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Peginterferon β-1a every 2 weeks increased achievement of no evidence of disease activity over 4 years in the ADVANCE and ATTAIN studies in patients with relapsing–remitting multiple sclerosis

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Abstract

Background: No evidence of disease activity (NEDA) is a composite measurement, incorporating clinical and magnetic resonance imaging (MRI) elements of disease activity to sensitively evaluate the therapeutic efficacy of treatments for relapsing–remitting multiple sclerosis (RRMS).

Objective: To assess the NEDA status of patients treated with peginterferon β-1a in the ADVANCE and ATTAIN studies and explore its predictive value on longer-term clinical outcomes.

Methods: ATTAIN was a 2-year extension of the pivotal 2-year ADVANCE study of peginterferon β-1a for RRMS. Achievement of clinical NEDA, MRI NEDA, or overall NEDA was calculated cumulatively and by year over 4 years. Clinical outcomes during ATTAIN were analyzed based on NEDA status at the end of ADVANCE.

Results: Significantly more patients treated with peginterferon β-1a every 2 weeks than every 4 weeks achieved clinical NEDA (60.6% *versus* 50.6%, $p = 0.0063$) and MRI NEDA (28.3% *versus* 15.8%, $p = 0.0005$) through year 4 and overall NEDA through year 3 (20.9% *versus* 13.9%, $p = 0.0160$). Over 4 years, 15.8% of patients in the every 2 weeks group and 10.7% of patients in the every 4 weeks group maintained overall NEDA ($p = 0.0584$). Achievement of clinical NEDA, MRI NEDA, or overall NEDA in ADVANCE was predictive of annualized relapse rate in ATTAIN; achievement of clinical NEDA in ADVANCE was also predictive of NEDA achievement and confirmed disability worsening in ATTAIN.

Conclusions: Peginterferon β-1a every 2 weeks is associated with higher levels of NEDA compared with placebo in year 1 or peginterferon β-1a every 4 weeks in years 2–4. Overall NEDA within the first 2 years of treatment may be prognostic of long-term clinical outcomes.

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Keywords: multiple sclerosis, peginterferon β-1a, pegylated interferon, relapse, relapsing–remitting multiple sclerosis

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Introduction

Peginterferon β-1a is a disease-modifying therapy (DMT) indicated for dosing once every 2 weeks in patients with relapsing forms of multiple sclerosis (MS) based on the pivotal, 2-year phase III ADVANCE trial.[1,2] In year 1 of ADVANCE, subcutaneous peginterferon β-1a 125 μg dosed every 2 or 4 weeks showed superior efficacy compared with placebo in patients with relapsing–remitting MS (RRMS).[3,4] In ADVANCE year 2,

placebo-treated patients were rerandomized to peginterferon β-1a 125 μg (i.e. delayed treatment), and continuous peginterferon β-1a 125 μg dosing similarly demonstrated superior efficacy to delayed treatment. ATTAIN was a 2-year extension study of ADVANCE.

The concept of no evidence of disease activity (NEDA) was first proposed as a composite measure to assess whether patients with RRMS were meeting treatment goals in the clinical trial setting.[5,6] Evidence suggests that NEDA may be a more sensitive measure of therapeutic efficacy than traditional endpoints, and achieving NEDA has been proposed as a principal aim for neurologists in their practices.[7] NEDA comprises clinical and magnetic resonance imaging (MRI) parameters and is defined as no evidence of relapses, no onset of confirmed disability worsening (CDW), and no active MRI lesions [i.e. new or newly enlarging T2 hyperintense (NET2) lesions or gadolinium-enhanced (Gd+) lesions]. NEDA has been evaluated, with varying definitions, in other DMTs (e.g. natalizumab, fingolimod, cladribine, and interferon β-1a combined with glatiramer acetate).[5,8–10]

In ADVANCE year 1, significantly more patients dosed with peginterferon β-1a every 2 weeks achieved NEDA than those dosed every 4 weeks or who received placebo.[11] In ADVANCE year 2, significantly more patients dosed continuously with peginterferon β-1a every 2 weeks achieved NEDA than those with delayed treatment.[12] The current *post hoc* analysis assessed NEDA status during the ADVANCE (years 1 and 2) and ATTAIN (years 3 and 4) studies and explored clinical outcomes, including annualized relapse rate (ARR), CDW, and achievement of NEDA in years 3 and 4 among patients stratified by NEDA achievement at year 2.

