Group, 2001]. All IFN β formulations are generally well tolerated, and improvements in injection technique, side effect management, and patient education have contributed to greater compliance with treatment regimens [Munschauer and Kinkel, 1997]. Regular testing for elevated hepatic enzyme levels and changes in leukocyte counts is recommended for all IFN products [Bayer Healthcare Pharmaceuticals, 2008; Biogen Idec, 2008; EMD Serono, 2008]. As a protein-based therapy, immune responses directed at IFNs have been documented. Antigenicity varies among these products, with SC IFN β -1b as the highest, then SC IFN β -1a, and IM IFN β -1a as the lowest, due to differences in formulation, production technique and additives, method of administration, pH, and *in vivo* aggregation of the product. Several studies have demonstrated that the risk of developing neutralizing antibodies to IFN within the first 9 to 18 months of treatment can compromise clinical efficacy beginning 18–24 months after treatment initiation [IFN β MS study group and the University of British Columbia MS/MRI Analysis group 1996; Bertolotto et al. 2002, Francis et al. 2005]. Thus, understanding the similarities and differences among the three IFN β formulations is essential for optimizing outcomes for patients with MS.

To date, there have been few well-controlled, clinical studies comparing the safety and efficacy of the three IFN β therapies in patients with RRMS; however, 11 open-label, phase IV studies have compared different doses or formulations of IFN β in order to assess the optimal efficacy (Table 1). The objective of this article is to review the data from these comparative studies and to examine possible efficacy advantages and dosing strategies for the different IFN β formulations. As novel agents are developed and approved for the treatment of MS, the combination of an IFN β -based therapy with these other disease-modifying agents will become the focus of future studies to improve patients' outcomes.

Direct comparative studies

A total of 11 comparative studies of IFN β products have been conducted in more than 10,000 patients with RRMS (Table 1); several of these studies qualify as class III and class IV evidence (Table 2). Most of the reviewed data are derived from postmarketing, open-label, phase IV studies. In these phase IV studies, unlike phase III

studies, patients were not randomized to a given treatment arm, which may have created a selection bias because more severely ill patients may have been assigned to therapeutic regimens perceived as more aggressive by the study investigator. Moreover, open-label studies may have an influence on the perspective of the treating physician or the patient; thus, subjective outcome measures may be skewed toward one or another treatment arm. As a result, outcomes for patients treated with active therapy in nonblinded, open-label studies may not be comparable, even when baseline characteristics (age, disease duration, EDSS scores) appear to be similar. The studies listed in Table 1 may have other limitations, such as small sample sizes and a lack of efficacy endpoints. In addition, few of these studies evaluated changes in disease activity by magnetic resonance imaging (MRI).

Comparison of relapse rates among IFN β products

Study 1. The largest study conducted thus far, Quality Assessment in Multiple Sclerosis Therapy (QUASIMS), retrospectively enrolled more than 4700 patients with RRMS from 510 sites in the German-speaking countries of Europe [Limmroth et al. 2007] and was extended to over 7000 patients worldwide in seven other countries [Limmroth et al. 2005]. The initial cohort represented 16% of all patients who had been treated with an IFN β preparation and approximately 27% of all patients in Germany, Austria, and Switzerland who received an IFN β preparation for 2 or more years [Limmroth et al. 2007]. QUASIMS was conducted according to a defined study protocol, and analyses were performed by an independent contract research organization. All patients meeting the inclusion criteria (RRMS, minimum treatment duration of 2 years, complete relapse history, documented EDSS scores) were included in the investigation. Patients receiving 2 years of uninterrupted treatment with one of the IFN β therapies or those who were treatment-naïve were considered the initial treatment (IT) group. Patients who started a different disease-modifying therapy (DMT) after initial treatment were considered the follow-up therapy (FT) group [Limmroth et al. 2007].

The results of QUASIMS suggest that there is comparable efficacy during 2 years of treatment among the available IFN β preparations in this

Table 1. Summary of comparative studies of interferon beta (IFN β) products for relapsing–remitting multiple sclerosis.

Study	Treatment group	Number of patients	Study design	Treatment duration	Evaluated endpoints	Outcome
1. Limmroth <i>et al.</i> [2007]	IM IFN β -1a SC IFN β -1b SC IFN β -1a 22 μ g SC IFN β -1a 44 μ g	1728 1706 932 388	Retrospective, observational, open label	≥ 2 years 3.7 years (mean)	Relapse rate, EDSS	No significant differences among IFN β s
2. Milanese <i>et al.</i> [2003]	IM IFN β -1a SC IFN β -1b	647 834	Prospective, observational, open label	1 year (mean in IM IFN β -1a group) 1.8 years (mean in SC IFN β -1b group) 2 years	% Relapse-free patients, EDSS	No significant differences between IM IFN β -1a and SC IFN β -1b*
3. Trojano <i>et al.</i> [2003]	IM IFN β -1a SC IFN β -1b	217 234	Observational, open label, nonrandomized		Relapse rate, EDSS	No significant differences among IFN β s
4. Río <i>et al.</i> [2006]	SC IFN β -1a 22 μ g IM IFN β -1a SC IFN β -1b SC IFN β -1a	89 148 185 136	Observational, open label	≥ 2 years	Relapse rate, EDSS	No significant differences among IFN β s
5. Romero-López <i>et al.</i> [2003] [†]	IM IFN β -1a SC IFN β -1b SC IFN β -1a	81 115 47	Retrospective, open label	2.1 years (mean)	Relapse rate, EDSS, tolerability	No significant differences among IFN β s
6. Haas and Firzlaff [2005]	IM IFN β -1a SC IFN β -1b SC IFN β -1a GA	177 325 114 140	Retrospective, open label	2 years	Relapse rate, %relapse-free patients, % progression-free patients, tolerability	No significant differences among IFN β s; GA demonstrated greatest decline in relapse rate after 24 months ($p < 0.001$)
7. Koch-Henriksen <i>et al.</i> [2006]	SC IFN β -1a 22 μ g [1 $\times$ /week] SC IFN β -1b	143 158	Prospective, open label, randomized	2 years	Annualized relapse rate	No significant differences between SC IFN β -1a once weekly and SC IFN β -1b
8. Minagar and Murray [2008]	tIM IFN β -1a SC IFN β -1b	69 67	Prospective/retrospective, open label	18–30 months (6 months prospective; 12–18 months retrospective)	EDSS, relapse rate, % relapse-free patients, MRI disease activity, immunogenicity	No significant differences between IM IFN β -1a and SC IFN β -1b for clinical or MRI end points; IM IFN β -1a less immunogenic than SC IFN β -1b
9. Panitch <i>et al.</i> [2002] (EVIDENCE)	IM IFN β -1a SC IFN β -1a	338 339	Prospective, open label, assessor blinded	48 weeks	% Relapse-free patients (primary end point), CU active lesions, tolerability	Significant benefit of SC IFN β -1a vs. IM IFN β -1a on relapses and CU active lesions

(continued)

Table 1. Continued.

Study	Treatment group	Number of patients	Study design	Treatment duration	Evaluated endpoints	Outcome
10. Durelli <i>et al.</i> [2002] (INCOMIN)	IM IFNβ-1a SC IFNβ-1b	92 96	Prospective, open label, randomized	2 years	% Relapse-free patients and % patients free from new T2 lesions (primary end points), multiple secondary end points, tolerability	Significant benefit of SC IFNβ-1b vs. IM IFNβ-1a on primary and secondary end points
11. Khan <i>et al.</i> [2001]	IM IFNβ-1a SC IFNβ-1b GA	40 41 42	Prospective, open label	18 months	Relapse rate	Significant benefit of SC IFNβ-1b and GA vs. IM IFNβ-1a

CU, combined unique; EDSS, Expanded Disability Status Scale; GA, glatiramer acetate; IFNβ, interferon beta; IM, intramuscular; IVlg, intravenous immunoglobulin; MRI, magnetic resonance imaging; SC, subcutaneous.

