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BRIEF REPORT

Standard Dose Weekly Intramuscular Beta Interferon-1a May Be Inadequate for Some Patients with Multiple Sclerosis: A 19-Year Clinical Experience Using Twice a Week Dosage

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ABSTRACT

Introduction: Results from several clinical trials suggest there is a dose–response effect for beta interferon-1a (INFβ1a) in multiple sclerosis (MS).

Methods: Our objective was to confirm these results through a retrospective analysis of patients with MS who had breakthrough disease (BD) on intramuscular (IM) INFβ1a (Avonex®) once per week (QW), who were switched to twice per week (BIW) IM INFβ1a between 1995 and 2015. The primary outcome measure was no further BD for at least 24 months. A secondary outcome measure was decrease in mean percentage of disease activity over time. BD was defined as continued relapses, new T2 or enhanced lesions on magnetic resonance imaging (MRI) of the brain, or worsening of the Expanded Disability Status Scale (EDSS) or the neurological examination.

Results: Among 92 patients on QW IM INFβ1a, 53 patients with BD were switched to BIW IM INFβ1a. Of these 53 patients, 44 had adequate follow-up for at least 2 years. Twenty-three of these had no further BD for 24 months or more (range 24–192 months). Beta interferon neutralizing antibody testing was negative in 19 patients. An intent-to-treat analysis of the uncensored data from 52 switched patients also supported a treatment benefit.

Conclusion: For patients with MS having breakthrough disease on QW INFβ1a, switching to more frequently administered INFβ may be an option. Advantages to using IM INFβ1a for this include no skin reactions and a lower incidence of neutralizing antibodies. Further pragmatic, observational, larger-group studies comparing treatment with Avonex® and higher dosed IM INFβ1a, such as the recently FDA-approved IM peginterferon beta-1a, may be indicated.

Keywords: Multiple sclerosis; Intramuscular beta interferon-1a; Twice a week dosage; Retrospective review

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Key Summary Points

In treating multiple sclerosis with beta interferon-1a, both dose and frequency of administration are important.

The standard dose of intramuscular (IM) beta interferon-1a may be too low for some patients and switching to a higher dose preparation of beta interferon-1a could ameliorate breakthrough disease activity.

In the past, currently available higher dose formulations of beta interferon-1a required switching to subcutaneous administration which is concerning for higher incidence of cutaneous side effects and neutralizing antibodies.

Our retrospective non-randomized, clinical data analysis provides limited evidence that increasing the frequency of IM beta interferon-1a to twice a week can ameliorate breakthrough disease activity in some cases. While we do not encourage the off-label use of higher doses of the standard preparation of IM beta interferon-1a, the recently FDA-approved IM preparation of peginterferon beta-1a, which gives a higher dose of beta interferon-1a over a 2-week period than weekly IM beta interferon-1a, would then be a commercially available option.

INTRODUCTION

Results from three phase III, double-blind, placebo-controlled trials [1–4], two prospective randomized single-blinded studies [5, 6], one prospective randomized non-blinded multicenter study [7], two prospective, non-randomized non-blinded studies [8, 9], and one retrospective, non-randomized, non-blinded, multicenter study [10] suggest there is a dose–response effect for beta interferon treatment in multiple sclerosis. Both the dose and the frequency of administration may be important [11, 12]. A few studies have reported on the effects of reducing dose or frequency of administration of beta interferon [10], increasing beta interferon dose and frequency [13], or comparing higher dosed beta interferon as first- or second-line treatment [14]. However, these changes in dose and frequency primarily involved switching to a different beta interferon preparation.

