Journal of the Neurological Sciences 379 (2017) 151–156

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Early MRI results and odds of attaining 'no evidence of disease activity' status in MS patients treated with interferon β-1a in the EVIDENCE study

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ARTICLE INFO

Article history:
Received 22 December 2016
Received in revised form 16 May 2017
Accepted 24 May 2017
Available online 25 May 2017

Keywords:
Multiple sclerosis
Interferon beta
NEDA
CAF
MRI
Disease activity

ABSTRACT

Introduction: 'No evidence of disease activity' (NEDA) is increasingly used as a treatment target with disease-modifying drugs for relapsing multiple sclerosis.
Methods: This post-hoc analysis of the randomised EVIDENCE trial compared interferon beta-1a injected subcutaneously three times weekly (IFN β-1a SC tiw) with interferon β-1a injected intramuscularly once weekly (IFN β-1a IM qw) on NEDA and clinical activity-free (CAF) status. The influence of the frequency of magnetic resonance imaging (MRI) scanning on NEDA and the effect of baseline T1 gadolinium-enhancing (Gd+) lesions on NEDA and CAF were also investigated.
Results: More patients in the IFN β-1a SC tiw group achieved NEDA compared with the IFN β-1a IM qw group, although rates were lower when monthly MRI scans through 24 weeks were included (35.0% vs. 21.6%, respectively; $p < 0.001$) versus the 24-week scan alone (59.5% vs. 41.2%; $p < 0.001$). Absence of baseline Gd+ lesions predicted NEDA through Week 72 in the IFN β-1a IM qw group ($p = 0.022$), and CAF through Week 48 in patients receiving IFN β-1a SC tiw ($p = 0.024$).
Conclusions: IFN β-1a SC tiw was associated with significantly higher rate of NEDA status compared with IFN β-1a IM qw. Baseline Gd+ lesions augured less frequent CAF or NEDA status. Inclusion of more MRI scans in the analysis reduced rates of NEDA status.

1. Introduction

The increasing number and different mechanisms of action of disease-modifying drugs (DMDs) for relapsing forms of multiple sclerosis (MS) has prompted the desire to raise the standard for clinical success to a comprehensive assessment. Clinical trials evaluating DMDs typically use primary endpoints of clinical disease activity, such as relapse rate or time to confirmed disability worsening as discrete assessments [1–3]. However, low relapse rates and the slowly developing disability in relapsing MS means clinical endpoints must be studied over prolonged periods or in very large numbers of patients to demonstrate statistical significance [4]. The most appropriate clinical endpoints may not always be apparent; for example, short-term increases in Expanded Disability Status Scale (EDSS) scores, as commonly measured in clinical trials, may not correlate with the long-term worsening of disability [5]. Results of these individual endpoints may be imperfectly translated to clinical practice, where endpoints may be considered in combination (e.g. relapse with new magnetic resonance imaging [MRI] activity and a change in EDSS).

No evidence of disease activity (NEDA) is a composite measure of MS treatment that includes freedom from clinical and MRI disease activity [6]. Since the concept was introduced, NEDA has been applied to evaluate relapsing MS treatment in recent trials of cladribine tablets [7], natalizumab [8], alemtuzumab [9], peginterferon β-1a [10], and fingolimod [11,12]. Placebo-controlled analyses demonstrated significant benefits of DMDs on the proportion of patients achieving NEDA compared with placebo, which could provide a treat-to-target approach in MS care [7,8]. Additionally, post-hoc analyses of the CLARITY (CLAdRIbine Tablets for treating MS orallY) trial showed significant

Abbreviations: ANCOVA, analysis of covariance; CAF, clinical activity-free; CUA, combined unique active; DMD, disease-modifying drug; EDSS, Expanded Disability Status Scale; Gd+, gadolinium enhancing; IFN β-1a, interferon beta-1a; IM, intramuscularly; ITT, intent-to-treat; MRI, magnetic resonance imaging; MS, multiple sclerosis; NEDA, no evidence of disease activity; SC, subcutaneously.

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http://dx.doi.org/10.1016/j.jns.2017.05.052
0022-510X/

benefit after 24 weeks for cladribine tablets versus placebo in the proportion of patients with NEDA, suggesting that NEDA may be a sensitive measure of disease activity [7]. NEDA status is influenced by the frequency of detection of new events, particularly highly sensitive MRI data; thus, a potential pitfall of using NEDA to evaluate DMDs or compare results across trials might be the non-standardised frequency of MRI assessments [6].