*Significant differences in favor of SC IFNβ-1b were observed for percentage reduction in relapse frequency, although the baseline imbalances between the two treatment groups prohibit any direct comparisons. At baseline, SC IFNβ-1b-treated patients had more severe disease than IM IFNβ-1a-treated patients.

†Study included patients with relapsing–remitting multiple sclerosis and secondary progressive multiple sclerosis.

population (approximately 50% of patients were progression free over 2 years) using these documented treatment outcomes. A greater percentage of patients who received IFNβ therapies initially (the IT group) remained relapse-free compared with patients who received IFNβ as a follow-up therapy (the FT group). Annualized relapse rates over 2 years were not significantly different in either group regardless of specific IFN treatment. For the IT group, the relapse rate was 0.51 for IM IFNβ-1a, 0.52 for IFNβ-1b, 0.53 for SC IFNβ-1a 22 µg, and 0.63 for SC IFNβ-1a 44 µg [Limmroth *et al.* 2007]

A subset analysis comparing patients who were switched from IM IFNβ-1a to SC IFNβ-1b with patients who were switched from SC IFNβ-1b to IM IFNβ-1a did not reveal any differences in the course of the disease at 2-year follow up [Limmroth and Putzki, 2005]. When comparing patients who changed to different IFNβ preparations due to side effects, QUASIMS confirmed data from earlier studies showing that patients treated with an SC formulation were more likely to discontinue treatment than those treated with the IM formulation, largely because of injection-site reactions [Durelli *et al.* 2002; Panitch *et al.* 2002]. Only 0.7% of patients discontinued IFNβ treatment because of central nervous system adverse events (e.g. depression). Despite the limitations of the QUASIMS trial, such as lack of MRI measurements and neutralizing antibody data, QUASIMS provided important data demonstrating similar efficacy of the different IFNβ preparations in a large cohort of patients.

Study 2. Another study involving 65 centers in northern Italy compared 834 patients with RRMS treated with SC IFNβ-1b (250 µg every other day) with 647 patients treated with IM IFNβ-1a (30 µg once weekly) [Milanese *et al.* 2003]. Mean treatment duration was 1.8 years in the SC IFNβ-1b group and 1 year in the IM IFNβ-1a group. The change in EDSS scores and percentage of relapse-free patients was comparable for both groups. Significant differences in favor of SC IFNβ-1b *versus* IM IFNβ-1a were noted for percentage reduction in relapse frequency at 6 months (68% *vs.* 55%, *p* < 0.001), 12 months (60.4% *vs.* 55%, *p* = 0.01), 18 months (63.7% *vs.* 57.1%, *p* = 0.01), and 24 months (64% *vs.* 56%, *p* = 0.02); however, patients in the SC IFNβ-1b group had greater disease severity at baseline. In addition, there were

Table 2. Levels of evidence of efficacy in clinical trials.

Class I	Prospective, randomized, controlled clinical trial (RCT) with masked outcome assessment, in a representative population. The following are required: (a). primary outcome(s) is/are clearly defined, (b). exclusion/inclusion criteria are clearly defined, (c). adequate accounting for dropouts and crossovers with numbers sufficiently low to have minimal potential for bias, (d). relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.
Class II	Prospective matched group cohort study in a representative population with masked outcome assessment that meets (a)–(d) above <i>or</i> a RCT in a representative population that lacks one criteria (a)–(d).
Class III	All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome assessment is independent of patient treatment.
Class IV	Evidence from uncontrolled studies, case series, case reports, or expert opinion.

significantly more dropouts seen in the SC IFN β -1b group than in the IM IFN β -1a group (41.1% *vs.* 15.3% over 3 years, $p < 0.001$), including withdrawals due to adverse events (15.3% *vs.* 3.8%) and disability progression (7.7% *vs.* 3.2%). The SC IFN β -1b formulation was associated with a higher incidence of local skin reactions (33% *vs.* 8%) and leukopenia (17% *vs.* 6%). The results of this study suggested that both formulations were effective, but differences in baseline characteristics of patients in each treatment arm precluded an accurate comparison.

Study 3. A population-based surveillance study of 1033 patients with RRMS was conducted in 15 centers in Italy [Trojano *et al.* 2003]. Patients were treated with SC IFN β -1b 250 μ g every other day, IM IFN β -1a 30 μ g once weekly, or SC IFN β -1a 22 μ g three times weekly. Results were reported at 12-month follow up for SC IFN β -1b ($n = 234$), IM IFN β -1a ($n = 217$), and SC IFN β -1a 22 μ g ($n = 89$) and at 24-month follow up for SC IFN β -1b ($n = 209$) and IM IFN β -1a ($n = 169$). No differences were observed in the proportion of relapse-free patients among the three treatment groups (53.7% for SC IFN β -1b, 54.4% for IM IFN β -1a, 49% for SC IFN β -1a; $p = 0.10$) after 12 months of treatment or between SC IFN β -1b (37.5%) and IM IFN β -1a (33%) after 24 months of treatment. Each of the IFN β products produced a significant reduction in relapse rate at the 12- and 24-month time points ($p < 0.001$). In addition, no significant differences were seen in mean changes in relapse rate or EDSS scores at 12 or 24 months. These results are consistent with the controlled phase III studies of each IFN β formulation [PRISMS

Study Group, 1998; Jacobs *et al.* 1996; IFNB Multiple Sclerosis Study Group, 1993].

Study 4. A single-center observational study evaluated 469 patients with RRMS who were observed for at least 2 years during therapy with SC IFN β -1b ($n = 185$), IM IFN β -1a ($n = 148$), or SC IFN β -1a ($n = 136$) [Rio *et al.* 2006]. The relapse rate was significantly reduced for all three formulations (70% for SC IFN β -1b, 64% for IM IFN β -1a, and 74% for SC IFN β -1a). Sustained progression of disability at 2 and 4 years was 17% and 23% for the IM IFN β -1a group, 11% and 24% for the SC IFN β -1b group, and 19% and 35% for the SC IFN β -1a group. There were no reports of unexpected adverse events with any of the treatments; however, efficacy data in this patient population was inconsistent with the previous phase III study results. Overall, however, there were no distinct differences among the three IFN β formulations.

Study 5. Romero-Lopez and colleagues evaluated IFN β preparations for the treatment of 313 patients with RRMS and secondary progressive MS (SPMS) in Galicia, Spain [Romero-Lopez *et al.* 2003]. IM IFN β -1a was administered to 26% of the patients, SC IFN β -1b to 52.4%, and SC IFN β -1a to 21.6% for a mean of 2.1 years [Romero-López *et al.* 2003]. Relapse rates were reduced by 73.3% in patients receiving IM IFN β -1a, by 68.8% in patients receiving SC IFN β -1b, and by 35.7% in patients receiving SC IFN β -1a. Of patients receiving IM IFN β -1a, 60.5% remained relapse free, compared with 33% of patients receiving SC IFN β -1b and 54.5% of patients receiving SC IFN β -1a. Despite differences in relapse rates among the

three IFN β formulations, the results of this study demonstrated that each was tolerable and effective in the daily clinical setting.