Therefore, breakthrough disease in patients with MS using the standard dose of IM beta interferon-1a (Avonex®) is quite common. There are now several treatment options for these patients, including switching to oral agents, such as dimethyl fumarate, fingolimod, siponimod, teriflunomide, or cladribine, or infusion therapy such as alemtuzumab, ocrelizumab, ofatumumab, or natalizumab. It has been our experience, however, that there is a subset of patients who are wary of the risk of more serious side effects with these agents and refuse to consider treatment with them. In addition, for women of child-bearing age who are planning a family, treatment options are more limited and certain agents such as teriflunomide and cladribine would not be appropriate. Because of the studies cited above, it might be advantageous for these patients if they were treated with an increased dose of beta interferon-1a, an agent they are familiar with, such as subcutaneous beta interferon-1a (Rebif® or Plegridy®). We have found this to be successful with some patients; however, it has been our experience that many patients making such a switch do not tolerate the subcutaneous side effects of these agents. Many years ago, when treatment options were more limited, we began to treat patients with breakthrough disease on weekly IM beta interferon-1a with off-label twice weekly dosing in the MS clinic at the Veterans Administration West Los Angeles Medical Center, and noted disease stability for extended periods in many. This was not a designed clinical trial, but was permitted by the VA pharmacy service in the interest of patient care. In order to assess the outcomes of this innovative practice and to assess the feasibility of future human subject research, we have conducted a retrospective analysis of

information compiled in VA medical records, focusing on clinical and imaging markers of disease activity, skin reactions, and neutralizing antibodies.

METHODS

This is a retrospective, non-randomized, clinical data analysis of the effectiveness of switching patients with multiple sclerosis (MS) with breakthrough disease on 30 μg of IM INFβ1a (Avonex®) once per week (QW) to 30 μg IM twice a week (BIW). Patients with both relapsing–remitting (RR) and secondary progressive (SP) multiple sclerosis being followed in the VA West Los Angeles Medical Center MS clinic between 1995 and 2014 who had breakthrough disease while being treated with 30 μg of IM INFβ1a QW were offered a switch in treatment to 30 μg of IM INFβ1a BIW. Patients were followed in the clinic an average of every 4 months. At each visit an interval history of any relapses and progression of symptoms was taken. The Incapacity Status Scale [15], the Functional Systems Scale, the Expanded Disability Status Scale (EDSS) [16], and a proprietary graded neurological examination were also obtained. The EDSS was determined by the unblinded treating neurologist for all the patients, who is a certified rater and has performed EDSS determinations in multiple clinical trials of MS in the past. An annual MRI of the brain using the Consortium of MS Centers contrast-enhanced MS protocol [17] was obtained in most patients. Conversion from RR to SP MS was defined as a significant worsening of EDSS or the graded neurological exam not related to a relapse that was confirmed at the next clinic visit 4 months later. There was no matched comparator group. There was no blinded examiner. MRIs were read by blinded neuroradiologists. A blinded biostatistician performed the statistical analyses. By 2014, 53 patients had accepted a switch to BIW IM beta interferon-1a treatment.

The primary outcome measure was no further breakthrough disease for at least 24 months. Breakthrough disease was defined as any continued clinical relapses, any new T2 or T1-enhanced lesions on MRI, significant worsening of baseline EDSS as defined in other MS studies [2, 18], or significant worsening on a graded neurological examination. A secondary outcome measure was an intent-to-treat analysis, where the dependent variable was the average number of disease activity events (relapses, new MRI lesions, episodes of significant EDSS or neurological exam worsening) and the independent variable was episodes in time over a 3-year period, either every month, half year, or quarter year.

Statistical Analysis

Descriptive statistics were generated for all variables. Student's *t* test was used to analyze continuous variables between patients who were stable on BIW INFβ1a for 24 months and those who were not. Chi-square test was used for categorical variables and Fisher's exact test for categorical variables with small cell sizes. In addition, an intent-to-treat analysis of the 53 patients switched to BIW INFβ1a was conducted. One patient was lost to follow-up before any data could be collected. On the remaining 52 patients, a linear regression model was used. All computations were done using SAS 9.4. The statistical analysis described was supported by the NIH/National Center for Advancing Translational Science (NCATS) UCLA CTSI Grant Number UL1TR001881.

Standard Protocol Approval, Registration, and Patient Consents

This study was submitted for Human Research Protection Program (HRPP) determination of non-human research/QI or other activity not requiring internal review board (IRB) approval. It was determined by the administrator of IRB00001531 VA Greater Los Angeles Healthcare System IRB #1 A as being a review of a clinical undertaking to treat MS and drive MS into remission by increasing the administration of an Federal Drug Administration (FDA)-approved medication in several patients, analyzing the clinical data in a systematic aggregate manner to determine whether the successful

outcome in these patients was more than anecdotal and warrants the undertaking of more systematic research. The HRPP agreed that the endeavors up to this point were clinically driven, endorsed this work as a write-up of clinical experiences suggesting the feasibility of future research, and is not human subject research per se. In light of this, it was also determined that participant consent was not required.