This paper presents post-hoc analyses of a head-to-head comparison of interferon beta-1a (IFN β-1a) 44 μg subcutaneously (SC) three times weekly (tiw) versus IFN β-1a 30 μg intramuscularly (IM) once weekly (qw) in patients with relapsing–remitting MS (RRMS), the EVIDENCE (EVidence of Interferon Dose-response: European–North American Comparative Efficacy) study [3]. In previously reported results, IFN β-1a 44 μg SC tiw was significantly more effective than IFN β-1a 30 μg IM qw on relapse measures and MRI outcomes when examined as distinct outcomes, and these benefits were sustained over at least 16 months [3,13]. The post-hoc analyses reported here evaluated: 1) the effects of including varying numbers of MRI scans on the proportions of patients who achieve NEDA status; 2) the proportion of patients who achieved NEDA status through 24 weeks and beyond and 3) the relationship of baseline MRI characteristics with treatment effects of IFNs on NEDA.

2. Methods

2.1. Study design

EVIDENCE was a randomised controlled trial involving 677 IFN-naïve patients with RRMS, with baseline EDSS scores of 0–5.5 and at least two MS relapses within the 2 years prior to enrolment [3]. During the initial comparative phase, patients were randomised to IFN β-1a 44 μg SC tiw or IFN β-1a 30 μg IM qw until the final patient completed 48 weeks (Supplementary Fig. 1) [13]. Patients then entered a transition phase, during which all patients received IFN β-1a 44 μg SC tiw for up to 45 weeks, or discontinued the study [14]. All patients provided written consent to participate in the study, and the study was approved by all applicable institutional review boards.

Patients returned to the study centre for scheduled follow-up every 4 weeks up to 24 weeks, and every 12 weeks thereafter. Full neurological and EDSS score assessments occurred every 3 months by physicians blinded to treatment (patients and treating physicians were not blinded) [3,13–15]. Relapses were assessed at every clinical visit. Patients were also contacted monthly to determine whether they had experienced symptoms suggesting a relapse, and were asked to inform the centre within 48 h of the onset of a possible relapse to determine whether they should come to the centre for evaluation. Relapses were defined as the appearance of a new symptom or worsening of an old symptom, accompanied by appropriate objective findings on neurological examination that lasted at least 24 h in the absence of fever and preceded by at least 30 days of clinical stability or improvement [14]. The primary study outcome was the proportion of patients free from relapses at 24 weeks.

Proton density T2-weighted MRI scans and pre- and post-gadolinium (Gd) T1-weighted scans were performed on study Day 1 and every 4 weeks thereafter through 24 weeks. In addition, T2-weighted scans were performed at Weeks 48 and 72 [3,14]. The primary MRI endpoint during the randomised phase was the number of combined unique active (CUA) lesions per patient per scan, defined as an active lesion on T1 post-Gd or T2 sequences, or both, avoiding double counting, as reported previously [3]. Additional MRI endpoints included the number of Gd-enhancing (Gd+) T1 and T2 lesions per patient per scan, the proportion of active scans (Gd+ T1, T2 and CUA) per patient and the proportion of patients with an active scan (Gd+ T1, new/enlarging T2 and CUA) during the randomised period [3,14]. All MRI scans were analysed at a central reading facility by neuroradiologists who were blinded to study treatment [14].

2.2. Analyses of MRI and clinical outcomes

Post-hoc analyses examined the effect of IFN β-1a 44 μg SC tiw, compared with IFN β-1a 30 μg IM qw, on changes in the number of active T2 and Gd+ lesions per patient per scan from baseline to 4, 8, 12, 16, 20 and 24 weeks. In addition, numbers and proportions of patients achieving clinical activity-free (CAF) status, defined as no relapses and no worsening of 12-week confirmed disability (increase of ≥1.0 point in EDSS score from baseline sustained for ≥12 weeks) through 24, 48 and 72 weeks were determined. MRI activity-free status was assessed through 24 weeks and was defined as no new or enlarging T2 or Gd+ lesions on six MRI scans through 24 weeks. Because only T2 scans were performed at 48 and 72 weeks, a second measure of MRI activity-free status, MRI-T2 activity-free status, was used at these time points; this was defined as no new or enlarging T2 lesions on all T2 MRI scans through the relevant time point.