Study 6. In another retrospective, open-label study, patients with RRMS treated with IM IFN β -1a ($n=79$), SC IFN β -1b ($n=77$), SC IFN β -1a 22 μ g ($n=48$), or glatiramer acetate (GA; $n=79$) were evaluated over a period of 24 months [Haas and Firzlauff, 2005]. Baseline characteristics were comparable across treatment groups. Compared with baseline, the mean relapse rate for all treatments decreased significantly at 24 months (0.8 *vs.* 1.09 for IM IFN β -1a, 0.69 *vs.* 1.20 for SC IFN β -1b, 0.66 *vs.* 1.16 for SC IFN β -1a, 0.36 *vs.* 1.16 for GA; all $p < 0.05$). There were no significant differences among the IFN β preparations, but the reduction in relapse rate for patients treated with GA was significantly higher than those in patients receiving any of the other therapies ($p < 0.001$). Percentages of patients who were free from relapse ranged from 35.4% to 58.2% ($p = 0.22$) and percentages of patients who were progression free (no increase in EDSS by ≥ 1 point) ranged from 71.7% to 87.5% ($p = 0.13$), with no statistically significant differences among the therapies. The progression index (final EDSS divided by disease duration) at 24 months, however, was significantly lower ($p < 0.05$; indicating less progression) in patients treated with GA and SC IFN β -1a compared with SC IFN β -1b. Despite small sample size and potential selection bias in treatment arms in this retrospective surveillance study, results indicated that these first-line therapies for patients with MS have consistent efficacies.

Study 7. A Danish group investigated the efficacy of SC IFN β -1a 22 μ g once weekly ($n=143$) and SC IFN β -1b 250 μ g every other day ($n=158$) in a prospective, multicenter, randomized, controlled, open-label, 2-year study [Koch-Henriksen *et al.* 2006]. The primary endpoints were annualized relapse rate, time to first relapse, and NAb formation. Annualized relapse rates (0.70 and 0.71, respectively) and time to sustained disability progression (a secondary endpoint) were similar for both groups. Development of NABs at 2-year follow-up did not affect efficacy of either formulation. The authors in this study acknowledged that its unblinded design could have masked a true difference between the two formulations. Even though the results were not robust due to a

small sample size and a large amount of missing data, a favorable trend toward SC IFN β -1b was noted in the MRI results.

Study 8. The Prospective and Retrospective Long-Term Observational Study of Avonex and Rebif (PROOF) was a phase IV, multicenter study that combined retrospective and prospective data from patients with RRMS [Minagar and Murray, 2008]. PROOF was intended to collect up to 5 years of comparative efficacy and tolerability data using combined chart review and prospective observational data. Owing to slow enrollment, however, the study was halted after collecting 6 months of prospective data. In total, 18–30 months of data were reported for PROOF (12–24 months retrospective data plus 6 months prospective data). Treatment consisted of IM IFN β -1a 30 μ g once weekly or SC IFN β -1a 44 μ g 3 times weekly. At study termination, the median treatment duration was 19.9 months for IM IFN β -1a ($n=69$) and 16.2 months for SC IFN β -1a ($n=67$, $p=0.003$). No significant differences were seen between treatment groups on stratified EDSS scores at any time point or on the proportion of patients with sustained disability progression (25.8% for IM IFN β -1a *vs.* 26.7% for SC IFN β -1a); on annualized relapse rate during last 6 months of treatment (0.35 *vs.* 0.48); or on changes in MRI endpoints. However, 19% of SC IFN β -1a-treated patients were positive for NABs at study enrollment and again 6 months later compared with none of the patients treated with IM IFN β -1a. Although no differences were observed between NAB-positive and NAB-negative patients on any of the clinical endpoints, NAB positivity was associated with disease activity on MRI. For example, more NAB-positive than NAB-negative patients had new or enlarging T2 lesions (63.6% *vs.* 41.7%, $p=0.003$) and larger gadolinium-enhanced (Gd+) lesions at enrollment (305.5 mm³ *vs.* 51.6 mm³, $p=0.015$). Owing to the combination of the retrospective and prospective design and the shortened time of the prospective phase, this study was not powered to detect statistical differences between the two IFN β -1a formulations.

Study 9. In the randomized, prospective, open-label Evidence of Interferon Dose Response: European–North American Comparative Efficacy (EVIDENCE) study, patients with RRMS were randomized to IM IFN β -1a 30 μ g

once weekly ($n = 338$) or SC IFN β -1a 44 μ g three times weekly ($n = 339$) for 48 weeks [Panitch *et al.* 2002]. The study was conducted at 56 centers in Canada, Europe, and the United States. Patients and treating physicians were not blinded to treatment, whereas evaluating physicians and radiologists were blinded.

The primary endpoint of EVIDENCE was the proportion of relapse-free patients at 24 weeks. A total of 75% of patients in the SC IFN β -1a group were relapse free at 24 weeks compared with 63% of patients in the IM IFN β -1a group (odds ratio, 1.9; 95% confidence interval, 1.3–2.6; $p = 0.0005$). Results at 24 weeks also showed a lower mean number of combined unique (CU) active lesions in the SC IFN β -1a group (0.8) than in the IM IFN β -1a group (1.2). However, the mean number of CU active lesions at baseline also was numerically lower in the SC IFN β -1a group than in the IM IFN β -1a group (2.4 *vs.* 2.9). Also, MRI outcomes for T1 and T2 lesions favored SC IFN β -1a [Panitch *et al.* 2002].

Although the study duration applied to the primary endpoint was only 24 weeks, the comparative phase of EVIDENCE lasted 48 weeks. Final results of the comparative phase (with an average study participation of 64 weeks) showed that the difference in the percentage of relapse-free patients had decreased but was still significant between SC IFN β -1a (56%) and IM IFN β -1a (48%, $p = 0.023$) [Panitch *et al.* 2005]. NAb (titer ≥ 20) were more frequent in the SC IFN β -1a group than in the IM IFN β -1a group (25% *vs.* 2%, respectively; $p < 0.001$), and presence of NAb were associated with increased MRI disease activity on some measures at 48 weeks in SC IFN β -1a-treated patients. The percentage of relapse-free patients in EVIDENCE was also higher than the percentage reported in the pivotal phase III PRISMS study [PRISMS Study Group, 1998] suggesting differences in baseline disease activity. The corresponding relapse-free data for IM IFN β -1a were nearly identical between EVIDENCE (63%) and the pivotal phase III study of IM IFN β -1a (60%) [Jacobs *et al.* 1996].

In summary, the results of EVIDENCE suggest a dose-dependent effect of IFN β -1a therapy on short-term relapse and measures of MRI activity. The mid- to long-term implications of the EVIDENCE study remain unclear. No firm

conclusions regarding potential differences between the 2 IFN β -1a preparations on disease progression can be drawn.

Study 10. The Independent Comparisons of Interferon (INCOMIN) was a prospective, randomized, multicenter, 2-year study comparing the clinical and MRI benefits of IM IFN β -1a ($n = 92$) and SC IFN β -1b ($n = 96$) administered over a 2-year period in patients with RRMS [Durelli *et al.* 2002]. Investigators evaluated clinical outcome measures in an open-label manner, whereas blinded readers evaluated brain MRI scans. The proportion of relapse-free patients and of patients free from new T2 hyperintense lesions comprised the primary outcome measures.

For the primary endpoint, 51% of SC IFN β -1b-treated patients and 36% of IM IFN β -1a-treated patients were relapse free over 2 years ($p = 0.03$) [Durelli *et al.* 2002]. In the pivotal phase III study of IFN β -1b conducted by the IFNB Multiple Sclerosis Study Group, 31% of SC IFN β -1b-treated patients were relapse free after 2 years [IFNB Multiple Sclerosis Study Group, 1993] *versus* the 51% in INCOMIN [Durelli *et al.* 2002]. For IM IFN β -1a, 38% of patients in the phase 3 study were relapse free [Jacobs *et al.* 1996] compared with the 36% in INCOMIN. The MRI results of INCOMIN corresponded to the clinical findings: 55% of SC IFN β -1b-treated and 26% of IM IFN β -1a-treated patients were free from new T2 lesions ($p < 0.001$) [Durelli *et al.* 2002].