RESULTS

Ninety-two patients, 30 with RR and 62 with active SP MS were started on IM INFβ1a from 1995 to 2014. This was a non-selected group of patients whose characteristics at the time of onset of QW treatment are depicted in Table 1. As this was a VA facility, 71 of these patients were male. Of these 92 patients, 6 were lost to follow-up, 10 had QW INFβ1a discontinued because of side effects, 2 were discontinued for other reasons, 15 (16%) were stable on QW INFβ1a for between 3 and 14 years, and 58 patients (63%) had breakthrough disease. Fifty-three patients with breakthrough disease, 10 with RR and 43 with SP disease, consented to be switched to BIW IM INFβ1a between 1999 and 2014. There was adequate follow-up for at least 2 years in 44 of these patients. Eight of the patients without a 2-year follow-up were included in the subsequent intent-to-treat analysis.

The duration of QW IM INFβ1a treatment for these 44 patients prior to the switch was

Table 1 Patient characteristics

	Entire cohort at onset of QW interferon treatment (*N* = 92)	**At time of switch to BIW interferon and stable after switching (*N* = 23)**	**At time of switch to BIW interferon and not stable after switching (*N* = 17)**
Mean age (years) and age range	51 (30–86)	50 (30–75)	48 (38–58)
Mean disease duration (years) and range	16 (0.2–54)	16 (1–36)	14 (2–33)
Sex			
Female	21 (23%)	4 (17%)	4 (14%)
Male	71 (77%)	19 (83%)	13 (76%)
Race/ethnicity			
Caucasian	68 (74%)	19 (83%)	12 (71%)
African American	19 (21%)	3 (13%)	5 (29%)
Hispanic	3 (3%)	1	0
Oriental	1	0	0
American Indian	1	0	0
Phase of disease			
Relapsing–remitting	30	6	7
Secondary progressive	62	17	10

between 1 and 96 months. Annual brain MRIs were obtained in 77% of these patients. Of these 44 patients, 23 patients (52%) had no further breakthrough disease activity for 24 months or more (range 24–192 months). Twenty patients were stable for 36 months or more, 15 for 48 or more months, and 10 for 60 or more months. Seventeen patients had new disease activity within 24 months after switching treatment and were defined as not stable on this regimen. Four patients could not tolerate the increase in dose. Of those who were not stable on the higher dose, 4 continued to have relapses, 10 had significant worsening on the neurological exam, 4 had worsening on the EDSS, and 3 had new lesions on the MRI.

Of the 16 RR patients who subsequently went on BIW INFβ treatment, 5 remained RR MS, 6 converted to SP MS during QW INFβ1a treatment, 5 converted to SP MS during BIW treatment, 4 of which failed to remain stable on BIW treatment for 24 months, and 1 converted to SP MS after a period of stability on BIW INFβ1a of 31 months.

INFβ neutralizing antibody testing was performed on 19 patients while on BIW dosing, and none of these patients had consistently elevated titers on two determinations. One patient treated with QW dosing was consistently positive, but this patient had previously been exposed to subcutaneous interferon beta-1b. INFβ neutralizing antibody testing was performed on 11 other patients while they were on QW dosing and all tests were negative.

An attempt was made to identify patient characteristics that would distinguish those whose disease stabilized on BIW INFβ1a from those whose disease did not (Table 2). Among all the parameters evaluated the only significant difference was the number of relapses in the 2 years prior to onset of treatment with weekly INFβ1a. Patients not stabilized on subsequent BIW INFβ1a had a higher number of relapses during this period than those who were. However, the number of relapses over a similar period prior to switching to twice per week INFβ1a was not significantly different between the two groups.