Materials and methods

Study design and participants

ADVANCE was a 2-year, international, randomized, double-blind phase III study with a 1-year placebo-controlled period. During year 1 of ADVANCE, patients were randomized (1:1:1) to placebo or peginterferon β-1a 125 μg every 2 or 4 weeks.[3] In year 2, placebo patients were rerandomized to peginterferon β-1a 125 μg every 2 or 4 weeks.[4] ATTAIN, the extension study of ADVANCE, was not considered complete until the last enrolled patient completed 96 weeks in the ATTAIN study; therefore, some patients received treatment for nearly 6 years.

Patients who were aged 18–65 years with a diagnosis of RRMS, a score of 0–5 on the Expanded Disability Status Scale (EDSS),[13] and at least two relapses in the previous 3 years (at least one within the past 12 months) were eligible for ADVANCE study inclusion. Exclusion criteria included progressive forms of MS, prespecified laboratory abnormalities, and previous treatment with interferon for MS for over 4 weeks or discontinuation less than 6 months before baseline.[3] Patients who had successfully completed the ADVANCE 2-year trial were eligible to enter the ATTAIN study.

All protocols were approved by the institutional review board at each site, and the study was conducted according to International Conference on Harmonization Guidelines for Good Clinical Practice and the Declaration of Helsinki. Patients provided written informed consent prior to beginning the ADVANCE study. ADVANCE and ATTAIN are registered with ClinicalTrials.gov [ClinicalTrials.gov identifier: NCT00906399 and NCT01939002].

Study procedures and endpoints

The proportion of patients in the ATTAIN intent-to-treat (ITT) population (all randomized patients who received at least one dose of active study treatment over 2 years) who experienced NEDA were evaluated annually. Clinical NEDA was defined as the absence of clinical disease activity [no relapses and no onset of 24-week CDW (defined as a ⩾1.0-point increase from an ADVANCE baseline EDSS score of ⩾1.0 or ⩾1.5-point increase from an ADVANCE baseline EDSS score of ⩾0.0, confirmed ⩾24 weeks later)]. MRI NEDA was defined as the absence of MRI disease activity (no Gd+ lesions and no NET2 lesions). Overall NEDA was defined as no evidence of clinical or MRI disease activity.

Statistical analysis

The NEDA analysis used observed data only; patients missing measurements who had achieved NEDA on all available measurements were

excluded, while patients missing measurements who had evidence of disease activity in at least one measurement were considered as not achieving NEDA. A logistic regression model was used to calculate odds ratios and corresponding p values. Patients in all dosing groups (including those receiving placebo in year 1) were stratified based on achievement of NEDA during ADVANCE years 1 and 2 (NEDA+/NEDA− for each clinical NEDA, MRI NEDA, or overall NEDA assessment). ARR, CDW, and NEDA achievement during ATTAIN were analyzed based on NEDA status at the end of year 2 in ADVANCE.

To assess NEDA status 6 months after peginterferon β-1a initiation, the NEDA analysis was repeated with baseline for each outcome set as month 6 data (to allow time after initiation for a therapeutic effect to be achieved). Relapses, EDSS scores, and MRI measurements on or after month 6 were assessed, whereas relapses, EDSS scores, and MRI measurements prior to month 6 were removed.

Results

Patients

In the ADVANCE study, a total of 1512 patients were randomized, with 500 receiving placebo, 512 receiving peginterferon β-1a every 2 weeks, and 500 receiving peginterferon β-1a every 4 weeks; four patients were not dosed. Of the 1332 patients who completed year 1, 456 patients from the placebo arm were rerandomized to receive either peginterferon β-1a every 2 or every 4 weeks (228 patients in each group); 876 patients remained on continuous peginterferon β-1a either every 2 or every 4 weeks (438 patients in each group; Supplemental Figure 1).[3,4]

Patient demographics and baseline disease characteristics have been reported previously and were generally well balanced across treatment groups.[3] Of the 1512 patients in the ITT population in ADVANCE, 260 (17%) had previously received treatment for MS, the mean age of patients across treatment groups was 36.3–36.9 years, and 70–72% were female.[3] Overall, of the 1512 patients who were randomized and dosed in ADVANCE, 842 patients (56%) completed the ATTAIN study. Baseline characteristics for the ATTAIN ITT population are shown in Supplemental Table 1.

NEDA assessment

Clinical NEDA, MRI NEDA, and overall NEDA outcomes over 4 years of treatment were analyzed year by year or cumulatively for patients who had been assigned to placebo or active treatment (peginterferon β-1a every 2 or 4 weeks) at initial randomization in ADVANCE.