With regard to methodology, clinicians in this study were unblinded, which would establish it as class III evidence. In addition, baseline characteristics such as more T2 lesions, a longer disease duration, and more advanced age at the time of MS diagnosis in the IM IFN β -1a group compared with the SC IFN β -1b group may have contributed to more positive outcomes for SC IFN β -1b-treated patients.

Study 11. A prospective study by Khan and colleagues also suggested superiority of SC IFN β -1b over once-weekly IM IFN β -1a [Khan *et al.* 2001]. The study compared the effect of the two interferons and also GA on relapse rates in 156 patients. In the IFN-treated patients, the mean annualized relapse rate in previously treatment-naïve patients decreased in SC IFN β -1b-treated patients (0.55, $p = 0.001$) but not in IM

IFN β -1a-treated patients (0.81, $p=0.106$) 18 months after treatment initiation. Owing to the open-label, unblinded design of this study, it qualifies as class III evidence.

Overall, the findings from comparative studies have been inconclusive regarding potential efficacy differences among first-line IFN β therapies. Whereas large retrospective studies including QUASIMS suggest no major differences in efficacy among these therapies, some prospective open-label studies suggest differences in efficacy between SC IFN β -1b or SC IFN β -1a and IM IFN β -1a.

Dose comparison trials: does dose matter?

The optimal dose of IFN β is pertinent to improve outcomes in patients with a lifelong disease such as RRMS. Three controlled studies represent class I evidence regarding the dose–response relationship for the commercially available IFN β formulations.

In the European IFN β -1a Dose Comparison Study, 802 patients with relapsing MS were treated with IM IFN β -1a 30 μ g or 60 μ g once weekly for 36 months [Clanet *et al.* 2002]. No significant dose-related differences were seen on measures of sustained disability progression, change in EDSS score, or relapse rate. An extension (up to year 4) of the same study also demonstrated similar efficacy between the two doses [Clanet *et al.* 2004].

Contrasting results were reported in the randomized, double-blind, placebo-controlled PRISMS study, which compared the two doses of SC IFN β -1a (22 μ g *vs.* 44 μ g). PRISMS demonstrated a trend toward more favorable outcomes in patients treated with the higher dose compared with the lower dose in all endpoints studied [PRISMS Study Group, 1998]. The dose effect favoring the 44 μ g formulation over the 22- μ g formulation was also apparent in a subsequent 4-year extension study (risk ratio, 0.88; $p=0.069$), but it did not quite reach statistical significance [PRISMS Study Group and University of British Columbia MS/MRI Analysis Group, 2001].

The placebo-crossover design of the PRISMS study allowed for a follow-up prospective study that compared pretreatment data from years 1 and 2 with posttreatment data from years 3 and 4 in patients who changed from placebo to active treatment at year 2 [Oger *et al.* 2005]. Patients in

both the 22 μ g ($n=85$) and 44 μ g ($n=87$) groups had a significant decrease in annualized relapse rate, disease progression, and number of T2 active lesions after switching to active treatment in years 3 and 4 [Oger *et al.* 2005]. No significant differences were observed between the two doses in any of these measures [Oger *et al.* 2005].

For IFN β -1b, the pivotal study demonstrated superior efficacy of the dose that is currently licensed (Betaseron® 250 μ g every other day) over a lower dose [IFNB Multiple Sclerosis Study Group, 1993]. A more recent study assessed whether a further twofold dose increase would have an acceptable tolerability profile and might provide additional benefits. Two formulations of IFN β -1b were evaluated in a multicenter, randomized, double-blind, dose-comparison study [Hurwitz *et al.* 2008]. Patients received either 250 or 500 μ g of SC IFN β -1b for ≥ 12 weeks. The primary endpoint was percentage of patients experiencing adverse events. MRI evaluation was included to monitor for new disease activity. A dose-response effect associated with the 500- μ g dose was detected in the more common adverse events, and no differences in MRI outcomes were observed.

Results of the Betaferon Efficacy Yielding Outcomes of a New Dose (BEYOND) study compared the efficacy and tolerability of a 250 μ g dose of SC IFN β -1b with a 500 μ g dose in a randomized study of patients with RRMS [O'Connor *et al.* 2009] who met the diagnostic criteria for MS recommended in 2001 [McDonald *et al.* 2001]. BEYOND was a prospective, multicenter study that included 2244 patients assigned to 250 or 500 μ g of SC IFN β -1b taken every other day, or 20 mg of SC GA taken daily.

No additional benefit was observed in patients treated with the 500 μ g dose of SC IFN β -1b compared with patients receiving the 250 μ g dose with respect to the primary endpoint, relapse risk [O'Connor *et al.* 2009], or for any of the secondary outcomes, including EDSS progression, change in T1 hypointense lesion volume, or change in normalized brain volume. Tolerability profiles were generally similar between the treatment groups, although flu-like symptoms were significantly more common in patients taking SC IFN β -1b compared with patients on GA ($p<0.0001$), and injection-site reactions were more common in patients on GA

compared with those on SC IFN β -1a ($p=0.0005$) Taken together, these data demonstrate a dose ceiling effect for IFN β -1b therapy in RRMS and suggest the efficacy of both doses of SC IFN β -1b is similar to that of GA.

Combination therapy with IFN β

The use of two or more therapeutic interventions with different mechanisms of action underlies the rationale for combination therapy in any disease state. To date, few studies have evaluated combination therapy with IFN β and agents from a different therapeutic class in patients with RRMS.

The Avonex Combination Trial (ACT) was a randomized, placebo-controlled evaluation of the efficacy and safety of the combination of IM IFN β -1a and methotrexate in patients with RRMS [Cohen *et al.* 2008] who met the 2001 diagnostic criteria [McDonald *et al.* 2001]. ACT was designed originally as a 2-year study that would enroll 900 patients. However, because of slow patient recruitment, the study was redesigned with a smaller enrollment target and shorter duration of follow up. In the redesigned study, 313 eligible patients entered the study on stable doses of IM IFN β -1a (30 μ g once weekly) and were randomized to a 12-month course of adjunctive therapy with placebo (group 1), oral methotrexate 20 mg once weekly (group 2), intravenous methylprednisolone 1000 mg/day for 3 consecutive days every other month (group 3), or oral methotrexate and intravenous methylprednisolone at the same doses as in groups 2 and 3 (group 4) [Cohen *et al.* 2009]. The primary endpoint was new or enlarged T2-hyperintense lesions, and secondary endpoints were EDSS scores, Multiple Sclerosis Functional Composite (MSFC) scores, and relapses. Results from the redesigned study did not suggest any significant benefit for either combination therapy; however, there was a reduction in neutralizing antibody titers with methylprednisolone.

Also using the 2001 diagnostic criteria for MS, the Nordic trial of oral methylprednisolone as add-on therapy to IFN β -1a for treatment of RRMS (NORMIMS) was a randomized, placebo-controlled study that evaluated the efficacy of oral methylprednisolone combined with SC IFN β -1a in 170 Scandinavian patients who were refractory to the higher (44 μ g) dose of SC IFN β -1a [Sorensen *et al.* 2009]. A significant reduction in annual relapse rate (62%) was reported for patients on oral methylprednisolone

and SC IFN β -1a compared with patients on SC IFN β -1a plus placebo. Despite the more favorable outcomes for patients on combination therapy, the study had a high rate of discontinuation. A total of 26% of patients on methylprednisolone and 17% of patients on placebo discontinued by the end of the study. The high rate of discontinuation combined with the small number of patients is a notable limitation of the study, and further evaluation in larger populations is required to confirm the efficacy of the addition of oral methylprednisolone to SC IFN β -1a. Similar results were reported in another recent randomized, double-blind 3-year study ($n=341$) in patients treated with IM IFN β -1a combined with oral methylprednisolone [Ravnborg *et al.* 2009]. Patients who received methylprednisolone/IM IFN β -1a had a significantly reduced relapse rate and significantly better MRI outcomes compared with patients receiving IM IFN β -1a/placebo. Favorable outcomes also were reported for the combination group on the MSFC and MS Impairment Scale. As in the NORMIMS study, a large proportion of patients receiving combination therapy discontinued treatment in the first year of the study due to adverse events.