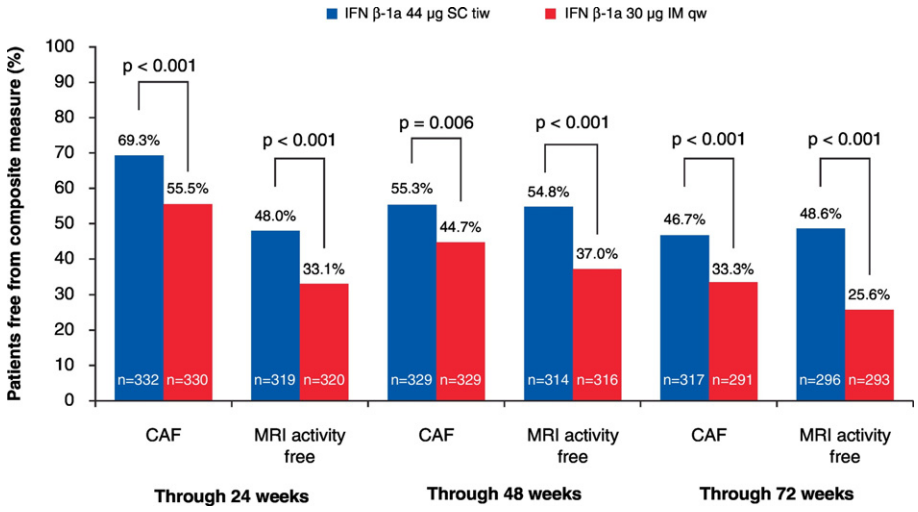

Fig. 1. Proportions of patients achieving CAF[a] and MRI activity-free[b] endpoints through 24, 48 and 72 weeks. [a]Defined as no relapses and no confirmed 12-week disability worsening (increase of ≥1.0 point in EDSS score from baseline sustained for ≥12 weeks). [b]Through 24 weeks, defined as no T1 Gd+ lesions or active (new/enlarging) T2 lesions on monthly scans through 24 weeks (six scans); through 48 and 72 weeks, defined as no active (new/enlarging) T2 lesions through that time point (48 weeks, seven scans; 72 weeks, eight scans). CAF, clinical activity-free; CUA, combined unique active; EDSS, Expanded Disability Status Scale; Gd+, gadolinium-enhancing; IFN β-1a, interferon beta-1a; IM, intramuscularly; MRI, magnetic resonance imaging; qw, once weekly; SC, subcutaneously; tiw, three times weekly.

Between-treatment differences in patients achieving NEDA status (defined as CAF and MRI activity-free status through 24 weeks) and NEDA-T2 status (defined as CAF and MRI-T2 activity-free status through 48 and 72 weeks) were also determined. To examine the effect of the frequency of MRI scans on NEDA, additional analyses assessed the following: NEDA at 24 weeks using T2 and Gd + results from the 24-week scan only, and NEDA through 24 weeks using all monthly T2 scans but Gd + results from the 24-week scan only (Fig. 1). Additional post-hoc analyses investigated the predictive value of Gd + lesions at baseline on NEDA-T2 outcomes through 48 and 72 weeks. Between-treatment differences in NEDA and NEDA-T2 endpoints were investigated in subgroup analyses according to age (<40 vs. ≥40 years), sex, time since onset of MS (≤4 vs. >4 years), previous use of MS treatment within 12 months of study Day 1, higher disease activity (defined as ≥2 relapses in the previous year and ≥1 Gd + lesion at study entry) or baseline EDSS scores (≤ median [2.0] vs. >median).

2.3. Statistical methods

Analyses of CAF rates used the intent-to-treat (ITT) population, which consisted of all randomised patients. MRI outcomes were performed in the MRI ITT population, which included all randomised patients except those from two centres (27 patients) who were granted a priori exemption from performing MRI scans. Between-group differences in the numbers of CUA lesions at baseline were analysed using a non-parametric analysis of covariance (ANCOVA) model on ranked data, with effects for treatment group. Between-group differences in the mean number of Gd + or active T2 lesions per patient per scan at baseline were analysed using similar ANCOVA models; differences at subsequent time points were analysed by means of a negative binomial model with treatment and baseline number of lesions as covariates and log number of scans as an offset variable.

Between-group differences in the proportions of patients who were free of relapses or 12-week confirmed disability progression, or who were CAF through 24, 48 and 72 weeks, were analysed using a logistic model with fixed effects for treatment, and age, sex, baseline EDSS score, number of relapses in the 24 months prior to screening and time since onset of MS as covariates. Differences in the proportions of patients who were MRI activity free or MRI-T2 activity free at the same time points were analysed using an adjusted logistic model with a fixed effect for treatment, and age, sex, baseline EDSS score, number of relapses in the 24 months prior to screening, number of CUA lesions at baseline and time since onset of MS as covariates. Similar models were used to analyse between-group differences in the proportion of patients meeting NEDA or NEDA-T2 criteria through 24, 48 or 72 weeks.