Significantly more patients treated with peginterferon β-1a every 2 weeks than with placebo achieved clinical NEDA, MRI NEDA, and overall NEDA in year 1 (Figure 1; $p = 0.0013$, $p < 0.0001$, and $p < 0.0001$, respectively). Moreover, significantly more patients treated with peginterferon β-1a every 2 weeks than every 4 weeks achieved clinical NEDA after year 1 and MRI NEDA over all 4 years. Overall NEDA was higher for peginterferon β-1a administered every 2 weeks than peginterferon β-1a administered every 4 weeks over 1 year (34.8% *versus* 22.0%, $p = 0.0001$), 2 years (27.3% *versus* 15.9%, $p = 0.0002$), and 3 years (20.9% *versus* 13.9%, $p = 0.0160$). Over 4 years, overall NEDA was maintained by 15.8% of patients in the every 2 weeks group and 10.7% of patients in the every 4 weeks group ($p = 0.0584$). After rebaselining at 6 months, a significantly higher percentage of patients treated every 2 weeks than every 4 weeks achieved clinical NEDA after year 1 and MRI NEDA and overall NEDA over all 4 years (Figure 2).

On a year-by-year basis, significantly more patients treated with peginterferon β-1a every 2 weeks than every 4 weeks achieved higher rates of clinical NEDA, MRI NEDA, and overall NEDA (Supplemental Figure 2). During years 2–4, over 80% of patients treated with peginterferon β-1a every 2 weeks achieved clinical NEDA each year, over 60% achieved MRI NEDA each year, and over 50% achieved overall NEDA each year.

Clinical outcome prediction

Clinical outcomes in years 3 and 4 were stratified by NEDA status over years 1 and 2 [NEDA+ (achieved clinical NEDA, MRI NEDA, or overall NEDA, as appropriate) or NEDA− (did not achieve clinical NEDA, MRI NEDA, or overall NEDA, as appropriate)]. Achievement of clinical NEDA, MRI NEDA, or overall NEDA over years 1 and 2 was predictive of ARR in years 3 and 4, with significantly lower ARRs in the NEDA+ groups than in the NEDA− groups (peginterferon

