P102

No evident disease activity at 24 weeks in patients with relapsing MS treated with interferon β-1a SC vs. interferon β-1a IM in the EVIDENCE study

PK Coyle,[1] J Fang,[2] A Hassan,[2] C Cha,[2] F Dangond,[2] AT Reder[3]

[1]Stony Brook University, Stony Brook, NY, USA; [2]EMD Serono, Inc.,* Rockland, MA, USA; [3]University of Chicago, Chicago, IL, USA

2014 Joint ACTRIMS-ECTRIMS Meeting; September 10–13, 2014; Boston, MA, USA

Introduction

- EVIDENCE (EVidence of Interferon Dose-response: European North American Comparative Efficacy) was an assessor-blinded, randomized, parallel-group study. It was designed as a head-to-head study comparing efficacy and safety of two interferon beta (IFN β) therapies for treatment of relapsing forms of multiple sclerosis (RMS), with efficacy evaluated at 24 and 48 weeks, with follow-up until all subjects had completed at least 48 weeks, for an average of 64 weeks on study.
- In EVIDENCE, more patients receiving IFN β-1a 44 mcg subcutaneously (SC) three times weekly (tiw) achieved the primary endpoint of remaining relapse-free at 24 weeks than patients receiving IFN β-1a 30 mcg intramuscularly (IM) once weekly (qw; 75% vs 63%, p<0.001).[1]
- Recent analyses of disease-modifying drugs for RMS have evaluated composite endpoints that combine assessment of relapse occurrence with measures of disability worsening and radiological disease activity.[2,3]
- In particular, the composite endpoint no evident disease activity (NEDA) has been defined as no relapses, no confirmed disability worsening on the Expanded Disability Status Scale (EDSS), no new or enlarging T2 lesions, and no T1 gadolinium-enhancing (Gd+) lesions.[2]

Objective

- A *post hoc* analysis examined the efficacy of IFN β-1a SC versus IFN β-1a IM in achieving NEDA and clinical activity free (CAF; defined as no relapses or disability worsening) status in the EVIDENCE study.

Methods

- EVIDENCE was a randomized, multicenter trial comparing the efficacy and safety of IFN β-1a 44 mcg SC tiw (n=339) versus IFN β-1a 30 mcg IM qw (n=338) in patients with RMS.
- Patients with RMS and EDSS scores of 0–5.5 were to have experienced at least two relapses in the prior 2 years. Principal exclusion criteria were previous use of IFN, cladribine, or total lymphoid irradiation; use of glatiramer acetate or cytokine therapy in the prior 3 months; use of intravenous immunoglobulin in the prior 6 months; and use of other immunomodulatory agents in the prior 12 months.[1]
- The primary endpoint was the proportion of patients remaining free of relapses during the 24 weeks. A relapse was defined as the appearance of a new symptom or worsening of an old symptom, accompanied by an appropriate objective finding on neurologic examination by the blinded evaluator, lasting at least 24 hours in the absence of fever, and preceded by at least 30 days of clinical stability or improvement.
- Magnetic resonance imaging (MRI) brain scans were performed with and without Gd at screening, on Study Day 1, and every 4 weeks thereafter up to Week 24. At Week 48, a final scan was performed without Gd.
- In this *post hoc* analysis, between-treatment differences were evaluated for numbers of patients achieving the following:
  - CAF (clinical activity free), defined as no relapses and no confirmed 12-week disability worsening (increase of ≥1.0 point in EDSS from baseline sustained for ≥12 weeks) at 24 and 48 weeks.
  - NEDA (no evident disease activity) at 24 weeks, defined as no relapses and no confirmed 12-week disability worsening, with no Gd+ lesions and no new or enlarging T2 lesions on the Week 24 MRI scan.
    - At 24 and 48 weeks, a less stringent definition of NEDA (LS-NEDA; composite of CAF and no new or enlarging T2 lesions on the MRI scan at that timepoint) was assessed, as only T2 (but not Gd-enhanced T1) scans were performed at 48 weeks.
  - MRI activity free at 24 weeks, defined as no new or enlarging T2 lesions and no Gd+ lesions on the Week 24 scan.
    - A less stringent definition of MRI activity free (LS-MRI activity free), defined as no new or enlarging T2 lesions, was assessed based on the Week 48 scan.
- Logistic regression was performed to assess the treatment difference.
- In addition, a *post hoc* analysis was conducted on the effects of IFN β-1a SC versus IFN β-1a IM on MRI outcomes.
  - A combined unique active (CUA) lesion was defined as a Gd+ lesion or new or enlarging T2 lesion, avoiding double counting.
  - Numbers of CUA lesions per patient per scan (from baseline [Study Day 1] up to Weeks 4, 8, 12, 16, 20, and 24) were compared between IFN β-1a SC and IFN β-1a IM using a non-parametric analysis of covariance model on ranked data with effects for treatment group and center and number of CUA lesions at baseline as covariate.
  - Proportions of patients with no CUA MRI scans during each successive 4-week period up to Week 24 were compared between IFN β-1a SC and IFN β-1a IM, using a logistic model with effects for treatment and center.