The logistic model for between-treatment comparisons of proportions of patients with NEDA-T2 with or without baseline Gd + lesions included fixed effects for treatment, and age, sex, baseline EDSS score, number of relapses in the 24 months before screening, number of CUA lesions at baseline and time since MS onset as covariates. For between-treatment comparison of proportions of patients with CAF with baseline Gd + lesions, the logistic model included fixed effects for treatment, and age, number of relapses in the 24 months before screening, baseline EDSS score, time since first attack and number of baseline lesions as covariates; for CAF without baseline Gd + lesions, the baseline lesions covariate was omitted. For proportions of patients with NEDA-T2 with or without baseline lesions within treatment groups, the logistic model included fixed effects for absence/presence of baseline Gd + lesions and age, sex, baseline EDSS score, number of relapses in the 24 months before screening, number of baseline CUA lesions and time since MS onset as covariates; for CAF with or without baseline lesions, the sex and number of CUA lesions at baseline covariates were omitted.

Statistical analyses were performed using SAS software; p values below 0.05 were considered significant.

3. Results

Patients were randomised to receive IFN β-1a 44 μg SC tiw ($n = 339$) or IFN β-1a 30 μg IM qw ($n = 338$), as described previously [3]. One subject randomised to the IFN β-1a 30 μg IM qw group was not treated and therefore excluded from these post-hoc analyses. There were no statistically significant differences in baseline demographic and disease characteristics between the two randomised groups (Table 1).

During the comparative phase, patients in the IFN β-1a 30 μg IM qw group received that dosage for a mean (standard deviation [SD]) of 63.3 (11.9) weeks (range, 48 to 92.4 weeks); 223 patients then switched to IFN β-1a 44 μg SC tiw for the transition phase while the remainder terminated the study (Supplementary Fig. 1). Therefore, at the 72-week time point, patients in the IFN β-1a 30 μg IM qw group may have entered the extension phase and had been receiving treatment with IFN β-1a SC tiw for a variable period of time (mean [SD] of 9.7 [5.85]

Table 1
Baseline demographic and disease characteristics.

	IFN β-1a 44 μg SC tiw ($n = 339$)	IFN β-1a 30 μg IM qw ($n = 337$)[a]
Age (years), mean (range)	38.3 (18–55)	37.4 (18–55)
Sex, n (%)		
Male	85 (25.1)	86 (25.5)
Female	254 (74.9)	251 (74.5)
Race, n (%)		
White	320 (94.4)	309 (91.7)
Black	13 (3.8)	23 (6.8)
Asian	0 (0)	1 (0.3)
Other	6 (1.8)	4 (1.2)
Baseline EDSS score, mean ± SD	2.34 ± 1.16	2.35 ± 1.17
Time since MS onset (years), mean (range)	6.36 (0.3–37.4)	6.51 (0.2–34.4)
Time since most recent relapse (months), mean (range)	5.2 (0.1–21.8)	5.0 (1.1–18.9)
Number of relapses within previous 24 months, mean (range)	2.7 (1.0–8.0)	2.6 (1.0–6.0)
Treatment for MS within 12 months of study Day 1, n (%)		
Yes	167 (49.3)	153 (45.4)
No	172 (50.7)	184 (54.6)
Number of Gd + lesions at baseline[b]		
Mean ± SD	2.0 ± 4.3	2.7 ± 7.2
Median (Q1, Q3)	0.0 (0.0, 2.0)	0.0 (0.0, 2.0)
	p = 0.459[c]	
Number of new or enlarging T2 lesions at baseline[b]		
Mean ± SD	1.2 ± 2.7	1.2 ± 2.5
Median (Q1, Q3)	0.0 (0.0, 1.0)	0.0 (0.0, 1.0)
	p = 0.856[c]	
Number of CUA lesions[b,d] at baseline		
Mean ± SD	2.4 ± 4.8	3.0 ± 7.4
Median (Q1, Q3)	1.0 (0.0, 3.0)	1.0 (0.0, 3.0)
	p = 0.926[c]	

CUA, combined unique active; EDSS, Expanded Disability Status Scale; Gd +, gadolinium-enhancing; IFN β-1a, interferon beta-1a; IM, intramuscularly; MS, multiple sclerosis; Q, quartile; qw, once weekly; SC, subcutaneously; SD, standard deviation; tiw, three times weekly.

[a] Excludes one patient from the intent-to-treat population who was randomised to IFN β-1a 30 μg IM qw but was not treated.

[b] Based on data from 309 and 305 subjects in the IFN β-1a 44 μg SC tiw and IFN β-1a 30 μg IM qw groups, respectively.

[c] p value was estimated using a non-parametric analysis of covariance model on ranked data with effects for treatment group.

[d] A CUA lesion was defined as a Gd + lesion, or new or enlarging T2 lesion, avoiding double counting.

weeks, with a maximum of 25.1 weeks' exposure to IFN β-1a 44 μg SC tiw at Week 72).