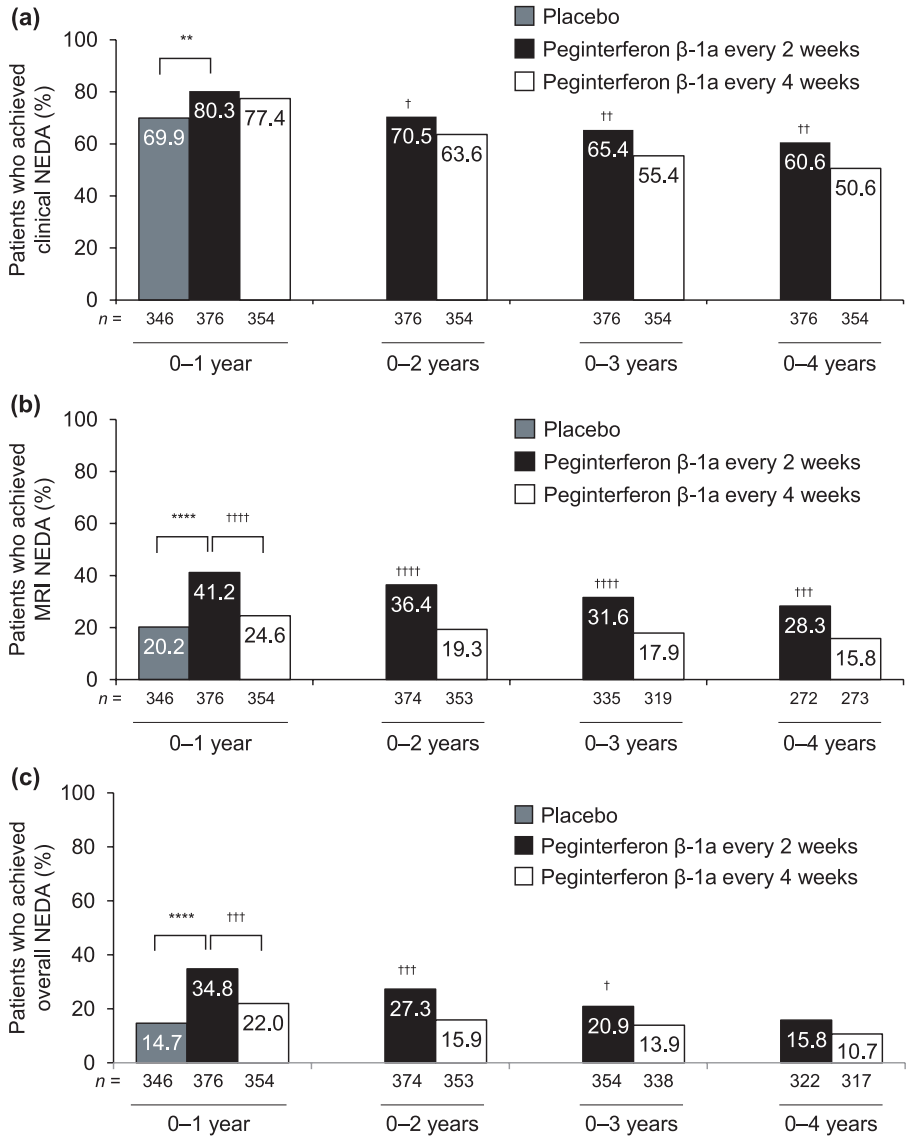

Figure 1. Patients who achieved (a) clinical NEDA, (b) MRI NEDA, and (c) overall NEDA over 4 years (cumulative).
$^{**}p < 0.01$; $^{****}p < 0.0001$ for peginterferon β-1a every 2 weeks *versus* placebo. $^{\dagger}p < 0.05$; $^{\dagger\dagger}p < 0.01$; $^{\dagger\dagger\dagger}p < 0.001$; $^{\dagger\dagger\dagger\dagger}p < 0.0001$ for peginterferon β-1a every 2 weeks *versus* peginterferon β-1a every 4 weeks. MRI, magnetic resonance imaging; NEDA, no evidence of disease activity.

β-1a dosing groups combined; clinical NEDA, $p < 0.0001$; MRI NEDA, $p = 0.0002$; overall NEDA, $p < 0.0001$; Figure 3). Achievement of clinical NEDA (but not of MRI NEDA or overall NEDA) over years 1 and 2 was predictive of 24-week CDW in years 3 and 4, with a significantly lower proportion of patients with 24-week CDW in the NEDA+ group than in the NEDA− group (Figure 4; $p = 0.0021$). Moreover, achievement of clinical NEDA, MRI NEDA, or overall NEDA over years 1 and 2 was predictive of achieving clinical NEDA, MRI NEDA, or overall NEDA, respectively, in years 3 and 4, with significantly greater proportions of NEDA+ ADVANCE patients achieving NEDA in ATTAIN (Figure 5; $p < 0.0001$ *versus* NEDA− ADVANCE patients).

Discussion

The outcomes of this analysis of NEDA status in ATTAIN are consistent with previously reported

