DX68

Predictive value of MRI measures in patients with relapsing multiple sclerosis receiving IFN β–1a SC tiw or IFN β–1a IM qw: *post hoc* analyses of EVIDENCE data

AT Reder,[1] MS Freedman,[2] F Dangond,[3] J Fang,[3] PK Coyle[4]

[1]University of Chicago, Chicago, IL, USA; [2]University of Ottawa and the Ottawa Hospital Research Institute, Ottawa, ON, Canada; [3]EMD Serono, Inc.,* Rockland, MA, USA; [4]Stony Brook University, Stony Brook, NY, USA

2015 Annual Meeting of the Consortium of Multiple Sclerosis Centers (CMSC); May 27–30, 2015; Indianapolis, IN, USA

Introduction

- In the pivotal placebo-controlled trials of interferon beta-1a (IFN β-1a) administered subcutaneously (SC) three times weekly (tiw) and IFN β-1a administered intramuscularly (IM) once weekly (qw) for treatment of relapsing forms of multiple sclerosis (RMS), both therapies were effective on clinical and magnetic resonance imaging (MRI) endpoints.[1,2]
- The randomized, head-to-head EVIDENCE (EVidence of Interferon Dose-response: European-North American Comparative Efficacy) study demonstrated the superiority of IFN β-1a SC tiw on reducing relapses and MRI disease activity over 24 and 48 weeks compared with IFN β-1a IM qw in patients with RMS.[3]
- *Post hoc* analysis from the EVIDENCE study also demonstrated that mean numbers of combined unique active (CUA) MRI lesions were significantly reduced with IFN β-1a SC tiw versus IFN β-1a IM qw as early as 4 weeks after treatment initiation (1.4 vs 1.8; p=0.019, based on a non-parametric analysis of covariance [ANCOVA] model).[4]
- As effective therapies for RMS increasingly become available, achieving no evidence of disease activity (NEDA) status, a single composite endpoint representing freedom from clinical and MRI activity, has emerged as a treatment goal.[5]
- Debate continues regarding which particular MRI measures are most relevant to clinical response. Recent research has explored the predictive value of MRI results on later clinical outcomes; however, these studies generally assess MRI activity over at least 6 or 12 months.[6-8]
- The ability of earlier (<6 months) MRI activity to predict later response to IFN β therapies, as indicated by composite endpoints such as NEDA, remains to be determined.

Objective

- To examine the predictive value of early MRI lesions for achieving endpoints including NEDA at Week 48 in patients treated with IFN β-1a.

Methods

- In the EVIDENCE trial, patients with RMS were randomized to IFN β-1a 44 µg SC tiw (n=339) or IFN β-1a 30 µg IM qw (n=338), with efficacy evaluated at 24 and 48 weeks and with follow-up until all patients had completed at least 48 weeks of treatment, for an average of 64 weeks on study.
- Patients with RMS (clinically definite or laboratory-supported, according to Poser's criteria[9]) and Expanded Disability Status Scale (EDSS) scores of 0–5.5 had to have experienced at least two relapses in the prior 2 years.
- The primary endpoint was the proportion of patients remaining free of relapses during the 24 weeks.
- Screening, including MRI scanning with proton density/T2-weighted and pre- and post-gadolinium (Gd) T1-weighted sequences, took place 4 weeks prior to randomization and initiation of therapy.
- Dosage of IFN β-1a SC tiw was up-titrated: 8.8 µg tiw was given for the first 2 weeks, 22 µg tiw was given for the third and fourth weeks, and the full 44 µg tiw was given for the remainder of treatment. IFN β-1a 30 µg IM qw was not up-titrated.
- MRI scans (T1 [with and without Gd enhancement] and T2) were performed on Study Day 1 and every 4 weeks thereafter up to Week 24.
  - In addition, a final T2-weighted scan was performed at Week 48.
  - An active T2 lesion was defined as a new or enlarging lesion.
  - Gadolinium-enhancing (Gd+) lesions were the sum of new T1 enhancing lesions and T1 persistently enhancing lesions.
  - A CUA (combined unique active) lesion was defined as an active lesion on the T1 Gd or T2 scan, or both, avoiding double counting.
- NEDA was defined as no relapses or no 12-week confirmed disability worsening (≥1-point EDSS increase) by Week 48, and no newly occurring or enlarging T2 lesions from Weeks 24 to 48. Gd+ lesion status was not collected at Week 48 and thus was not used in this definition of NEDA, but treatment effects on Gd+ lesions up to Week 24 were compared in separate analyses to examine independent effects. Clinical activity free (CAF) was defined as no relapses or no 12-week confirmed disability worsening.
- Differences in lesion numbers at baseline between treatments were assessed using a non-parametric ANCOVA model on ranked data with effects for treatment group. Numbers of Gd+ lesions per patient per scan were compared between IFN β-1a SC and IFN β-1a IM from the start of dosing up to 4, 8, 12, 16, 20, and 24 weeks after the start of dosing, using a negative binomial model with treatment and baseline number of lesions as covariates and log number of scans as an offset variable.
- A logistic model with effects for absence/presence of Gd+ lesions at baseline and age, number of relapses within 24 months prior to the study, baseline EDSS, and time since first attack as covariates was used to compare percentages of patients achieving NEDA at Week 48 by presence or absence of Gd+ lesions at baseline within and between treatment groups. This model was also used to compare the percentages of patients with or without baseline Gd+ lesions who achieved CAF at Week 48.
- A logistic model with presence versus absence of Gd+ lesions at Week 8 as predictor, and age, baseline EDSS, number of relapses within 24 months prior to study entry, and time since MS onset as covariates, assessed the effect of presence/absence of Week 8 Gd+ lesions on proportion of patients achieving NEDA at Week 48. A similar comparison assessed the effect of presence/absence of Week 8 CUA lesions on proportion of patients achieving NEDA at Week 48.