3.1. Effects of treatment on MRI and clinical disease activity

Mean Gd + and active T2 lesion numbers decreased from baseline to 24 weeks in both groups. However, mean Gd + lesion numbers were significantly lower with IFN β-1a 44 μg SC tiw versus IFN β-1a 30 μg IM qw treatment from 8 weeks (0.79 vs. 1.34; $p = 0.002$) and remained so through the last monthly scan at 24 weeks; mean active T2 lesions were significantly lower with IFN β-1a 44 μg SC tiw versus IFN β-1a 30 μg IM qw treatment from 12 weeks (0.42 vs. 0.55; $p = 0.008$) and remained so through 24 weeks. At 24, 48 and 72 weeks, a higher proportion of patients in the IFN β-1a 44 μg SC tiw group was free from clinical and MRI activity versus the IFN β-1a 30 μg IM qw group (Fig. 1).

3.2. Proportion of patients meeting NEDA/NEDA-T2 criteria

Regardless of the number of scans included, more patients treated with IFN β-1a 44 μg SC tiw achieved NEDA compared with those treated with IFN β-1a 30 μg IM qw (Fig. 2). The percentages of patients achieving NEDA were 35.0% versus 21.6%, respectively, when all monthly contrast and T2 scans were included ($p < 0.001$), 43.1% versus 27.1%, respectively, when all T2 scans were included along with only the Week 24 contrast scan ($p < 0.001$), and 59.5% versus 41.2%, respectively, when including contrast and T2 MRI activity only at the 24-week scan ($p < 0.001$).

In addition to the NEDA outcomes through 24 weeks, the proportion of patients with NEDA-T2 criteria through 48 and 72 weeks was significantly higher in patients randomised to IFN β-1a 44 μg SC tiw compared with those randomised to IFN β-1a 30 μg IM qw ($p < 0.001$; Fig. 3). Subgroup analyses reflected the analysis in the overall patient population, showing that the proportions of patients meeting NEDA-T2 criteria through 48 and 72 weeks were consistently higher with IFN β-1a 44 μg SC tiw than with IFN β-1a 30 μg IM qw, irrespective of age, sex, duration of MS, previous DMD therapy or baseline EDSS scores (Supplementary Fig. 2).

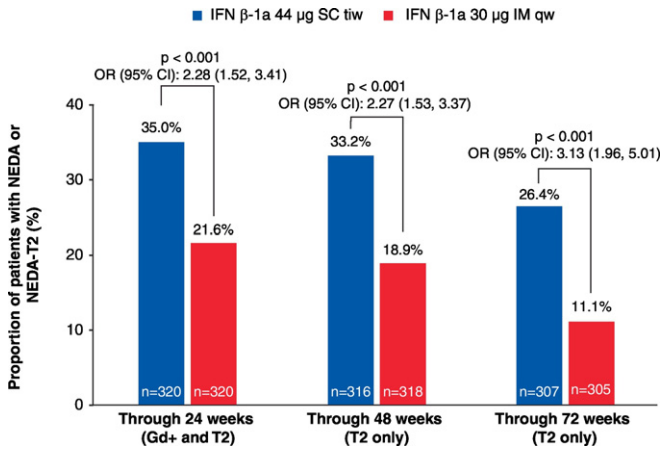

Fig. 3. Proportions of patients with NEDA[a] status through 24 weeks (including all scans) and with NEDA-T2[b] status through 48 and 72 weeks (including all T2 scans). [a]Defined as no relapses, no confirmed 12-week disability worsening (increase of ≥1.0 point in EDSS score from baseline sustained for ≥12 weeks) and no Gd + lesions or active T2 lesions on MRI scans from Week 4 to Week 24 (six scans). [b]Defined as no relapses, no confirmed 12-week disability worsening and no new or enlarging T2 lesions on T2 MRI scans through the respective time point (48 weeks, seven scans; 72 weeks, eight scans). CI, confidence interval; CUA, combined unique active; EDSS, Expanded Disability Status Scale; Gd +, gadolinium-enhancing; IFN β-1a, interferon beta-1a; IM, intramuscularly; MRI, magnetic resonance imaging; MS, multiple sclerosis; NEDA, no evidence of disease activity, OR, odds ratio; qw, once weekly; SC, subcutaneously; tiw, three times weekly.