Results

Baseline demographic and disease characteristics

- Baseline demographics and disease characteristics did not differ significantly between treatment groups, nor did baseline numbers of Gd+ lesions, new or enlarging T2 lesions (showing new activity between screening and baseline), or CUA lesions (**Table 1**). The proportion of patients with no CUA lesions at baseline was 47% in the IFN β-1a SC group and 48% in the IFN β-1a IM group (p=0.705).

Table 1. Baseline demographic and disease characteristics.

	IFN β-1a 44 mcg SC tiw (n=339)	IFN β-1a 30 mcg IM qw (n=337)[a]
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 MRI lesions at baseline		
n	309	305
Gd+ lesions		
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	
New or enlarging T2 lesions		
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	
CUA lesions		
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	

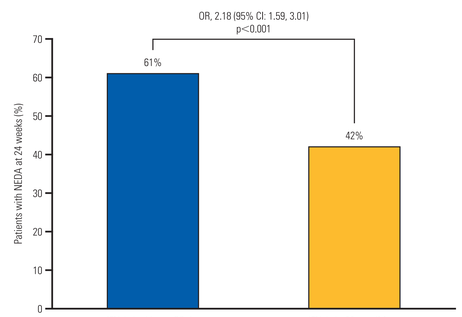
A CUA lesion was defined as a Gd+ lesion or new or enlarging T2 lesion, avoiding double counting. p-values for treatment group comparisons of baseline MRI characteristics were estimated using a non-parametric ANCOVA model on ranked data with effects for treatment group. New or enlarging T2 lesions at baseline were those showing new activity since screening.

ANCOVA, analysis of covariance; 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; Q, quartile; qw, once weekly; SC, subcutaneously; SD, standard deviation; tiw, three times weekly

[a]338 subjects were randomized to IFN β-1a 30 mcg IM qw; one subject was not treated and was excluded from this *post hoc* analysis.

Post hoc analysis of NEDA and CAF status

- At 24 weeks, NEDA was observed in more patients receiving IFN β-1a SC than those receiving IFN β-1a IM (61% vs 42%; p<0.001; **Figure 1**).
- More patients receiving IFN β-1a SC achieved CAF status than patients receiving IFN β-1a IM at 24 weeks (72% vs 58%; p<0.001; **Table 2**) and at 48 weeks (56% vs 46%; p=0.01; **Figure 2**).
- More patients receiving IFN β-1a SC than patients receiving IFN β-1a IM had LS-NEDA at 24 weeks (66% vs 50%; p<0.001; **Table 2**) and at 48 weeks (44% vs 32%; p=0.003; **Figure 3**).
- Percentages of patients free of MRI activity at 24 weeks and free of LS-MRI activity at 48 weeks were also greater with IFN β-1a SC than with IFN β-1a IM (p<0.001 for both timepoints; **Table 2**).