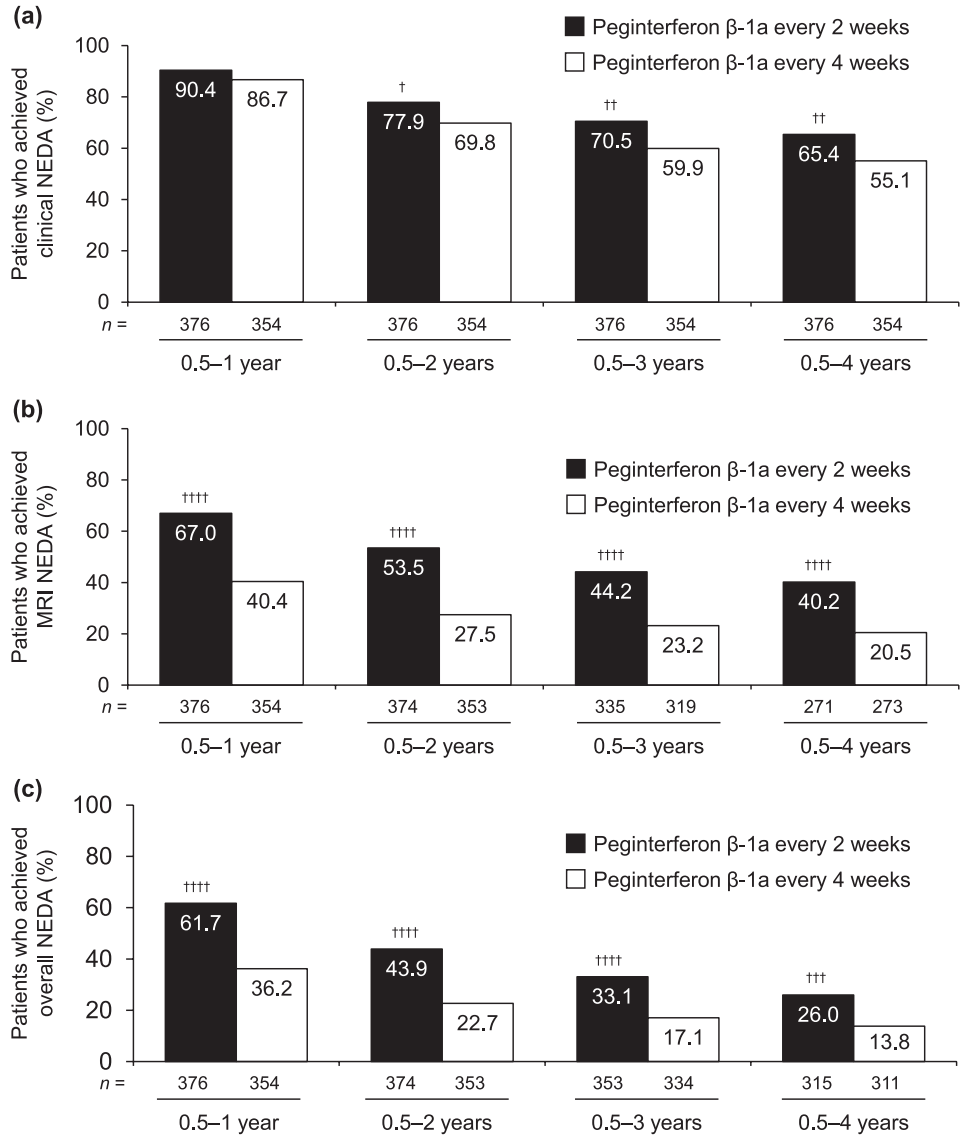

Figure 2. Patients who achieved (a) clinical NEDA, (b) MRI NEDA, and (c) overall NEDA over 4 years (cumulative, baseline at 6 months).
$^{\dagger}p < 0.05$; $^{\dagger\dagger}p < 0.01$; $^{\dagger\dagger\dagger}p < 0.001$; $^{\dagger\dagger\dagger\dagger}p < 0.0001$ for peginterferon β-1a every 2 weeks *versus* peginterferon β-1a every 4 weeks. MRI, magnetic resonance imaging; NEDA, no evidence of disease activity.

data from the ADVANCE study and support the sustained efficacy of peginterferon β-1a every 2 weeks.[11,12] In this study, analyses of cumulative (year over year) and yearly (year by year) NEDA achieved in the ADVANCE/ATTAIN studies demonstrated that peginterferon β-1a continues to provide significant improvement on clinical and MRI endpoints through 4 years of treatment. Just over one third of patients receiving peginterferon β-1a every 2 weeks achieved overall NEDA in year 1, which was significantly higher than the percentage of overall NEDA observed in year 1 in patients receiving peginterferon β-1a every 4 weeks or placebo (Figure 1). The relatively low percentage of NEDA in year 1 for patients treated with peginterferon β-1a, compared with later yearly NEDA rates (Supplemental Figure 2), is likely attributable to patients having disease not yet stabilized on the medication and to the several months that the medication may require to have an appreciable effect,[14] a trend similar to that observed with other DMTs (depending on the pharmacodynamics of the DMT).[5,15] Based on this trend, it

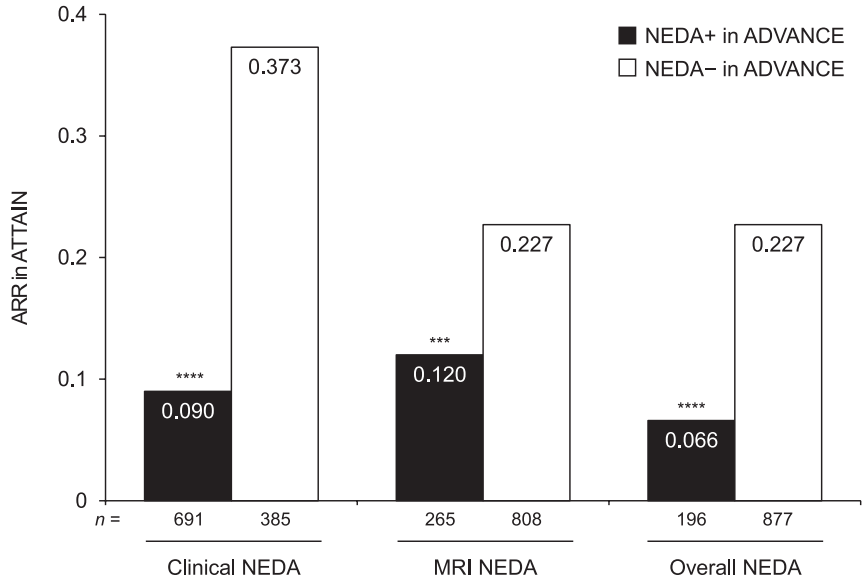

Figure 3. ARR in years 3 and 4 by clinical NEDA, MRI NEDA, and overall NEDA in the 2-year ADVANCE study.
Mean ARRs during years 3 and 4 are shown for subgroups of patients who did (NEDA+) or did not (NEDA–) achieve clinical NEDA, MRI NEDA, or overall NEDA at year 2 in ADVANCE. ***$p < 0.001$; ****$p < 0.0001$ for NEDA+ *versus* NEDA–. ARR, annualized relapse rate; MRI, magnetic resonance imaging; NEDA, no evidence of disease activity.

