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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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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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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.

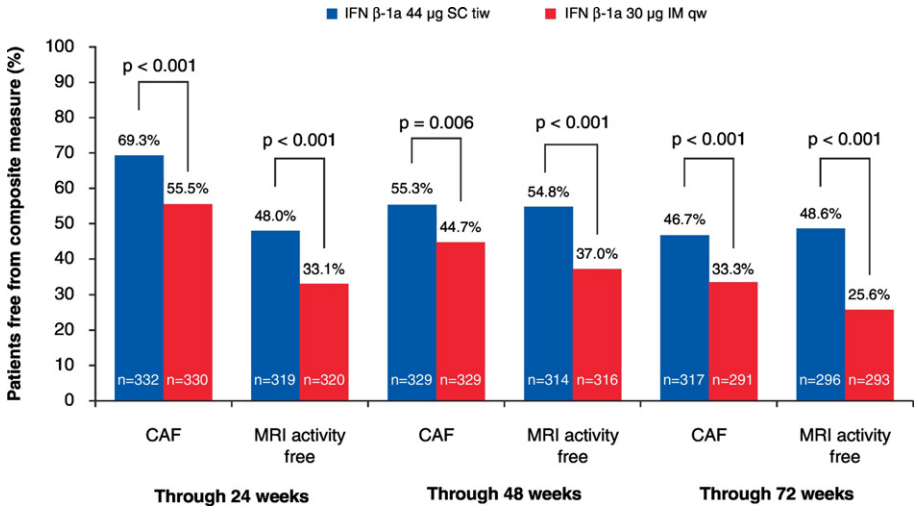

Fig. 1. Proportions of patients achieving CAF[a] and MRI activity-free[b] endpoints through 24, 48 and 72 weeks. [a]Defined as no relapses and no confirmed 12-week disability worsening (increase of ≥1.0 point in EDSS score from baseline sustained for ≥12 weeks). [b]Through 24 weeks, defined as no T1 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.