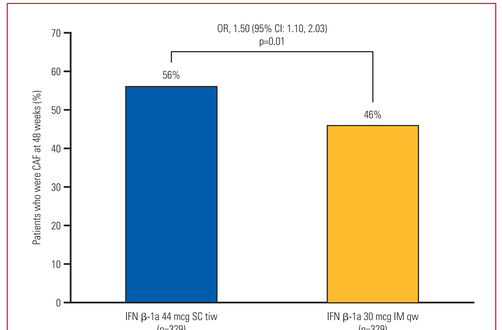
NEDA was defined as no relapses, no confirmed 12-week disability worsening (increase of ≥1.0 point in EDSS from baseline sustained for ≥12 weeks), no Gd+ lesions, and no new or enlarging T2 lesions.
CI, confidence interval; EDSS, Expanded Disability Status Scale; Gd+, gadolinium-enhancing; IFN β-1a, interferon beta-1a; IM, intramuscularly; NEDA, no evident disease activity; OR, odds ratio; qw, once weekly; SC, subcutaneously; tiw, three times weekly

Figure 1. Percentage of patients with NEDA at 24 weeks.

Table 2. Percentages of patients with CAF status at 24 weeks, LS-NEDA status at 24 weeks, or MRI/LS-MRI activity free status at 24 or 48 weeks.

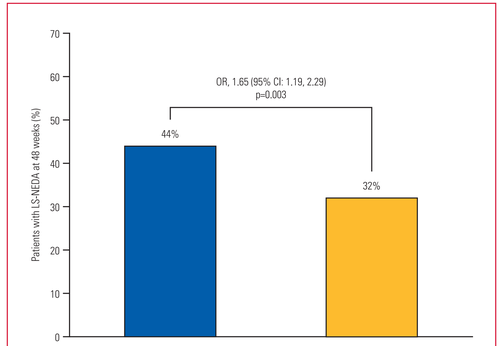
Endpoint	Proportion of patients: IFN β-1a 44 mcg SC tiw	Proportion of patients: IFN β-1a 30 mcg IM qw	OR (95% CI) p-value
	n=339	n=337	
CAF[a] at 24 weeks	72%	58%	1.87 (1.35, 2.58) p<0.001
	n=325	n=324	
LS-NEDA[b] at 24 weeks	66%	50%	1.99 (1.44, 2.75) p<0.001
MRI activity free[c] at 24 weeks	81%	67%	2.14 (1.48, 3.11) p<0.001
LS-MRI activity free[d] at 48 weeks	75%	63%	1.81 (1.28, 2.57) p<0.001

All p-values are for IFN β-1a 44 mcg SC tiw versus IFN β-1a 30 mcg IM qw.
CAF, clinical activity free; CI, confidence interval; EDSS, Expanded Disability Status Scale; Gd+, gadolinium-enhancing; IFN β-1a, interferon beta-1a; IM, intramuscularly; LS-MRI; less stringent definition of magnetic resonance imaging; LS-NEDA, less stringent definition of no evident disease activity; MRI, magnetic resonance imaging; OR, odds ratio; qw, once weekly; SC, subcutaneously; tiw, three times weekly
[a]Defined as no relapses and no confirmed 12-week disability worsening (increase of ≥1.0 point in EDSS from baseline sustained for ≥12 weeks).
[b]Defined as no relapses, no confirmed 12-week disability worsening, and no new or enlarging T2 lesions on the Week 24 scan.
[c]Defined as free of both Gd+ lesions and new or enlarging T2 lesions on the Week 24 scan.
[d]Defined as free of new or enlarging T2 lesions on the Week 48 scan.



CAF was defined as no relapses and no confirmed 12-week disability worsening (increase of ≥1.0 point in EDSS from baseline sustained for ≥12 weeks).
CAF, clinical activity free; CI, confidence interval; EDSS, Expanded Disability Status Scale; IFN β-1a, interferon beta-1a; IM, intramuscularly; OR, odds ratio; qw, once weekly; SC, subcutaneously; tiw, three times weekly

Figure 2. Percentage of patients who achieved CAF status at 48 weeks.

