Early treatment responses to peginterferon beta-1a are associated with longer-term clinical outcomes in patients with relapsing-remitting multiple sclerosis: subgroup analyses of ADVANCE and ATTAIN

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Early treatment responses to peginterferon beta-1a are associated with longer-term clinical outcomes in patients with relapsing-remitting multiple sclerosis: subgroup analyses of ADVANCE and ATTAIN

Scott D. Newsome, Thomas F. Scott, Douglas L. Arnold, Arman Altincatal, Maria L. Naylor

Scott D. Newsome
Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD 21287, USA
Tel: +1 443 287 4656
Fax: +1 410 502 8075
Email: snewsom2@jhmi.edu

Thomas F. Scott
Department of Neurology, Allegheny General Hospital, Pittsburgh, PA, USA

Douglas L. Arnold
Montreal Neurological Institute, McGill University, and NeuroRx Research, Montreal, QC, Canada

Arman Altincatal

Maria L. Naylor
Biogen, Cambridge, MA, USA, at the time of these analyses

Correspondence to: Scott D. Newsome
Keywords: brain atrophy; early treatment; no evidence of disease activity; peginterferon beta-1a; persistent T1 hypointensities

Highlights (limit: 85 characters including spaces)

- Early peginterferon beta-1a initiation was associated with better 2-year outcomes
- Early treatment reduced black hole conversion from new/enlarging T2 or Gd+ lesions
- Peginterferon beta-1a Q2W increased rates of no evidence of disease activity (NEDA)
- MRI activity and NEDA status at 2 years predicted clinical outcomes at 3–4 years
- Improved disease control was seen in newly and non–newly diagnosed patients
ABSTRACT

Background: Early intervention with well-tolerated disease-modifying therapies (DMTs) for relapsing-remitting multiple sclerosis (RRMS) is recommended in order to delay disease progression, reduce neurologic damage, preserve brain volume, and optimize long-term patient outcomes. Lack of conversion of new/newly enlarging T2 (NET2) or gadolinium-enhancing (Gd+) lesions to chronic hypointensities (black hole conversion) and achievement of no evidence of disease activity (NEDA) early in the course of treatment are considered potential indicators of treatment effect and predictors of longer-term clinical outcomes.

Methods: Patients with RRMS who were treated with peginterferon beta-1a in the 2-year ADVANCE phase 3 clinical trial (NCT0090639) and its 2-year open-label extension study, ATTAIN (NCT01332019), were grouped as newly diagnosed (diagnosed ≤1 year prior to enrollment and DMT naive) or non–newly diagnosed. For analyses of the impact of early treatment and disease activity control, the newly diagnosed and non–newly diagnosed subgroups were further divided based on whether they initiated peginterferon beta-1a every 2 weeks (Q2W) starting in study year 1 (continuously treated) or peginterferon beta-1a Q2W or every 4 weeks in study year 2 (delayed treatment). Patient subgroups were evaluated for conversion of NET2 or Gd+ lesions to persistent black holes (PBHs), brain atrophy (percentage change in whole brain volume [WBV]), achievement of NEDA composite outcomes, and the association of these disease activity measures with longer-term clinical outcomes (annualized relapse rate [ARR] and confirmed disability worsening [CDW]).

Results: At 2 years, significantly fewer PBHs developed from NET2 lesions or Gd+ lesions in newly diagnosed and non–newly diagnosed patients continuously treated with peginterferon beta-1a than in the corresponding delayed-treatment groups (all p<0.0001). Percentage decrease in WBV from 6 months (rebaselined) to 2 years was significantly lower for newly
diagnosed and non–newly diagnosed patients who received continuous peginterferon beta-1a treatment than for patients who received delayed treatment (both \( p \leq 0.0442 \)). In study year 1, a higher proportion of newly diagnosed and non–newly diagnosed patients treated with peginterferon beta-1a than those treated with placebo achieved NEDA (newly diagnosed: 28.3% vs 13.5% \( [p=0.0010] \); non–newly diagnosed: 40.8% vs 15.8% \( [p<0.0001] \)). NEDA rates remained stable over study years 2–4 for the newly diagnosed (range: 50.0%–53.9%) and non–newly diagnosed (range: 54.4%–57.0%) subgroups. Patients without PBH conversion had significantly lower ARR at 2 years (newly diagnosed: \( p=0.0109 \); non–newly diagnosed: \( p=0.0044 \)) and a lower proportion of patients with 12-week CDW at 2 years (newly diagnosed: \( p=0.2787 \); non–newly diagnosed: \( p=0.0045 \)) than the corresponding patient subgroups with PBH conversion. Patients who achieved NEDA in ADVANCE (study years 1–2) had a significantly lower ARR in ATTAIN (study years 3–4) than patients who did not achieve NEDA (newly diagnosed, \( p=0.0003 \); non–newly diagnosed, \( p=0.0001 \)). Over 4 years, safety outcomes did not differ for the newly diagnosed and non–newly diagnosed patient subgroups.