The combination of IFN β -1a and the immunosuppressant azathioprine has been studied in several small, open-label studies that suggested stabilization on MRI or improvement in neurological disability [Pulicken *et al.* 2005]. In a larger, double-blind, placebo-controlled study, 181 patients were randomized to IM IFN β -1a monotherapy, IM IFN β -1a plus azathioprine or IM IFN β -1a plus azathioprine and prednisone [Havrdova *et al.* 2009]. Patients were treated under double-blind conditions for 2 years, with the option of a 3-year, open-label extension phase. No differences were observed at 2 or 5 years between the monotherapy and combination therapy groups in annualized relapse rate, mean EDSS scores, or cumulative probability of sustained disability progression [Havrdova *et al.* 2009]. The percentage change in T2 lesion volume at 2 years was lower for patients receiving IFN β -1a plus azathioprine and prednisone compared with monotherapy (+14.5% *vs.* +30.3%, $p=0.015$). Median change from baseline in T2 lesion volume at 2 years was also lower for triple combination therapy compared with IFN β -1a and azathioprine (+585.0 mm³ *vs.* +2011.5 mm³, $p<0.05$) and IFN β -1a alone (+585.0 mm³ *vs.* +1532.5 mm³, $p<0.01$)

[Havrdova *et al.* 2009]. These changes, however, were not sustained over the 3-year extension period, suggesting that this combination offers no additional benefit over IFN β -1a alone [Havrdova *et al.* 2009].

The addition of statins to IFN β -1b therapy seemed promising based on experimental data showing that atorvastatin, an HMG-CoA reductase inhibitor used to lower cholesterol, reduced the rate and severity of relapses in an animal model of MS, alone and in combination with other MS therapies [Stuve *et al.* 2006]. However, results from two clinical studies did not show any additional benefit from combining statins with IFN β . Birnbaum and colleagues conducted a small, randomized, placebo-controlled study to test this hypothesis in patients with RRMS [Birnbaum *et al.* 2008]. A total of 26 patients who were on SC IFN β -1a therapy (44 μ g three times weekly) were randomized to receive combination therapy with atorvastatin, either 40 mg or 80 mg, or placebo daily for 6 months. In contrast to expectations, relapses and disease activity on MRI were more common among patients treated with atorvastatin (10/17 patients; 59%) than placebo (1/9 patients; 11%) ($p=0.22$). Relapses occurred in some patients who had been stable for years, and some relapses required treatment with glucocorticoids. Based on these findings, the authors conclude that caution and careful monitoring are needed when patients with MS are treated with high-dose IFN β and high-dose statins. The small cohort size and nonsignificant statistical findings make this trial difficult to interpret. Results from a double-blind, randomized, placebo-controlled study adding another statin, simvastatin, to IFN β -1a therapy for patients with treatment-naïve RRMS revealed no additional benefit with the combination, and perhaps even negative effects of statins on IFN β -1a activity [Sorensen *et al.* 2010].

The randomized, placebo-controlled, phase III Safety and Efficacy of Natalizumab in Combination with Interferon Beta-1a in Patients with Relapsing Remitting Multiple Sclerosis (SENTINEL) study assessed the efficacy of IM IFN β -1a in combination with natalizumab in patients ($n=1171$) with RRMS who experienced at least one relapse while on IFN therapy. Compared with IM IFN β -1a/placebo,

patients receiving IM IFN β -1a/natalizumab demonstrated a greater reduction in the risk of sustained disability progression, a lower annualized relapse rate, and improved MRI outcomes. However, two cases of progressive multifocal leukoencephalopathy (PML), one of them fatal, were reported in the combination therapy group [Rudick *et al.* 2006]. Natalizumab is indicated as monotherapy for the treatment of patients with relapsing forms of multiple sclerosis to delay the accumulation of physical disability and reduce the frequency of clinical exacerbations.

Data from a small study ($n=55$) involving patients with aggressive RRMS (≥ 2 relapses with incomplete recovery in prior year and Gd+ lesions on MRI) showed that 6 months of mitoxantrone induction therapy followed by IFN β -1b resulted in a significantly longer time to disability progression (i.e. a ≥ 1 -point deterioration in EDSS score) compared with IFN β -1b/methylprednisolone [LePage and Edan, 2009].

In addition, the combination of IFN β and GA, both first-line therapies, is being evaluated to improve efficacy in patients with MS. The putative principal mechanism of action of IFN β (nonselective blockade of T-cell migration into the central nervous system) and GA (increased production of anti-inflammatory TH2 cells that migrate to the central nervous system) are not overlapping, and might have potential synergistic or complementary additive effects when combined. Results from studies in animal models of MS in conjunction with somewhat equivocal results from a small observational study suggest that the combination of IFN β and GA could be investigated further [Gold, 2008; Ytterberg *et al.* 2007]. In a study using peripheral blood lymphocytes from patients with MS, Zang and colleagues observed potentially antagonistic effects on the regulatory function of GA (previously referred to as copolymer 1 [COP-1]) and IFN β -1a [Zang *et al.* 2003]. Based on this preclinical evidence, a multicenter, randomized, phase III National Institutes of Health (NIH)-funded study (COMBI-RX) is evaluating the combination of GA and IM IFN β -1a *versus* either agent alone in patients with RRMS in the United States [Gold, 2008].

Overall, current evidence from clinical studies is insufficient to support the broad use of combination therapies for long-term therapy of RRMS

Table 3. Common adverse events associated with interferon beta (IFN β) therapies in patients with multiple sclerosis (MS). [Adapted with permission from Moses and Brandes [2008]].

	IM IFN β -1a 30 μ g	SC IFN β -1b 250 μ g	SC IFN β -1a 44 μ g
Flu-like symptoms, %			
Flu-like symptoms	49 (29)	60 (41)	59 (51)
Myalgia	29 (22)	27 (16)	25 (20)
Fever	20 (9)	36 (22)	28 (16)
Chills	19 (5)	25 (11)	—
Malaise	—	8 (4)	5 (1)
Injection-site complications, %			
Injection-site reaction	3 (1)	85 (29)	92 (39)
Injection-site necrosis	—	5 (0)	3 (0)
Other effects, %			
Asthenia	24 (18)	61 (54)	—
Depression	18 (14)	—	25 (25)
Headache	58 (55)	57 (48)	70 (63)
Hypertonia	—	50 (40)	6 (5)
Rash	—	24 (18)	5 (3)
Abnormal vision/eye disorder	4 (2)	—	13 (7)

IM, intramuscular; SC, subcutaneous.
Numbers in parentheses represent the incidence in placebo groups.

patients. Additional, well-designed studies are needed to identify combination treatment strategies that not only provide significantly greater long-term benefits than first-line monotherapies but also are associated with favorable tolerability and minimal additional risk.