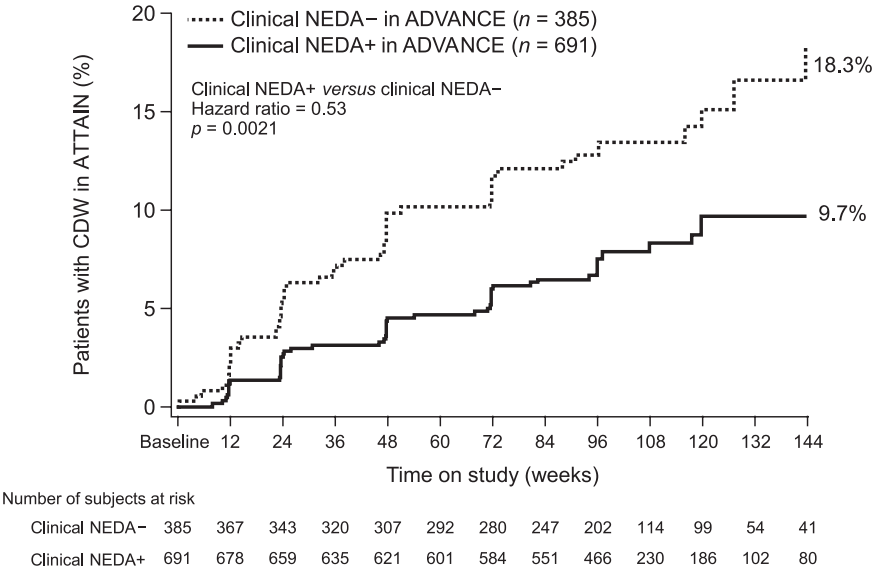

Figure 4. Twenty-four-week CDW in years 3 and 4 in patients by achievement of clinical NEDA in the 2-year ADVANCE study.
Kaplan–Meier estimate; CDW is defined as ⩾1.0-point increase from an ATTAIN baseline EDSS score of ⩾1.0 or a ⩾1.5-point increase from an ATTAIN baseline EDSS score of ⩾0.0, confirmed ⩾24 weeks later; *p* value is based on a Cox proportional hazards model, with adjustment for baseline EDSS score and age (<40 or ⩾40). CDW, confirmed disability worsening; EDSS, Expanded Disability Status Scale; NEDA, no evidence of disease activity; NEDA+, achieved NEDA during ADVANCE; NEDA–, did not achieve NEDA during ADVANCE.

has been recommended that patients be rebaselined after 3–6 months of interferon β therapy to determine more accurately whether NEDA has been achieved.[14] Indeed, a higher percentage of patients who rebaselined at 6 months than who did not rebaseline achieved clinical NEDA, MRI NEDA, and overall NEDA over 4 years (Figures 1 and 2).

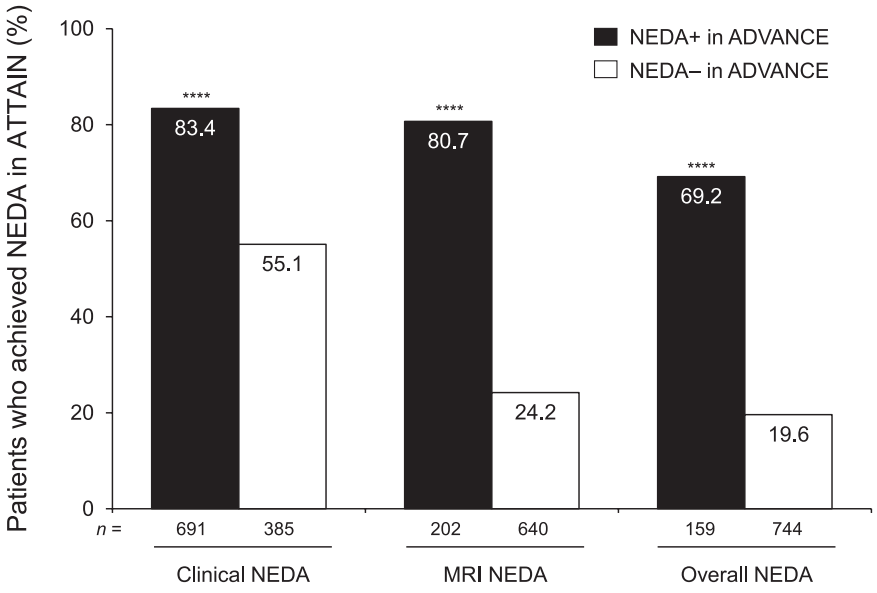

Figure 5. NEDA achievement in years 3 and 4 by NEDA achievement in the 2-year ADVANCE study.
Proportion of patients achieving clinical NEDA, MRI NEDA, or overall NEDA during years 3 and 4 are shown for subgroups of patients who did (NEDA+) or did not (NEDA–) achieve clinical NEDA, MRI NEDA, or overall NEDA, respectively, at year 2. Only patients for whom NEDA data were available were included in the analysis. ****$p < 0.0001$ for NEDA+ *versus* NEDA–.
MRI, magnetic resonance imaging; NEDA, no evidence of disease activity.