Poor compliance on BIW INFβ1a was noted in the records of six patients. Nine patients were

Table 2 Analysis of patient characteristics distinguishing success or failure with BIW INFβ1a treatment

	Stable on BIW interferon	Active on BIW interferon	*P* value
Age at onset of MS, $N = 40$ mean (SD)	33.9 (12.5)	33.4 (9.6)	0.955
Sex, $N = 40$			
Male (%)	19 (82.6)	12 (70.6)	0.456
Female (%)	4 (17.4)	5 (29.4)	
Race, $N = 40$			
African American (%)	3 (13)	5 (29.4)	0.333
Hispanic (%)	1 (4.3)	0	
White (%)	19 (82.6)	12 (70.6)	
Duration of disease prior to QW INFβ, $N = 40$			
Mean years (SD)	16 (11.5)	13.7 (10.3)	0.506
Type of MS disease, $N = 40$			
RR (%)	6 (26.1)	7 (41.2)	0.718
SP (%)	17 (73.9)	10 (58.8)	
Age at start of QW INFβ, $N = 40$ mean (SD)	50.3 (10.4)	47.8 (8.7)	0.410
Age at start of BIW INFβ, $N = 40$ mean (SD)	52.1 (10.4)	49.8 (8.4)	0.457
Duration of disease prior to BIW INFβ, $N = 40$			
Mean years (SD)	17.8 (12)	13.7 (10.3)	0.506
Type of MS disease at start of BIW INFβ, $N = 40$			
RR (%)	5 (21.7)	7 (41.2)	0.715
SP (%)	18 (78.3)	10 (58.8)	
EDSS score at start of QW INFβ, $N = 40$ mean (SD)	5 (1.6)	5.3 (1.4)	0.575
Number of relapses in the 2 years prior to start of QW INFβ, $N = 40$			

Table 2 continued

	Stable on BIW interferon	Active on BIW interferon	*P* value
Mean (SD)	1 (1.2)	2.1 (1.6)	**0.020**
Number of relapses in the 2 years prior to start of BIW INFβ, *N* = 40			
Mean (SD)	1.3 (1.5)	1.9 (1.4)	0.254
EDSS score at start of BIW INFβ, *N* = 40 mean (SD)	5.3 (1.6)	5.4 (1.4)	0.804
Stable on QW INFβ prior to switch to BIW, *N* = 40			
Yes (%)	5 (21.7)	3 (17.6)	0.999
No (%)	18 (78.3)	14 (82.4)	
Duration of QW stability prior to switch to BIW, *N* = 8			
Mean years (SD)	4.2 (3.5)	5.7 (2.1)	0.540
Worsening EDSS as reason for BIW INFβ, *N* = 40			
Yes (%)	9 (39.1)	5 (29.4)	0.763
No (%)	14 (60.9)	12 (70.6)	
Worsening neurological exam as reason for BIW INFβ, *N* = 40			
Yes (%)	9 (39.1)	10 (58.8)	0.361
No (%)	14 (60.9)	7 (41.2)	

lost to follow-up less than 2 years after starting BIW dosing. Because of this an intent-to-treat analysis of 52 patients switched to BIW INFβ1a was conducted. The regression analysis showed that the mean percentage of disease activity decreased among the patients being followed over a 3-year period on a monthly (estimated slope = − 0.0023, *p* value = 0.0002), half yearly (estimated slope = − 0.0829, *p* value = 0.04), and quarter yearly (estimated slope = − 0.0204, *p* value = 0.0033) basis.

DISCUSSION

This is the retrospective experience of relapsing–remitting and secondary progressive patients with MS treated with QW intramuscular beta interferon-1a once per week at one VA MS center for up to 20 years. Among 44 patients with breakthrough disease switched to BIW beta interferon-1a and followed for at least 2 years, 52% had no evidence of further breakthrough disease. The majority of these patients were stable for a period of 4 years or more, the longest being 17 years. The only factor that differentiated those patients who were stabilized on the higher dose from those that were not was the number of relapses in the 2 years prior to initially starting QW beta interferon-1a. The intent-to-treat analysis showed a statistically significant reduction in disease activity over a 3-year period and lends further support for a beneficial effect of BIW beta interferon-1a in some patients with breakthrough disease on the standard QW dose.