IFN safety and tolerability

As with any lifelong chronic illness, patient adherence to therapy is a critical factor in the management of MS. Acceptable safety and tolerability, as well as successful management of adverse events (AEs) when they do occur, is important to ensure continued adherence to therapy. In most patients, all of the IFN preparations are generally well tolerated. Flu-like symptoms are a commonly reported AE for all three IFNs (Table 3), but are manageable with the use of nonsteroidal anti-inflammatory drugs or other medications, such as acetaminophen. Injection-site reactions are the most commonly reported AE for SC IFN β -1a and IFN β -1b (reported in approximately 89% and 78% of patients, respectively), but are uncommon in patients on IM IFN β -1a (approximately 3%) [Bayer Healthcare Pharmaceuticals, 2008; EMD Serono, 2008; Biogen Idec, 2008]. Injection-site necrosis has also been reported in patients taking SC IFN injections, but has not been reported in the IM

preparation. Other adverse events include asthenia, headache, hypertonia, and visual disturbances. Abnormal laboratory values (leukopenia, lymphopenia, and neutropenia, elevated liver enzymes) have also been reported and are more commonly associated with SC IFN β use, although postmarketing data indicates a higher overall incidence of abnormal laboratory values for all the IFNs. Long-term studies have reported hyperthyroid and hypothyroid disorders and thyroid autoimmunity in patients treated with IM IFN β -1a and IFN β -1b [Moses and Brandes, 2008].

Although it has been suggested that a higher incidence of depression occurs among patients taking IFNs, results from all of the phase III studies, along with QUASIMS and other studies, did not report a definitive association between patients taking IFN and the development or worsening of depressive symptoms [Moses and Brandes, 2008; Limmroth *et al.* 2007; PRISMS Study Group, 1998; Jacobs *et al.* 1996; IFNB Multiple Sclerosis Study Group and The University of British Columbia MS/MRI Analysis Group, 1995]. Depression, however, is more common among patients with MS than among those with other chronic illnesses and more common than in the general population

[Patten *et al.* 2003]. As a result, patients with MS should be routinely monitored for signs of depression regardless of therapy [Moses and Brandes, 2008].

Since MS can develop during a woman's child-bearing years, it is important to understand whether use of IFN therapy can impact pregnancy outcomes. A retrospective longitudinal cohort study comparing pregnancy outcomes in patients on IM IFN β -1a, SC IFN β -1a, or IFN β -1b therapy *versus* healthy controls reported higher rates of miscarriage, stillbirths, and lower mean birth weight in women who became pregnant while on IFN therapy [Boskovic *et al.* 2005]. In contrast, one retrospective study on pregnancy outcomes in patients participating in clinical studies of SC IFN β -1a and IM IFN β -1a suggested that the rate of spontaneous pregnancy loss in women on therapy at the time of conception, or who discontinued within 2 weeks prior to conception, was similar to that of the general population [Sandberg-Wollheim *et al.* 2005]. A recent report from the AVONEX Pregnancy Exposure Registry of women with MS who were exposed to IM IFN β -1a within 1 week of conception or in their first trimester did not suggest any evidence of increased rate of miscarriages or birth defects [Foulds *et al.* 2010].

Conclusion

The postmarketing experience with the IFNs as documented in the literature, mostly as comparator open-label studies, demonstrates a significant reduction of disease activity in the treatment of RRMS with all currently available IFN β therapies. The effects seen in the majority of the studies were comparable to the results of the pivotal studies. Most of these studies (all class III/IV evidence) suggested that there are no significant differences in efficacy among the three available IFN β preparations.

Aside from drawbacks in methodology, the primary criticisms for all of the trials discussed here include short treatment duration, unblinded treatment regimens, and some imbalances in demographic parameters or baseline disease activity between the treatment groups. Potential selection bias resulting from unbalanced demographics, in particular, can be problematic when interpreting results. This was demonstrated in a study published by Sørensen and colleagues that used the Danish nationwide database (which contains data all patients with MS receiving

immunomodulatory therapy, including all IFN preparations and GA) to evaluate effects of immunomodulatory therapy use in patients with RRMS [Sørensen *et al.* 2006]. While the study applied Cox regression analyses to account for differences in baseline characteristics, the authors concluded any differences in therapeutic effect were likely due to selection bias rather than to differences in the preparations themselves. The study also provided evidence that large, open-label studies are unsuitable for evaluating comparison of treatment effects between different immunomodulatory therapies.

One of the challenges inherent in comparing these many studies is that the variation in specific endpoints can limit the ability to make comparisons across studies. Furthermore, because the comparative IFN β preparations are delivered by different routes, doses, and frequencies, none of these studies can definitively address whether any differences in efficacy are related to these different variables. Although documenting the actual relapse rates of the baseline and posttreatment groups for each of these studies was not practical for this review, it must be noted that, although the effect was similar in these reports to that of the phase III trials, the phase IV study participants typically have had larger reductions in relapse rates in every group, often double the effect seen in the original studies, for reasons which have not yet been definitively established. Entry criteria, selection bias, and ascertainment bias in evaluating and documenting sentinel events may have caused our process of studying these cohorts to 'evolve' over the years. It is important to note that MS trial design and execution is largely based on the pivotal clinical studies of the three IFN preparations on the market, and in many ways, the MS research community has drawn many of its practices from them.

Future design of clinical trials for patients with RRMS should capitalize on increased understanding of the pathogenesis and molecular basis of the disease. More robust surrogate markers of disease activity may be available in the near future. MRI-based technology examining volumetric changes in tissue damage and subtle inflammation, the amount and location of cortical disease, tract losses, and spinal disease in all of its aspects, may force a re-evaluation of the clinical relevance of the endpoints used to establish the basis of IFN therapy. We must also recognize that the increasingly strong evidence for

immunopathologic heterogeneity in MS, in spite of the phenotypic convergence as expressed in the clinical presentations, may establish better indicators of those patients who will respond to IFNs, and those who do not. Testing of IFN-induced gene expression using RNA or protein measures may soon help in establishing likely responders to treatment [Weinstock-Guttman *et al.* 2008]. These measures may also contribute to identification of confounding occult variables in all of our clinical trials and may force re-examination of the results, in light of imbalances of treatment groups that they reveal.

Although a need exists for well-designed, long-term studies to answer the question of the absolute and relative efficacy of IFN β drugs in the treatment of RRMS, it is likely that the expenditures required for such studies will be reasonably applied to the development of new therapies. It is clear that issues such as NAb, safety, tolerability, and efficacy (or lack thereof) in combination with agents having different mechanisms of action will be critical determinants of the continued first-line role of IFN β in the MS armamentarium.

A new oral preparation (fingolimod) has been approved recently and other oral preparations are currently being evaluated in phase III studies (e.g. cladribine, teriflunomide, BG-12, laquinomod, and firtagrast). In addition, parenteral drugs with innovative therapeutic targets (such as rituximab, ocrelizumab, alemtuzumab, immune ablation/stem cell reconstitution regimens, and various vaccine strategies) are becoming promising alternatives to IFN β therapy. Neural and glial reconstitution and regeneration strategies, as they are tested, will increasingly challenge all of these interventions to demonstrate positive synergistic effects with them on repair of the damaged nervous system.

As these potential new therapeutics become available, there will be considerable advantage to establishing risk–benefit for individuals across the disability spectrum with respect to treatment decisions at critical points in their disease course. This will necessarily lead to a transition from protocols that focus only on monotherapies used until patients become refractory to combination treatment plans. These combinations could exploit therapies with different mechanisms of action and/or toxicity and utilize models such as pulse+maintenance, sequential regimens, and simultaneous positive synergy regimens. The

mechanics of designing and performing such trials, especially the decision on whether to retreat using drugs with high potential for toxicity, have not yet been established. In any case, it is likely that IFNs will continue to play an important role as the platform therapy for patients with MS.

Acknowledgments

The authors acknowledge Sabrina Maurer and Matthew Hasson, Scientific Connexions, Newtown, PA, USA, for editorial and technical assistance in preparing this manuscript for submission. This support was funded by Biogen Idec.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest statement

V. Limmroth has received research funding, compensation, travel grants, and/or honoraria from Almirall, Bayer-Schering, Biogen Idec, EMD Serono, GSK, Merck, Novartis, Sanofi-Aventis, and Teva Neuroscience. N. Putzki has received research funding, compensation, travel grants, and/or honoraria from Allergan, Almirall, Bayer Schering, Biogen Idec, GlaxoSmithKline, Ipsen, Merck-Serono, Novartis, Sanofi-Aventis, Teva Neuroscience, and Wyeth and is now and employee of Biogen Idec. M. Bertelmann declares that she has no conflicts of interest. N.J. Kachuck has received research funding, compensation, travel grants, and/or honoraria from Bayer-Schering, Bayhill Pharmaceuticals, Biogen Idec, EMD Serono, the National Multiple Sclerosis Society, Peggen, and Teva Neuroscience.