Results

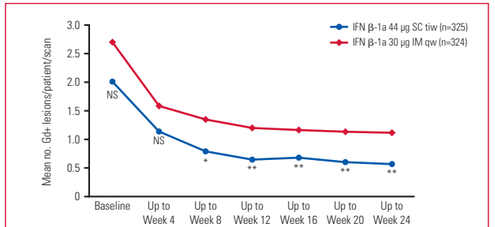
- Baseline characteristics were similar; there were no significant differences in baseline lesion numbers between treatment groups (**Table 1**). Patients had a mean baseline EDSS of 2.3–2.4 and had suffered an average of 2.6 relapses over the past 24 months.

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)
Age (years), mean ± SD	38.3 ± 9.0	37.4 ± 8.6
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 ± SD	6.36 ± 6.38	6.51 ± 6.47
Number of relapses within previous 24 months, mean ± SD	2.7 ± 0.9	2.6 ± 0.9
Number of Gd+ lesions at baseline		
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[a]	
Number of new or enlarging T2 lesions at baseline		
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[a]	
Number of CUA[b] lesions 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[a]	

ANCOVA, analysis of covariance; 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]p value was estimated using a non-parametric ANCOVA model on ranked data with effects for treatment group.
[b]A CUA lesion was defined as a Gd+ lesion or new or enlarging T2 lesion, avoiding double counting.

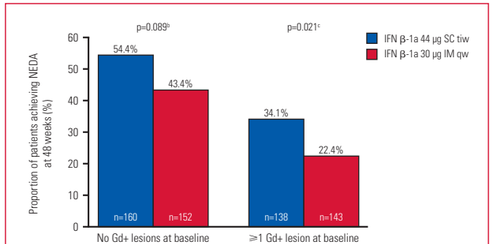
- Although the dose of IFN β-1a SC tiw (but not IFN β-1a IM qw) was up-titrated over the first 4 weeks of treatment, differences between treatment groups were seen on MRI as early as within 1–2 months. The mean numbers of Gd+ lesions per patient per scan were significantly lower in the IFN β-1a SC tiw group compared with the IFN β-1a IM qw group at Week 8 (0.8 vs 1.3; odds ratio 0.66; 95% confidence interval, 0.50–0.86; p=0.002) and at all subsequent time points (**Figure 1**).



Differences at baseline were assessed using a non-parametric ANCOVA model on ranked data with effects for treatment group. Differences at subsequent time points were assessed with a negative binomial model with treatment and baseline number of Gd+ lesions as covariates and log number of scans as an offset variable.
ANCOVA, analysis of covariance; Gd+, gadolinium-enhancing; IFN β-1a, interferon beta-1a; IM, intramuscularly; NS, not significant; qw, once weekly; SC, subcutaneously; tiw, three times weekly.
*p<0.05.
**p<0.001.

Figure 1. Gd+ lesions per patient per scan.