This study is unique for several reasons. It reports on the real-world experience of using intramuscular beta interferon-1a to treat MS at one VA MS center where access to MS medications is not limited by third-party payers. Patients were followed for extended periods of time, up to 20 years. It includes all patients without restrictions on age, race, duration of disease, degree of disability, or whether the patients had relapsing–remitting or secondary progressive disease. In addition, this is the first reported study of the efficacy and tolerability of increasing the dose of intramuscular beta interferon-1a (Avonex®) to twice per week dosing in patients with MS and breakthrough disease on the standard dose of once per week.

This study supports the conclusion that the standard dose of IM beta interferon-1a may be too low for some patients, and the conclusions of numerous previous studies [1–10] of a dose–response relationship for the treatment of MS with beta interferon. Both dose and frequency of administration seem to be important [11, 12]. There have been several reported studies which have not found a dose–response effect for beta interferon in MS [13, 14, 18–24]. In the only one that was a randomized, double-blind, phase III trial, IM beta interferon-1a at a dose of 60 μg once per week was compared with the standard dose of 30 μg once per week in 802 patients followed for at least 36 months. There

was no significant difference in the primary endpoint of disability progression on the EDSS, or in patient-reported relapses, or in multiple MRI lesion parameters [18]. However, this study did not address the possibility that the frequency of administration of beta interferon administration per week may also be important in maximizing its efficacy in the treatment of MS [11, 12]. There is a significant reduction of indicators of beta interferon activity-1a in healthy volunteers as early as 4 days after subcutaneous and intramuscular administration [25]. Additionally, the study leaves open the question of whether increasing the dose in the subset of patients failing on the standard dose would be beneficial. One other controlled, prospective, randomized study compared treatment with 22 μg of subcutaneous beta interferon-1a once per week with 250 μg of subcutaneous beta interferon-1b every other day [20]. There was no significant difference in the annual relapse rate, time to first relapse, time to sustained progression on the EDSS, or new or enlarging T2 lesions on MRI, although there was a trend favoring beta interferon-1b in the MRI data. However, the follow-up period for this study was short. In addition, the main cause for dropping out while taking the lower dose was for treatment failure, and half of these patients were subsequently treated with higher dose beta interferon preparations.

A few previous studies have reported on the effect of altering the dose of frequently administered beta interferon in MS treatment. In a retrospective analysis of patients with relapsing–remitting MS whose dose of subcutaneous beta interferon-1a or -1b was reduced from three times per week to twice per week, or were switched to IM beta interferon-1a once per week because of side effects, there was an increase in relapse rate, MRI activity, or both [10].

In the current study we made an attempt to identify the characteristics of patients with breakthrough disease on weekly beta interferon-1a who respond to twice weekly administration. The only factor that reached significance was a lower number of relapses in the 2 years prior to starting any beta interferon treatment in responders. A higher number of relapses over a 2-year period may be an indication of more active MS disease in these patients. This may indicate that patients with more active disease initially are less likely to respond to a higher dose of beta interferon. However, Prosperini et al. [10] found that patients with MS were more likely to have increased disease activity when their dose of beta interferon was reduced if they were younger or had a higher annual relapse rate prior to starting beta interferon. This suggests that patients with a higher baseline disease activity are more likely to respond in an unfavorable way to reductions in dose of beta interferon.

Significant elevations in neutralizing antibodies to beta interferon were not found in any of the subset of patients treated with twice per week IM beta interferon-1a whose serum was assayed in the current study. Neutralizing antibodies to beta interferon were monitored in a number of previous studies [1–3, 7, 19–21, 23]. Persistently elevated neutralizing antibodies were found in 14.3–30% of patients with MS treated with subcutaneous beta interferon-1b [7, 23] or beta interferon-1a [2, 3, 19], while the incidence in patients treated with intramuscular beta interferon-1a is much lower, 0–6% [3, 7, 19, 23]. In some of these studies patients positive for neutralizing antibodies were found to have a higher relapse rate [2, 20], more disease progression [19], and increased numbers or volume of gadolinium-enhanced or T2 lesions on their MRIs [2, 3, 19]. The mitigating effect of neutralizing antibodies on the efficacy of beta interferon treatment in MS has also been well substantiated by other reports [11, 26].