References

- Bayer Healthcare Pharmaceuticals. (2008) Betaseron (interferon beta-1b) prescribing information. Bayer Healthcare Pharmaceuticals, Inc: Montville, NJ.
- Bertolotto, A., Malucchi, S., Sala, A., Orefice, G., Carrieri, P.B., Capobianco, M. *et al.* (2002) Differential effects of three interferon betas on neutralising antibodies in patients with multiple sclerosis: a follow up study in an independent laboratory. *J Neurol Neurosurg Psychiatry* 73: 148–153.
- Biogen Idec. (2008) Avonex (intramuscular interferon beta-1a) prescribing information. Biogen Idec, Inc: Cambridge, MA.

- Birnbaum, G., Cree, B., Altafullah, I., Zinser, M. and Reder, A.T. (2008) Combining beta interferon and atorvastatin may increase disease activity in multiple sclerosis. *Neurology*, DOI: 10.1212/01.wnl.0000319698.40024.1c.
- Boskovic, R., Wide, R., Wolpin, J., Bauer, D.J. and Koren, G. (2005) The reproductive effects of beta interferon therapy in pregnancy. A longitudinal cohort. *Neurology* 65: 807–811.
- Clanet, M., Kappos, L., Hartung, H.P., Hohlfeld, R. and the European Interferon-1a Dose-Comparison Study Investigators (2004) Interferon 1a in relapsing multiple sclerosis: four-year extension of the European IFN 1a Dose-Comparison Study. *Mult Scler* 10: 139–144.
- Clanet, M., Radue, E.W., Kappos, L., Hartung, H.P., Hohlfeld, R., Sandberg-Wollheim, M. *et al.* (2002) A randomized, double-blind, dose-comparison study of weekly interferon-beta 1a in relapsing MS. *Neurology* 59: 1507–1517.
- Cohen, J.A., Calabresi, P.A., Chakraborty, S., Edwards, K.R., Eikenhorst, T., Felton, W.L.III. *et al.* for the ACT Investigators. (2008) Avonex combination trial in relapsing–remitting MS: rationale, design and baseline data. *Mult Scler* 14: 370–382.
- Cohen, J.A., Imrey, P.B., Calabresi, P.A., Edwards, K.R., Eikenhorst, T., Felton, W.L.III. *et al.* for the ACT Investigators. (2009) Results of the Avonex Combination Trial (ACT) in relapsing–remitting MS. *Neurology* 72: 535–541.
- Durelli, L., Verdun, E., Barbero, P., Bergui, M., Versino, E., Ghezzi, A. *et al.* (2002) Every-other-day interferon beta-1b versus once-weekly interferon beta-1a for multiple sclerosis: results of a 2-year prospective randomised multicentre study (INCOMIN). *Lancet* 359: 1453–1460.
- EMD Serono. (2008) Rebif (subcutaneous interferon beta-1a) prescribing information. EMD Serono, Inc: Rockland, MA.
- Foulds, P., Rickman, S., Glick, G., Onigman, T. and Hyde, R. (2010) Pregnancy outcomes from the AVONEX® (interferon beta-1a) Pregnancy Exposure Registry. *Mult Scler* 16: S7, abstract 894.
- Francis, G.S., Rice, G.P. and Alsop, J.C. (2005 Jul 12) PRISMS Study Group; Interferon beta-1a in MS: results following development of neutralizing antibodies in PRISMS. *Neurology* 65(1): 48–55.
- Gold, R. (2008) Combination therapies in multiple sclerosis. *J Neurol* 255(Suppl. 1): 51–60.
- Haas, J. and Firzloff, M. (2005) Twenty-four-month comparison of immunomodulatory treatments—a retrospective open label study in 308 RRMS patients treated with beta interferons or glatiramer acetate (Copaxone). *Eur J Neurol* 12: 425–431.
- Havrdova, E., Zivadinov, R., Krasensky, J., Dwyer, M.G., Novakova, I., Dolzal, O. *et al.* (2009) Randomized study of interferon beta-1a, low-dose azathioprine, and low-dose corticosteroids in multiple sclerosis. *Mult Scler*, DOI: 10.1177/1352458509105229.
- Hurwitz, B.J., Arnason, B., Bigley, K., Coyle, P., Goodin, D., Kaba, S. *et al.* (2008) Tolerability and safety profile of 12- to 28-week treatment with interferon beta-1b 250 and 500 microg QOD in patients with relapsing–remitting multiple sclerosis: a multicenter, randomized, double-blind, parallel-group pilot study. *Clin Ther* 30: 1102–1112.
- IFNB Multiple Sclerosis Study Group. (1993) Interferon beta-1b is effective in relapsing–remitting multiple sclerosis. I. Clinical results of a multicenter, randomized, double-blind, placebo-controlled trial. *Neurology* 43: 655–661.
- IFNB Multiple Sclerosis Study Group and the University of British Columbia MS/MRI Analysis Group. (1995) Interferon beta-1b in the treatment of multiple sclerosis: final outcome of the randomized controlled trial. *Neurology* 45: 1277–1285.
- IFNB Multiple Sclerosis Study Group and the University of British Columbia MS/MRI Analysis Group. (1996) Neutralizing antibodies during treatment of multiple sclerosis with interferon beta-1b: experience during the first three years. *Neurology* 47: 889–894.
- Jacobs, L.D., Cookfair, D.L., Rudick, R.A., Herndon, R.M., Richert, J.R., Salazar, A.M. *et al.* (1996) Intramuscular interferon beta-1a for disease progression in relapsing multiple sclerosis. *Ann Neurol* 39: 285–294.
- Khan, O.A., Tselis, A.C., Kamholz, J.A., Garbern, J.Y., Lewis, R.A. and Lisak, R.P. (2001) A prospective, open label treatment trial to compare the effect of IFNbeta-1a (Avonex), IFNbeta-1b (Betaferon), and glatiramer acetate (Copaxone) on the relapse rate in relapsing remitting multiple sclerosis: results after 18 months of therapy. *Mult Scler* 7: 349–353.
- Koch-Henriksen, N., Sørensen, P.S., Christensen, T., Frederiksen, J., Ravnborg, M., Jensen, K. *et al.* (2006) A randomized study of 2 interferon-beta treatments in relapsing remitting multiple sclerosis. *Neurology* 66: 1056–1060.
- LePage, E. and Edan, G. (2009) Long-term experience with induction treatment regimens in multiple sclerosis. *J Neurol Sci* 277(Suppl. 1): S46–S49.
- Limmroth, V., Malessa, R., Zettl, U.K., Koehler, J., Japp, G., Haller, P. *et al.* for the QUASIMS Study Group. (2007) Quality Assessment in Multiple Sclerosis Therapy (QUASIMS): A comparison of interferon beta therapies for relapsing–remitting multiple sclerosis. *J Neurol* 254: 67–77.
- Limmroth, V. and Putzki, N. (2005) High dose, frequently administered interferon beta. *J Neurol Sci* 228: 240–242.
- Limmroth, V., Werneck, L., Nagels, G., Lugaes, A., Kalski, G. and Wernsdörfer, C. (2005) Results from

the Global QUASIMS Study: comparison of the efficacy and tolerability of interferon beta (IFN β) products for the treatment of relapsing multiple sclerosis in Australia, Brazil, Belgium, Italy and Slovakia [abstract]. *Neurology* 64(Suppl. 1): A325–A326.