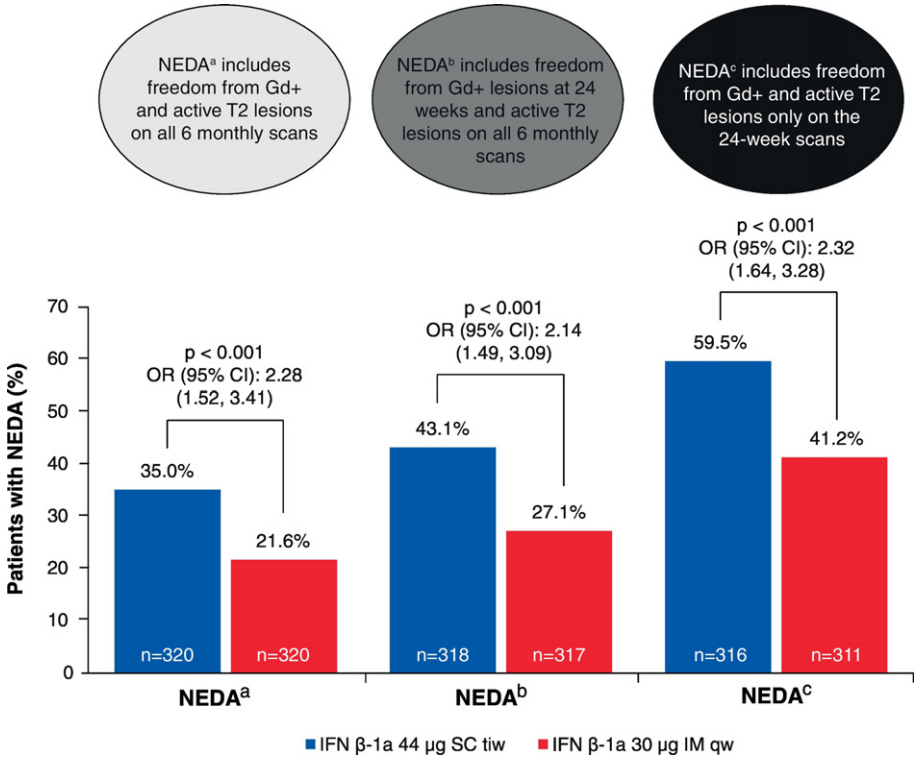

Fig. 2. Proportions of patients having 24-week NEDA status according to varying numbers of MRI scans in the analysis. All NEDA definitions included absence of clinical activity (relapse or 12-week confirmed EDSS worsening). [a]NEDA through 24 weeks (six-monthly Gd + and T2 scans) included freedom from Gd + and active T2 lesions on all six monthly scans. [b]NEDA at, and through, 24 weeks (Week 24 Gd + and six monthly T2 'semi-cumulative' scans) included freedom from Gd + lesions at Week 24 and active T2 lesions on all six monthly scans. [c]NEDA at Week 24 (Gd + and T2 scan at 24 weeks) included freedom from Gd + and active T2 lesions only on the Week 24 scans. CI, confidence interval; CUA, combine unique active; EDSS, Expanded Disability Status Scale; Gd +, gadolinium-enhancing; IFN β-1a, interferon beta-1a; IM, intramuscularly; NEDA, no evidence of disease activity; OR, odds ratio; qw, once weekly; SC, subcutaneously; tiw, three times weekly.