The present study is deficient in many respects. It is retrospective, non-randomized, open-label, and selective in being VA-based with a much higher number of male patients than other studies. The intent-to-treat analysis lacks a comparison group of patients with breakthrough disease who were not switched to BIW INFβ1a.

In the intent-to-treat analysis, 10 patients were lost to follow-up over the 3-year period. Mean EDSS at the start of treatment was high as many secondary progressive patients were included, but the sample size was too small to do individual cohort analysis. Also, an argument can be raised that it only indicates an

expected regression to the mean of disease activity in a patient population with MS. As a retrospective study confounding factors can be numerous.

Despite these deficiencies, this study suggests that for patients with MS having breakthrough disease on standard dose IM beta interferon-1a, switching to a higher dose of more frequently administered beta interferon may be an option, especially in patients who are tolerating IM beta interferon-1a treatment well and resistive to a change in treatment to another agent, or who are afraid of the possibility of adverse side effects with other agents. However, the present study also suggests that patients with more severe clinical disease activity, especially early in their disease course, are less likely to respond to an alteration in dose of beta interferon. This study included a large proportion of patients with secondary progressive MS, which calls into question its relevancy for the present day. One would now not consider beta interferon a treatment of choice for secondary progressive MS. However, we would argue the results of this study are consistent with those of a number of previous studies reviewed in two publications [11, 12] involving exclusively patients with clinically active relapsing–remitting MS, where dose and frequency of beta interferon treatment have been found to be important factors for its efficacy.

CONCLUSIONS

Because of the track record of safety for beta interferon over several decades, patients with MS who are started on this form of treatment should have an adequate trial, which includes adequate dosage. For patients who have breakthrough disease on the standard dose of IM beta interferon-1a, a switch to a higher dosed beta interferon preparation should be considered. There are advantages to using more frequently administered IM beta interferon-1a for this. It avoids the introduction of a new class of side effects, namely skin reactions, and it reduces the likelihood of inducing neutralizing antibodies to beta interferon. Despite this, we do not want to encourage the off-label use of higher doses of the standard preparation of IM beta interferon-1a. Third-party payment approval outside a health maintenance organization environment for a change to twice a week IM beta interferon-1a is also likely to be a major obstacle. However, the recent FDA approval of an IM preparation of peginterferon beta-1a, which gives a higher dose of beta interferon-1a over a 2-week period than weekly IM beta interferon-1a, may provide a viable option. A prospective, blinded, randomized trial comparing once per week IM beta interferon-1a with peginterferon beta-1a every 2 weeks may lend further justification for this type of treatment change.

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Compliance with Ethics Guidelines A VA HRPP determination was made that this endeavor was an evaluation of a clinical undertaking to assess the feasibility of more systematic research in the future, and a report of clinical experiences that did not require formal IRB approval.

Data Availability The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable written request.

REFERENCES

1. The IFN beta Multiple Sclerosis Study Group. Interferon beta-1b is effective in relapsing-remitting multiple sclerosis: I. Clinical results of a multicenter, randomized, double-blind, placebo-controlled trial. Neurology. 1993;43:655–61.

2. PRISMS Study Group. University of British Columbia MS/MRI Analysis Group. PRISMS-4. Long-term efficacy of interferon beta-1a in relapsing MS. Neurology. 2001;56:1628–36.

3. Schwid SR, Panitch HS. Full results of the evidence of interferon dose-response-European North American comparative efficacy (EVIDENCE) study: a multicenter, randomized, assessor-blinded comparison of low-dose weekly versus high-dose, high-frequency interferon beta-1a for relapsing multiple sclerosis. Clin Ther. 2007;29:2031–48.

4. Panitch H, Goodin D, et al. 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. 2005;239:67–74.

5. Calabrese M, Bernardi V, Atzori M, el al. Effect of disease-modifying drugs on cortical lesions and atrophy in relapsing-remitting multiple sclerosis. Mult Scler. 2012;18:418–24.

6. Etemadifar M, Janghorbani M, Shaygannejad V. Comparison of Betaferon, Avonex, and Rebif in treatment of relapsing-remitting multiple sclerosis. Acta Neurol Scand. 2006;113:283–7.