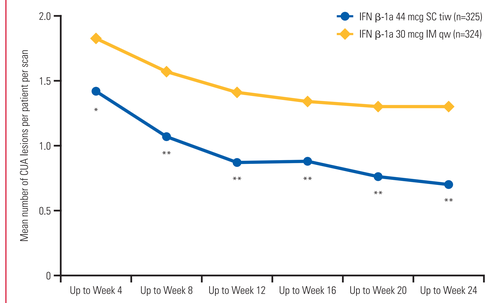


LS-NEDA was defined as no relapses, no confirmed 12-week disability worsening (increase of ≥1.0 point in EDSS from baseline sustained for ≥12 weeks), and no new or enlarging T2 lesions.
CI, confidence interval; EDSS, Expanded Disability Status Scale; IFN β-1a, interferon beta-1a; IM, intramuscularly; LS-NEDA, less stringent definition of no evident disease activity; OR, odds ratio; qw, once weekly; SC, subcutaneously; tiw, three times weekly

Figure 3. Percentage of patients with LS-NEDA at 48 weeks.

Post hoc analysis of early effects of treatment on MRI activity

- The number of CUA lesions per patient per scan was significantly lower with IFN β-1a SC than with IFN β-1a IM at Week 4 (p=0.019; **Figure 4**) and remained lower with IFN β-1a SC than with IFN β-1a IM during all subsequent times (p<0.001; **Figure 4**).
- The proportion of patients with no CUA MRI scans was higher with IFN β-1a SC than with IFN β-1a IM at Week 4 (61% vs 53%, odds ratio, 1.4 [95% confidence interval: 1.0, 2.0]; p=0.045), and remained so during each successive 4-week period evaluated (p≤0.001).
- The proportion of patients with no CUA MRI scans during the entire 24-week period was 49% with IFN β-1a SC versus 33% with IFN β-1a IM (p<0.001).



A CUA lesion was defined as a Gd+ lesion or new or enlarging T2 lesion, avoiding double counting.
*p<0.05 versus IFN β-1a 30 mcg IM. **p<0.001 versus IFN β-1a 30 mcg IM.
CUA, combined unique active; Gd+, gadolinium-enhancing; IFN β-1a, interferon beta-1a; IM, intramuscularly; qw, once weekly; SC, subcutaneously; tiw, three times weekly

Figure 4. Mean number of CUA lesions per patient per scan from baseline up to Weeks 4, 8, 12, 16, 20, and 24.

Conclusions

- In this *post hoc* analysis of the randomized, head-to-head EVIDENCE trial, significantly more patients treated with IFN β-1a 44 mcg SC tiw than with IFN β-1a 30 mcg IM qw had NEDA (no relapses, no confirmed 12-week disability worsening, no Gd+ lesions, and no new or enlarging T2 lesions) at 24 weeks.
- Greater responses in clinical and/or MRI activity free status, including CAF at 24 and 48 weeks and LS-NEDA at 48 weeks, were also achieved in patients treated with IFN β-1a 44 mcg SC tiw than in those treated with IFN β-1a 30 mcg IM qw.
- Numbers of CUA lesions were significantly lower in patients treated with IFN β-1a 44 mcg SC tiw than in those treated with IFN β-1a 30 mcg IM qw by as early as 4 weeks (the time of the first post-baseline MRI scan), and differences continued to be seen at subsequent timepoints.

CAF, clinical activity free; CUA, combined unique active; LS-NEDA, less stringent definition of no evident disease activity; NEDA, no evident disease activity

References

1. Panitch H, *et al. Neurology* 2002;59:1496–506.
2. Bamwell B, *et al. Mult Scler Relat Disord* 2013;2:65–7.
3. Bevan CJ, Cree BA. *JAMA Neurol* 2014;71:269–70.

Acknowledgments

The authors thank Reza Sayeed of Caudex Medical, New York, NY (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.

Disclosures

PKC received consulting fees from AbbVie, Accordant, Acorda, Bayer, Biogen, EMD Serono, Inc., Genentech/Roche, Genzyme/Sanofi, Mylan, Novartis, and Teva Pharmaceuticals, and contracted research with Actelion, Genzyme/Sanofi, Novartis, and Opexa. JF, AH, CC, and FD are employees of EMD Serono, Inc.* ATR received consulting fees from Acorda, Bayer, Biogen, EMD Serono, Inc., Genzyme, Novartis, Pfizer, Questcor, Sanofi, and Teva Pharmaceuticals.

*A subsidiary of Merck KGaA, Darmstadt, Germany.

To view the ePoster, scan the QR code or go to http://www.emdseronocongressposters.com/ACTRIMS-ECTRIMS14/P102.pdf