Experts have debated the prognostic significance of NEDA status.[16] A recent study found that patients with MS who achieve NEDA during the first 2 years of observation had similar long-term outcomes to the cohort as a whole, suggesting that NEDA in the first 2 years is not predictive of long-term disease stability.[16] Conversely, in the current study, patients who achieved NEDA (clinical, MRI, or overall) over years 1 and 2 of treatment had significantly reduced ARR during treatment years 3 and 4 compared with patients who did not achieve NEDA, suggesting that NEDA status after the first 2 years of treatment is indeed prognostic of long-term clinical outcomes. This finding, particularly for clinical NEDA, is consistent with data from earlier studies. For example, one long-term observational study of patients with MS found that achieving NEDA in year 1 and year 2 was 72% and 78% predictive, respectively, of no disease progression (defined as an EDSS change of $\leqslant 0.5$) at 7 years.[17] In addition, a prediction model for the progression of disability in MS found the number of brain T2 lesions on MRI at baseline was highly predictive of long-term prognosis.[18]

Since the introduction of NEDA, several *post hoc* analyses have been published on clinical trials of DMTs and found improvements in NEDA achievement with active treatment compared with placebo.[5,15,19,20] Although these studies cannot be directly compared because of differences between patient populations, study methodologies, and endpoints (e.g. 3- *versus* 6-month CDW), NEDA analyses allow for an improved understanding of the benefits and limitations of other DMTs. In the current analysis, a significantly higher percentage of patients treated with peginterferon β-1a every 2 weeks achieved overall NEDA compared with placebo patients (year 1) and compared with patients treated with peginterferon β-1a every 4 weeks (years 2–4). It must be noted that study dropouts could contribute to the higher yearly rates as the study progresses.

These results are limited by the *post hoc* nature of the analyses. As ATTAIN is the open-label extension of ADVANCE, patients in years 3 and 4 of this analysis may have been selected for those with a tendency to experience a greater therapeutic response. The finding that clinical NEDA was more common than MRI NEDA supports previous data indicating that MRI activity may be a determining factor for achievement of overall NEDA.[12] Although NEDA has traditionally been defined as no evidence of disease activity as defined by relapses, CDW, and MRI activity (Gd+ and NET2 lesions) (i.e. NEDA-3), no

standard definition of NEDA has been established, and definitions vary across studies. Methods of analyses (e.g. to account for missing data), the sensitivity of MRI analyses, and the number of scans may also vary between studies. Other studies have suggested moving beyond the three-component NEDA to include additional endpoints. For example, the incorporation of brain volume loss as a component of NEDA (i.e. NEDA-4) has been proposed.[19] However, analysis of MRI data from the ADVANCE study suggests that brain volume is unsuitable as a component of NEDA because of the small changes observed over periods of clinical interest (1 or 2 years), the noise in this measurement, and the potential complication of pseudoatrophy.[12]

The ATTAIN study provided long-term data demonstrating that peginterferon β-1a every 2 weeks remained safe and effective on clinical and MRI endpoints over 4 years of treatment.[21] These analyses also provide evidence that peginterferon β-1a every 2 weeks increases the likelihood of achieving NEDA in patients with RRMS and suggest that achieving NEDA over the first 2 years of treatment may predict improved long-term outcomes.

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Conflict of interest statement

DA: had an equity interest in NeuroRx during the conduct of the study and has received personal fees from Acorda, Biogen, EMD Serono, Genentech, Genzyme, Hoffman–La Roche, Innate Immunotherapy, MedImmune, Mitsubishi, Novartis, Receptos, Sanofi, and Teva, and grants from Biogen and Novartis. SS, QD: full-time employees and stockholders of Biogen at the time of the analysis. MM, MLN: full-time employees and stockholders of Biogen.