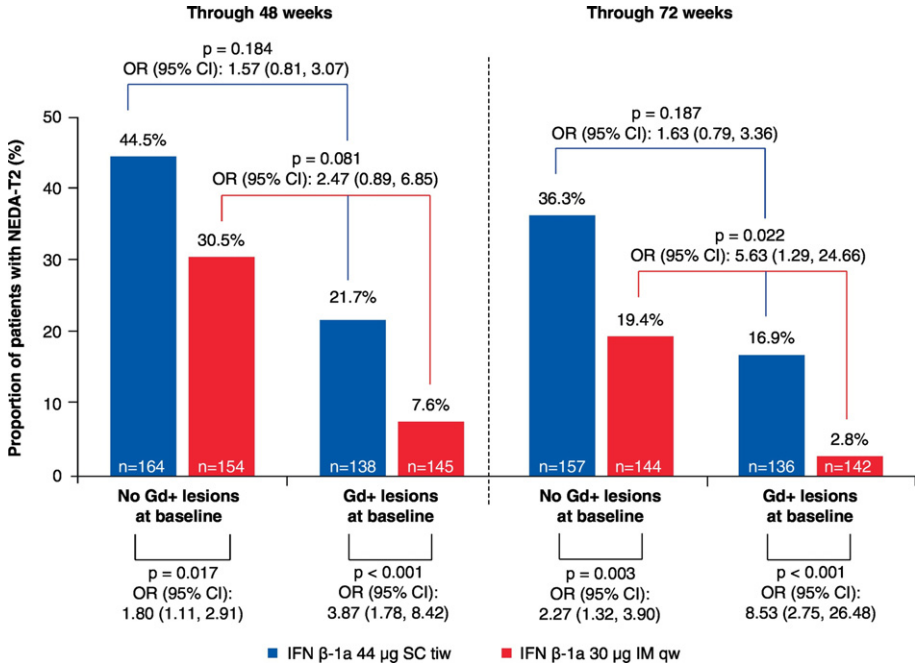

Fig. 4. Comparison of the proportions of patients with NEDA-T2[a] through 48 and 72 weeks between treatment groups. [a]Defined as no relapses, no confirmed 12-week disability worsening (increase of ≥1.0 point in EDSS score from baseline sustained for ≥12 weeks) and no new or enlarging T2 lesions on cumulative T2 MRI scans through the respective time point (48 weeks, seven scans; 72 weeks, eight scans). Brackets above bars show comparisons within treatment groups; brackets below bars show comparisons between treatment groups. CI, confidence interval; CUA, combined unique active; EDSS, Expanded Disability Status Scale; Gd+, gadolinium-enhancing; IFN β-1a, interferon beta-1a; IM, intramuscularly; MRI, magnetic resonance imaging; NEDA, no evidence of disease activity; OR, odds ratio; qw, once weekly; SC, subcutaneously; tiw, three times weekly.

In addition, patients with no Gd+ lesions at baseline who were treated with IFN β-1a 44 µg SC tiw were more likely to achieve NEDA-T2 and CAF status through Week 48 (NEDA-T2, $p = 0.017$; CAF, $p = 0.040$) and Week 72 (NEDA-T2, $p = 0.003$; CAF, $p = 0.014$), compared with patients with no Gd+ lesions at baseline randomised to IFN β-1a 30 µg IM qw (Fig. 4 and Supplementary Fig. 3). Similarly, among patients with Gd+ lesions at baseline, those treated with IFN β-1a 44 µg SC tiw were more likely to achieve NEDA-T2 through 48 weeks ($p < 0.001$) and 72 weeks ($p < 0.001$) compared with patients randomised to IFN β-1a 30 µg IM qw (Fig. 4). For patients with Gd+ lesions at baseline, treatment with IFN β-1a 44 µg SC tiw was associated with a higher proportion of patients achieving CAF status through 48 and 72 weeks; however, these differences were not statistically significant (Supplementary Fig. 3).

The presence or absence of Gd+ lesions at baseline did not predict NEDA-T2 status through Week 48 in either treatment group, although the proportion of patients achieving NEDA-T2 was numerically higher among those without Gd+ lesions, compared with patients with Gd+ lesions, in both groups (Fig. 4). The presence of Gd+ lesions at baseline predicted NEDA-T2 through Week 72 in the IFN β-1a 30 µg IM qw group ($p = 0.022$), but not in the IFN β-1a 44 µg SC tiw group (Fig. 4). The presence or absence of Gd+ lesions at baseline predicted CAF status through Week 48 in patients receiving IFN β-1a 44 µg SC tiw ($p = 0.024$), but not in patients receiving IFN β-1a 30 µg IM qw (Supplementary Fig. 3). The presence or absence of Gd+ lesions at baseline did not predict CAF status through Week 72 in either IFN β-1a group (Supplementary Fig. 3).

4. Discussion

In these post-hoc analyses from the EVIDENCE study, treatment with IFN β-1a 44 µg SC tiw was associated with significantly greater performance on NEDA and CAF composite disease activity endpoints assessed, compared with IFN β-1a 30 µg IM qw. NEDA status was influenced by the number of included MRI scans.

While 59.5% and 41.2% of patients receiving IFN β-1a 44 µg SC tiw and IFN β-1a 30 µg IM qw, respectively, achieved NEDA status at 24 weeks when only the Week 24 MRI results were included, NEDA rates fell to 35.0% and 21.6% when including all monthly MRI scans as well. Including all Gd+ lesions made a substantial difference in NEDA rates; this suggests that there were Gd+ lesions early in treatment that did not develop into active T2 lesions by Week 24.

In this analysis, patients receiving IFN β-1a 44 µg SC tiw were more likely to achieve NEDA-T2 and CAF status at Weeks 48 and 72 than those treated with IFN β-1a 30 µg IM qw, regardless of whether they had Gd+ lesions at baseline. A lower proportion of patients with baseline Gd+ lesions achieved CAF status at Weeks 48 and 72; this effect was statistically significant only in the IFN β-1a 44 µg SC tiw group at 48 weeks. Baseline Gd+ lesions predicted a significantly reduced likelihood of achieving NEDA-T2 status through 72 weeks in the IFN β-1a 30 µg IM qw group and a numerical reduction in the IFN β-1a 44 µg SC tiw group. These results are broadly consistent with results of analyses comparing IFN β-1a 30 µg IM qw versus placebo, in which baseline Gd+ lesions were associated with inflammatory activity over 2 years of treatment, regardless of treatment arm (although these analyses did not employ composite measures such as NEDA) [16,17].