7. Durelli L, Verdun E, Barbero P, el al. Every-other-day interferon beta-1b versus once-weekly interferon beta-1a for multiple sclerosis: results of a 2-year prospective randomized multicenter study (INCOMIN). Lancet. 2002;359:1453–60.

8. Kan OA, Tselis AC, Kamholz JA, et al. A prospective, open-label treatment trial to compare the effect of IFN beta-1a (Avonex), IFNbeta-1b (Betaseron), and glatiramer acetate (Copaxone) on the relapse rate in relapsing-remitting multiple sclerosis. Eur J Neurol. 2001;8:141–8.

9. Cocco E, Marchi P, Floris G, et al. Effect of dose and frequency of interferon beta-1a administration, on clinical and magnetic resonance imaging parameters in relapsing-remitting multiple sclerosis. Func Neurol. 2006;21:145–9.

10. Prosperini L, Mancinelli CR, Pozzilli C, et al. From high- to low-frequency administered interferon-beta for multiple sclerosis: a multicenter study. Eur Neurol. 2014;71:233–41.

11. Goodin DS, Frohman EM, 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;58:169–78.

12. Sharief MK. Dose and frequency of administration of interferon-β affect its efficacy in multiple sclerosis. Clin Drug Invest. 2003;23:551–9.

13. Limmroth V, Malessa R, et al. Quality assessment in multiple sclerosis therapy (QUASIMS): a comparison of interferon beta therapies for relapsing-remitting multiple sclerosis. J Neurol. 2007;254:67–77.

14. Gobbi C, Zecca C, et al. Swiss analysis of multiple sclerosis: a multicenter non-interventional, retrospective cohort study of disease-modifying therapies. Eur Neurol. 2013;70:35–41.

15. Kurtzke JF. A proposal for a uniform minimal record of disability in multiple sclerosis. Acta Neurol Scand. 1981;64:110–29.

16. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology. 1983;33:1444–52.

17. Traboulsee A, Simon JH, et al. Revised recommendations of the Consortium of MS Centers task force for a standardized MRI protocol and clinical guidelines for the diagnosis and follow-up of multiple sclerosis. Am J Neuroradiol. 2016;37:394–401.

18. Clanet M, Radue EW, et al. A randomized, double-blind, dose-comparison study of weekly interferon beta-1a in relapsing MS. Neurology. 2002;59: 1507–17.

19. Minagara A, Murray TJ, et al. Efficacy and tolerability of intramuscular interferon beta-1a compared with subcutaneous interferon beta-1a in relapsing MS: results from PROOF. Curr Med Res Opin. 2008;24:1049–55.

20. Koch-Henriksen N, Sorensen PS, et al. A randomized study of two interferon-beta treatments in relapsing-remitting multiple sclerosis. Neurology. 2006;66:1056–60.

21. Patti F, Pappalardo A, Florio C, et al. Effects of interferon beta-1a and -1b over time: 6-year results of an observational head-to-head study. Acta Neurol Scand. 2006;113:241–7.

22. Rio J, Tintore M, Nos C, et al. Interferon beta in relapsing-remitting multiple sclerosis: an eight years experience in a specialist multiple sclerosis center. J Neurol. 2005;252:795–800.

23. Trojano M, Liguori M, Paolicelli D, et al. Interferon beta in relapsing-remitting multiple sclerosis: an independent postmarketing study in southern Italy. Mult Scler. 2003;9:451–7.

24. Einarson TR, Bereza BG, Machado M. Comparative effectiveness of interferon in relapsing-remitting multiple sclerosis: a meta-analysis of real-world studies. Curr Med Res Opin. 2017;33:579–93.

25. Munafo A, Trinchard-Lugan I, Nguyen TXQ, et al. Comparative pharmacokinetics and pharmacodynamics of recombinant human interferon beta-1a after intramuscular and subcutaneous administration. Eur J Neurol. 1998;5:187–93.

26. Van der Voort LF, Gilli F, Bertolotto A, et al. Clinical effect of neutralizing antibodies to interferon beta that persist long after cessation of therapy for multiple sclerosis. Ann Neurol. 2010;67:402–7.