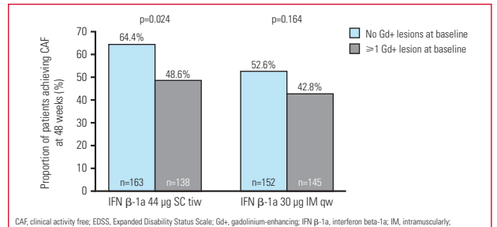
- In the IFN β-1a SC tiw group, there were 160 patients without baseline Gd+ lesions, versus 152 in the IFN β-1a IM qw group; of these, 54.4% in the IFN β-1a SC tiw group and 43.4% in the IFN β-1a IM qw group achieved NEDA at 48 weeks (p=0.089; **Figure 2**). Of those with baseline Gd+ lesions (n=138 and 143 in the respective groups), 34.1% and 22.4% achieved NEDA at 48 weeks (p=0.021; **Figure 2**).
  - Presence of baseline Gd+ lesions was associated with a significantly lower percentage of patients achieving NEDA at 48 weeks in both the IFN β-1a SC tiw (p=0.005) and IFN β-1a IM qw (p<0.001) treatment groups.



EDSS, Expanded Disability Status Scale; Gd+, gadolinium-enhancing; IFN β-1a, interferon beta-1a; IM, intramuscularly; NEDA, no evidence of disease activity; qw, once weekly; SC, subcutaneously; tiw, three times weekly.
[a]Defined as no relapses or confirmed 12-week disability worsening (≥1-point EDSS increase) by Week 48, and no T2 lesions newly occurring or enlarging from Weeks 24 to 48.
[b]From a logistic model with effects for treatment and age, number of relapses prior to the study within 24 months, baseline EDSS, and time since first attack as covariates.
[c]From a logistic model with effects for treatment and age, number of relapses prior to the study within 24 months, baseline EDSS, time since first attack, and number of baseline Gd+ lesions as covariates.

Figure 2. Percentages of IFN β–1a 44 µg SC tiw and IFN β–1a 30 µg IM qw achieving NEDA[a] at 48 weeks, in subgroups according to presence or absence of Gd+ lesions at baseline.

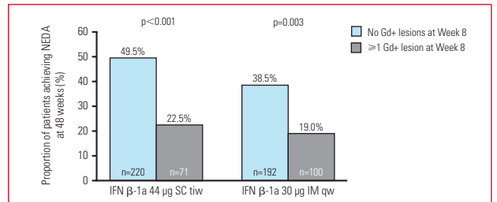
- Baseline Gd+ lesions predicted clinical disease activity, as indicated by CAF (**Figure 3**); more patients without baseline Gd+ lesions achieved CAF status at 48 weeks compared with patients with baseline Gd+ lesions in both groups; however, this difference was not statistically significant for the IFN β-1a IM qw group.



CAF, clinical activity free; EDSS, Expanded Disability Status Scale; Gd+, gadolinium-enhancing; IFN β-1a, interferon beta-1a; IM, intramuscularly; MS, multiple sclerosis; qw, once weekly; SC, subcutaneously; tiw, three times weekly.
[a]Defined as no relapses or confirmed 12-week disability worsening (≥1-point EDSS increase) by Week 48. From a logistic regression model with presence versus absence of Gd+ lesions at Week 8 as predictor and the following as covariates: age, baseline EDSS, number of relapses within 24 months prior to study entry, and time since MS onset.

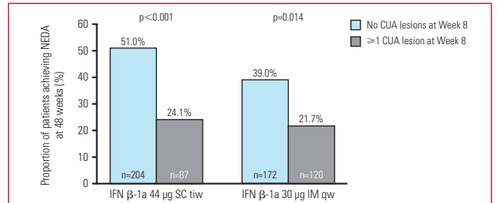
Figure 3. Percentages of patients with presence or absence of Gd+ lesions at baseline achieving CAF[a] status at 48 weeks in each treatment group.

- Among those patients for whom data were available to assess NEDA at 48 weeks, 220 of 291 patients in the IFN β-1a SC tiw group were free of Gd+ lesions at Week 8, up from the 160 of 312 who were free of Gd+ lesions at baseline. In the IFN β-1a IM qw group, 192 of 292 were free of Gd+ lesions at Week 8, up from 152 of 295 at baseline. These reductions are consistent with the treatment effect of IFN β-1a on Gd+ lesions over 8 weeks.
  - Freedom from Gd+ lesions at Week 8 was associated with significantly higher percentages of patients reaching NEDA at Week 48 in both treatment groups (**Figure 4**).
- Similarly, absence of CUA lesions (an active lesion on the T1 Gd or T2 scan, or both, avoiding double counting) at Week 8 was associated with significantly higher percentages of patients achieving NEDA at Week 48 in both treatment groups (**Figure 5**).



EDSS, Expanded Disability Status Scale; Gd+, gadolinium-enhancing; IFN β-1a, interferon beta-1a; IM, intramuscularly; MS, multiple sclerosis; NEDA, no evidence of disease activity; qw, once weekly; SC, subcutaneously; tiw, three times weekly.
[a]Defined as no relapses or confirmed 12-week disability worsening (≥1-point EDSS increase) by Week 48, and no T2 lesions newly occurring or enlarging from Weeks 24 to 48. From a logistic regression model with presence versus absence of Gd+ lesions at Week 8 as predictor and the following as covariates: age, baseline EDSS, number of relapses within 24 months prior to study entry, and time since MS onset.