Of note, NEDA in this study was likely also affected by the way relapses were assessed in the trial. Patients were contacted monthly and asked to come in for a full assessment in case of new symptoms; therefore, it is likely that all potential relapses were actually accounted for compared to other studies where less frequent interaction often leads to missed relapses [3]. It is likely that the frequency of visits or patient contacts in a study would also affect the relapse rate and therefore NEDA rates.

Limitations of this study include the post-hoc nature of the analyses and the fact that patients were not blinded to treatment; however, MRI assessments throughout the study and clinical assessments in the comparative phase were conducted by radiologists or neurologists who were blinded to treatment allocation [13,14]. A further limitation is

that patients who were randomised to IFN β-1a 30 μg IM qw switched to IFN β-1a 44 μg SC tiw or discontinued after the final patient completed 48 weeks in the comparative phase (average of 64 weeks on study). Therefore, patients in the IFN β-1a 30 μg IM qw group received a mean of 9.7 weeks of IFN β-1a 44 μg SC tiw treatment before the 72-week cut-off. Finally, no between-treatment differences in the proportion of patients with confirmed disability worsening was seen at any time point, suggesting that the significant treatment benefits of IFN β-1a 44 μg SC tiw versus IFN β-1a 30 μg IM qw on NEDA-T2 status was primarily driven by MRI and relapse outcomes. NEDA is considered to be driven by MRI rather than clinical results.

5. Conclusion

Post-hoc analyses demonstrate favourable effects of IFN β-1a 44 μg SC tiw, compared with IFN β-1a 30 μg IM qw, on early measures of MRI disease activity and NEDA. Including only the MRI scans at 24 weeks resulted in absolute increases of approximately 20% more patients achieving NEDA compared with including all monthly scans up to that point; however, more patients in the IFN β-1a 44 μg SC tiw arm achieved NEDA status regardless of the number and type of scans included. Baseline Gd + lesions were associated with reduced likelihood of achieving NEDA-T2 or CAF status, although a statistically significant effect was not consistently seen. IFN β-1a 44 μg SC tiw demonstrated superiority over IFN β-1a 30 μg IM qw on composite disease activity endpoints through Week 24, highlighting NEDA-T2 and CAF status as sensitive measures of disease activity in this randomised clinical trial population.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.jns.2017.05.052.

Conflicts of interest

PKC: consulting fees from Accordant, Bayer, Biogen, EMD Serono, Inc. (a business of Merck KGaA, Darmstadt, Germany), Genentech/Roche, Genzyme/Sanofi, Mallinckrodt, and Novartis, and received fees for contracted research from Actelion, Genentech/Roche, Novartis, and Opexa.

ATR: consulting fees from Acorda, Bayer, Biogen, EMD Serono, Inc. (a business of Merck KGaA, Darmstadt, Germany), Genzyme, Novartis, Pfizer, Questcor, Sanofi, and Teva Pharmaceuticals.

MSF: honoraria or consulting fees from Actelion, Bayer HealthCare, Biogen, Chugai, EMD Serono (Canada), Genzyme, Hoffmann-La Roche, Merck Serono, Novartis, Sanofi-Aventis, and Teva Canada Innovation; served on an advisory board or board of directors for Actelion, Bayer HealthCare, Biogen, Hoffmann-La Roche, Merck Serono, Novartis, Opexa, and Sanofi-Aventis; and served on a speakers bureau for Genzyme.

JF: former employee of EMD Serono, Inc., Rockland, MA, USA (a business of Merck KGaA, Darmstadt, Germany).

FD: employee of EMD Serono, Inc., Billerica, MA, USA (a business of Merck KGaA, Darmstadt, Germany).

Funding

The study was supported by EMD Serono, Inc., Rockland, MA, USA (a business of Merck KGaA, Darmstadt, Germany) and Pfizer Inc., New York, NY, USA.

Acknowledgements

The authors thank Michael Shaw, PhD, and Matthew Thomas, PhD, of Caudex, New York, NY, USA (supported by EMD Serono, Inc., Rockland, MA, USA [a business of Merck KGaA, Darmstadt, Germany] and Pfizer Inc., New York, NY, USA) for editorial assistance in drafting the manuscript, collating the comments of authors and assembling tables and figures.

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