References

1. Biogen. *Plegridy (peginterferon beta-1a) injection, for subcutaneous injection* [package insert]. Cambridge, MA: Biogen, 2016.
2. Biogen Idec Ltd. *Plegridy (peginterferon beta-1a) [summary of product characteristics]*. Maidenhead, UK: Biogen Idec Ltd., 2017.
3. Calabresi PA, Kieseier BC, Arnold DL, *et al*; ADVANCE Study Investigators. Pegylated interferon beta-1a for relapsing-remitting multiple sclerosis (ADVANCE): a randomised, phase 3, double-blind study. *Lancet Neurol* 2014; 13: 657–665.
4. Kieseier BC, Arnold DL, Balcer LJ, *et al*. Peginterferon beta-1a in multiple sclerosis: 2-year results from ADVANCE. *Mult Scler* 2015; 21: 1025–1035.
5. Havrdova E, Galetta S, Hutchinson M, *et al*. Effect of natalizumab on clinical and radiological disease activity in multiple sclerosis: a retrospective analysis of the Natalizumab Safety and Efficacy in Relapsing-Remitting Multiple Sclerosis (AFFIRM) study. *Lancet Neurol* 2009; 8: 254–260.
6. Stangel M, Penner IK, Kallmann BA, *et al*. Towards the implementation of 'no evidence of disease activity' in multiple sclerosis treatment: the multiple sclerosis decision model. *Ther Adv Neurol Disord* 2015; 8: 3–13.
7. Giovannoni G, Turner B, Gnanapavan S, *et al*. Is it time to target no evident disease activity (NEDA) in multiple sclerosis? *Mult Scler Relat Disord* 2015; 4: 329–333.
8. Giovannoni G, Cook S, Rammohan K, *et al*. Sustained disease-activity-free status in patients with relapsing-remitting multiple sclerosis treated with cladribine tablets in the CLARITY study: a post-hoc and subgroup analysis. *Lancet Neurol* 2011; 10: 329–337.
9. Lindsey JW, Scott TF, Lynch SG, *et al*. The CombiRx trial of combined therapy with interferon and glatiramer acetate in relapsing remitting MS: design and baseline characteristics. *Mult Scler Relat Disord* 2012; 1: 81–86.
10. Kappos L, Radue EW, O'Connor P, *et al*. Fingolimod treatment increases the proportion

of patients who are free from disease activity in multiple sclerosis: results from a phase 3, placebo-controlled study (FREEDOMS). *Neurology* 2011; 76: A563.

11. Arnold DL, Calabresi PA, Kieseier BC, *et al*. Effect of peginterferon beta-1a on MRI measures and achieving no evidence of disease activity: results from a randomized controlled trial in relapsing-remitting multiple sclerosis. *BMC Neurol* 2014; 14: 240.
12. Arnold DL, Calabresi PA, Kieseier BC, *et al*. Peginterferon beta-1a improves MRI measures and increases the proportion of patients with no evidence of disease activity in relapsing-remitting multiple sclerosis: 2-year results from the ADVANCE randomized controlled trial. *BMC Neurol* 2017; 17: 29.
13. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology* 1983; 33: 1444–1452.
14. Giovannoni G, Tomic D, Bright JR, *et al*. "No evident disease activity": The use of combined assessments in the management of patients with multiple sclerosis. *Mult Scler* 2017; 23: 1179–1187.
15. Kappos L, Havrdova E, Giovannoni G, *et al*. No evidence of disease activity in patients receiving daclizumab versus intramuscular interferon beta-1a for relapsing-remitting multiple sclerosis in the DECIDE study. *Mult Scler* 2017; 23: 1736–1747.
16. University of California San Francisco MS Epic Team; Cree BA, Gourraud PA, Oksenberg JR, *et al*. Long-term evolution of multiple sclerosis disability in the treatment era. *Ann Neurol* 2016; 80: 499–510.
17. Rotstein DL, Healy BC, Malik MT, *et al*. Evaluation of no evidence of disease activity in a 7-year longitudinal multiple sclerosis cohort. *JAMA Neurol* 2015; 72: 152–158.
18. Tintore M, Rovira A, Rio J, *et al*. Defining high, medium and low impact prognostic factors for developing multiple sclerosis. *Brain* 2015; 138: 1863–1874.
19. Kappos L, De Stefano N, Freedman MS, *et al*. Inclusion of brain volume loss in a revised measure of 'no evidence of disease activity' (NEDA-4) in relapsing-remitting multiple sclerosis. *Mult Scler* 2016; 22: 1297–1305.
20. Havrdova E, Giovannoni G, Stefoski D, *et al*. Disease-activity-free status in patients with relapsing-remitting multiple sclerosis treated with daclizumab high-yield process in the SELECT study. *Mult Scler* 2014; 20: 464–470.
21. Fiore D, Hung S, Tang W, *et al*. ADVANCE phase 3 extension study (ATTAIN): peginterferon beta-1a 125 mcg every 2 weeks demonstrated sustained efficacy in RMS patients treated up to 5 years [abstract]. *Neurology* 2016; 87: e22.