Figure 4. Percentages of patients with presence or absence of Gd+ lesions at Week 8 achieving NEDA[a] at 48 weeks in each treatment group.



CUA, combined unique active; EDSS, Expanded Disability Status Scale; Gd+, gadolinium-enhancing; IFN β-1a, interferon beta-1a; IM, intramuscularly; MS, multiple sclerosis; NEDA, no evidence of disease activity; qw, once weekly; SC, subcutaneously; tiw, three times weekly.
[a]Defined as no relapses or confirmed 12-week disability worsening (≥1-point EDSS increase) by Week 48, and no T2 lesions newly occurring or enlarging from Weeks 24 to 48. From a logistic regression model with presence versus absence of CUA lesions at Week 8 as predictor and the following as covariates: age, baseline EDSS, number of relapses within 24 months prior to study entry, and time since MS onset. A CUA lesion was defined as an active lesion on the T1 Gd or T2 scan, or both, avoiding double counting.

Figure 5. Percentages of patients with presence or absence of CUA lesions at Week 8 achieving NEDA[a] at 48 weeks in each treatment group.

Conclusions

- In this active relapsing population, patients treated with IFN β-1a SC tiw had fewer MRI lesions compared with IFN β-1a IM qw, beginning shortly after treatment initiation. Despite the fact that IFN β-1a SC tiw was gradually up-titrated to the full dose over 4 weeks, by Week 8, there were already significantly fewer Gd+ lesions in patients receiving IFN β-1a SC tiw versus those receiving IFN β-1a IM qw.
  - These findings are supported by a previous *post hoc* analysis of EVIDENCE, which demonstrated that the mean number of CUA lesions was significantly reduced by IFN β-1a SC tiw compared with IFN β-1a IM qw as early as 4 weeks after treatment initiation.
- More patients with RMS receiving IFN β-1a SC tiw than patients receiving IFN β-1a IM qw achieved CAF and NEDA status.
- Gd+ lesions at baseline, as well as at 8 weeks, predicted future disease activity. However, patients treated with IFN β-1a SC tiw were more likely to achieve NEDA status at Week 48 versus those treated with IFN β-1a IM qw, whether or not early lesions were present.

References

1. PRISMS Study Group. *Lancet* 1998;352:1498–504.
2. Jacobs LD, *et al. Ann Neurol* 1996;39:285–94.
3. Panitch H, *et al. Neurology* 2002;59:1496–506.
4. Reder AT, *et al. Neurology* 2015;84(14 Suppl):P7.257.
5. Rotstein DL, *et al. JAMA Neurol* 2015;72:152–8.
6. Rio J, *et al. Mult Scler* 2008;14:479–84.
7. Durelli L, *et al. J Neurol Neurosurg Psychiatry* 2008;79:646–51.
8. Prosperini L, *et al. Eur J Neurol* 2009;16:1202–9.
9. Poser CM, *et al. Ann Neurol* 1983;13:227–31.

Acknowledgments

The authors thank Rob Coover, MPH, of Caudex, New York, NY, USA (supported by EMD Serono, Inc.,* Rockland, MA, USA and Pfizer Inc, New York, NY, USA) for editorial assistance in drafting the poster, collating the comments of authors, and assembling tables and figures.

Study supported by EMD Serono, Inc.,* Rockland, MA, USA and Pfizer Inc, New York, NY, USA.

Disclosures

ATR has received consulting fees from Acorda, Bayer, Biogen, EMD Serono, Inc.,* Genzyme, Novartis, Pfizer, Questcor, Sanofi, and Teva Pharmaceuticals.

MSF has received personal compensation from Novartis, Teva Canada Innovation, Sanofi-Aventis, Bayer HealthCare, Biogen, EMD Serono (Canada), Genzyme, and Opexa; and has received research support from Bayer HealthCare.

FD and **JF** are employees of EMD Serono, Inc.,* Rockland, MA, USA.

PKC has received consulting fees from AbbVie, Accordant, Acorda, Bayer, Biogen, EMD Serono, Inc.,* Genentech/Roche, Genzyme/Sanofi, Mylan, Novartis, and Teva Pharmaceuticals; and has received fees for contracted research with Actelion, Genzyme/Sanofi, Novartis, and Opexa.

*A subsidiary of Merck KGaA, Darmstadt, Germany.

To view the ePoster, scan the QR code or go to http://medpub-posternetwork.com/CMSC2015_DX68.pdf