McDonald, W.I., Compston, A., Edan, G., Goodkin, D., Hartung, H.P., Lublin, F.D. *et al.* (2001) Recommended diagnostic criteria for multiple sclerosis: Guidelines from the International Panel on the diagnosis of multiple sclerosis. *Ann Neurol* 50: 121–127.

Milanese, C., La Mantia, L., Palumbo, R., Martinelli, V., Murialdo, A., Zaffaroni, M. *et al.* (2003) A post-marketing study on interferon β 1b and 1a treatment in relapsing–remitting multiple sclerosis: different response in drop-outs and treated patients. *J Neurol Neurosurg Psychiatry* 74: 1689–1692.

Minagar, A. and Murray, T.J. for the PROOF Study Investigators. (2008) Efficacy and tolerability of intramuscular interferon beta-1a compared with subcutaneous interferon beta-1a in relapsing MS: results from PROOF. *Curr Med Res Opin* 24: 1049–1055.

Moses, H. and Brandes, D.W. (2008) Managing adverse effects of disease-modifying agents used for treatment of multiple sclerosis. *Curr Med Res Opin* 24: 2679–2690.

Munschauer, F.E.III. and Kinkel, R.P. (1997) Managing side effects of interferon-beta in patients with relapsing–remitting multiple sclerosis. *Clin Ther* 19: 883–893.

O'Connor, P., Filippi, M., Arnason, B., Comi, G., Cook, S., Goodin, D. *et al.* (2009) 250 μ g or 500 μ g interferon beta-1b versus 20 mg glatiramer acetate in relapsing–remitting multiple sclerosis: a prospective, randomized, multicenter study. *Lancet Neurol* 10: 889–890.

Oger, J., Francis, G. and Chang, P. on behalf of the PRISMS Study Group. (2005) Prospective assessment of changing from placebo to IFN beta-1a in relapsing MS: the PRISMS Study. *J Neurol Sci* 237: 4552.

Panitch, H., Goodin, D., Francis, G., Chang, P., Coyle, P., O'Connor, P. *et al.* (2005) Benefits of high-dose, high-frequency interferon beta-1a in relapsing–remitting multiple sclerosis are sustained to 16 months: final comparative results of the EVIDENCE trial. *J Neurol Sci* 239: 67–74.

Panitch, H., Goodin, D.S., Francis, G., Chang, P., Coyle, P.K., O'Connor, P. *et al.* (2002) Randomized, comparative study of interferon β -1a treatment regimens in MS. The EVIDENCE trial. *Neurology* 59: 1496–1506.

Patten, S.B., Beck, C.A., Williams, J.V.A., Barbui, C. and Letz, L.M. (2003) Major depression in multiple sclerosis: a population-based perspective. *Neurology* 61: 1524–1527.

PRISMS (Prevention of Relapses and Disability by Interferon β -1a Subcutaneously in Multiple Sclerosis) Study Group (1998) Randomised double-blind

placebo-controlled study of interferon β -1a in relapsing–remitting multiple sclerosis. *Lancet* 352: 1498–1504.

PRISMS (Prevention of Relapses and Disability by Interferon β -1a Subcutaneously in Multiple Sclerosis) Study Group and The University of British Columbia MS/MRI Analysis Group. (2001) PRISMS-4: long-term efficacy of interferon- β -1a in relapsing MS. *Neurology* 56: 1628–1636.

Pulicken, M., Bash, C.N., Costello, K., Said, A., Cuffari, C., Wilterdink, J.L. *et al.* (2005) Optimization of the safety and efficacy of interferon beta 1b and azathioprine combination therapy in multiple sclerosis. *Mult Scler* 11: 169–174.

Ravnborg, M., Sorensen, P.S., Andersson, M., Celius, E.G., Elovaara, I., Jongen, P. *et al.* (2009) A multi-center, double blind, randomized, placebo-controlled, parallel group trial investigating methylprednisolone (MP) in combination with interferon- β -1a i.m. for the treatment of relapsing–remitting multiple sclerosis (RRMS). Poster presented at the 61st Annual Meeting of the American Academy of Neurology. 25 April–2 May 2009, Seattle, WA; Poster LB.002.

Río, J., Tintoré, M., Nos, C., Téllez, N., Galán, I. and Montalban, X. (2006) Interferon beta in relapsing–remitting multiple sclerosis. An eight years experience in a specialist multiple sclerosis centre. *J Neurol* 252: 795–800.

Romero-López, J., Seijo-Martinez, M., Del Campo, V., Amigo-Jorin, M.C., Arias, M., Cortes-Laino, J.A. *et al.* (2003) [Experience in the treatment of multiple sclerosis with interferon beta in Galicia]. *Rev Neurol* 37: 1001–1004, in Spanish.

Rudick, R.A., Stuart, W.H., Calabresi, P.A., Confavreux, C., Galetta, S.L., Radue, E. *et al.* (2006) Natalizumab plus interferon beta-1a for relapsing multiple sclerosis. *N Engl J Med* 354: 911–923.

Sandberg-Wollheim, M., Frank, D., Goodwin, T.M., Giesser, B., Lopez-Bresnahan, M., Stam-Moraga, M. *et al.* (2005) Pregnancy outcomes during treatment with interferon beta-1a in patients with multiple sclerosis. *Neurology* 65: 802–806.

Sørensen *et al.* (2006).

Sorensen, P.S., Lycke, J., Eralinna, J.-P., Edland, A., Wu, X., Frederiksen, J. *et al.* (2010) No beneficial effect of simvastatin as add-on therapy to interferon-beta-1a for the treatment of relapsing–remitting multiple sclerosis: Results of a large double blind, randomised, placebo controlled trial. *Mult Scler* 16: S7, abstract 134.

Sorensen, P.S., Mellgren, S.I., Svenningsson, A., Elovaara, I., Frederiksen, J.L., Beiske, A.G. *et al.* (2009) NORdic trial of oral methylprednisolone as add-on therapy to interferon beta-1a for treatment of relapsing–remitting multiple sclerosis (NORMIMS study): a randomized, placebo-controlled trial. *Lancet Neurol* 8: 519–529.

Stuve, O., Youssef, S., Weber, M.S., Nessler, S., von Budingen, H., Hemmer, B. *et al.* (2006) Immunomodulatory synergy by combination of atorvastatin and glatiramer acetate in treatment of CNS autoimmunity. *J Clin Invest* 116: 1037–1044.

Trojano, M., Liguori, M., Paolicelli, D., Zimatore, G.B., De Robertis, F., Avolio, C. *et al.* (2003) Interferon beta in relapsing–remitting multiple sclerosis: an independent postmarketing study in southern Italy. *Mult Scler* 9: 451–457.

Weinstock-Guttman, B., Bhasi, K., Badgett, D., Tamaño-Blanco, M., Minhas, M., Feichter, J. *et al.* (2008) Genomic effects of once-weekly, intramuscular

interferon-beta1a treatment after the first dose and on chronic dosing: Relationships to 5-year clinical outcomes in multiple sclerosis patients. *J Neuroimmunol* 2005: 113–125.

Ytterberg, C., Johansson, S., Andersson, M., Olsson, D., Link, H., Holmqvist, L.W. *et al.* (2007) Combination therapy with interferon-beta and glatiramer acetate in multiple sclerosis. *Acta Neurol Scand* 116: 96–99.

Zang, Y., Hong, J., Robinson, R., Lia, S., Rivera, V.M., Zhang, J.Z. *et al.* (2003) Immune regulatory properties and interactions of Copolymer-1 and beta-interferon 1a in multiple sclerosis. *J Neuroimmunol* 137: 144–153.

Visit SAGE journals online
<http://tan.sagepub.com>

SAGE JOURNALS
Online