**Conclusions:** These results indicate that newly diagnosed and non–newly diagnosed patients treated continuously with peginterferon beta-1a Q2W experienced better disease control over time than those who received delayed treatment. Patients with NEDA or evidence of less radiological disease activity in the first 2 years of treatment had better longer-term clinical outcomes than those with evidence of greater disease activity.
1 INTRODUCTION

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disorder of the central nervous system affecting more than 2 million people worldwide (Wallin et al., 2019). The most common MS disease course is relapsing-remitting MS (RRMS), characterized by clearly defined attacks of new or increasing neurologic symptoms (Lublin et al., 2014). Early treatment with disease-modifying therapies (DMTs) for MS, including interferon beta formulations, has been shown to impact the natural history of the disease and slow disease progression in patients with RRMS (Johnson et al., 2005; Kappos et al., 2015; Kappos et al., 2007; Trojano et al., 2007).

Based on results from the pivotal 2-year ADVANCE phase 3 clinical trial (Calabresi et al., 2014; Kieseier et al., 2015), peginterferon beta-1a, a pegylated form of interferon beta-1a (Kieseier and Calabresi, 2012), was approved in 2014 to treat relapsing forms of MS (Plegridy Prescribing Information, 2021) and RRMS (Plegridy Summary of Product Characteristics, 2021), with recommended dosing of 125 mcg injected every 2 weeks (Q2W).

Information about treatment outcomes in patients newly diagnosed with MS can provide insight on the impact of early DMT use on longer-term clinical outcomes. Here we report on treatment outcomes in a subgroup of newly diagnosed patients who were diagnosed with RRMS ≤1 year prior to the start of the ADVANCE clinical trial and were MS DMT naive. We also examine a subgroup of non–newly diagnosed patients who were diagnosed >1 year prior to the trial start and/or had received prior DMT treatment. Outcomes were assessed using clinical and radiological endpoints, including conversion of new or newly enlarging T2 (NET2) lesions or gadolinium-enhancing (Gd+) lesions to persistent T1 hypointense lesions (black hole conversion) on magnetic resonance imaging (MRI). Black hole conversion is an indicator of irreversible neurologic damage and disability and has been suggested as a marker of treatment efficacy (Akaishi et al., 2020; Arnold et al., 2017b; Sahraian et al., 2010). Outcomes in newly diagnosed and non–newly diagnosed patients were also evaluated using no evidence of
disease activity (NEDA), a composite assessment of clinical and radiological outcomes that has been proposed as a “treat-to-target” approach to monitor patient response to treatment with MS DMTs and guide treatment selection (Giovannoni et al., 2017; Kappos et al., 2016; Parks et al., 2017). The association of successful disease activity control, as measured by the absence of black hole conversion or by the achievement of NEDA after 2 years of treatment, with longer-term clinical outcomes (up to 4 years) was also examined.

2 METHODS

2.1 Study design

ADVANCE (NCT00906399) was a 2-year, double-blind, placebo-controlled phase 3 study of peginterferon beta-1a 125 mcg in patients with RRMS (Calabresi et al., 2014; Kieseier et al., 2015). Briefly, at the beginning of ADVANCE, patients were randomized 1:1:1 to receive peginterferon beta-1a treatment Q2W or every 4 weeks (Q4W) (continuous treatment) or placebo (delayed treatment). At the end of year 1, placebo patients were re-randomized to receive peginterferon beta-1a either Q2W or Q4W in year 2. After completion of the 2-year ADVANCE trial, patients were eligible to enter ATTAIN (NCT01332019), a 2-year, open-label extension study (Newsome et al., 2018). During ATTAIN, patients were maintained on their ADVANCE dosing schedule (peginterferon beta-1a Q2W or Q4W). ATTAIN continued until the last patient completed 2 years; thus, some patients were followed for nearly 4 years in ATTAIN, for a total of nearly 6 years in ADVANCE and ATTAIN combined. For the analyses described here, study years 1 and 2 refer to years 1 and 2 in ADVANCE, and study years 3 and 4 refer to years 1 and 2 in ATTAIN (see Supplementary Fig. S1).

2.2 Patients
Inclusion and exclusion criteria for ADVANCE have been described previously (Calabresi et al., 2014; Kieseier et al., 2015). For the analyses presented here, the ADVANCE and ATTAIN analysis populations include all patients who received at least one dose of peginterferon beta-1a in ADVANCE (ADVANCE intent-to-treat [ITT]) or ATTAIN (ATTAIN ITT). For the ADVANCE ITT population, continuously treated patients were defined as those who received peginterferon beta-1a Q2W beginning in year 1; delayed-treatment patients received placebo in study year 1 and peginterferon beta-1a Q2W or Q4W beginning in year 2, as described previously (Kieseier et al., 2015). For the ATTAIN ITT population, continuously treated patients were defined as those who received peginterferon beta-1a Q2W beginning in year 1 and had ≥1 dose of peginterferon beta-1a Q2W in years 3–4; delayed-treatment patients received placebo in study year 1 and peginterferon beta-1a Q2W or Q4W beginning in year 2 and ≥1 dose of peginterferon beta-1a (at the same dosing frequency as in year 2) in study years 3–4. Patients in both treatment arms (continuous and delayed treatment) were further categorized by diagnosis status. For all analyses, newly diagnosed patients were defined as those who were diagnosed with RRMS ≤1 year prior to enrollment in the ADVANCE study and were naive to prior treatment with MS DMTs. Non–newly diagnosed patients were defined as those who were diagnosed with RRMS >1 year prior to enrollment in ADVANCE and/or had prior treatment with MS DMTs.

2.3 Assessments

2.3.1 Clinical assessments

For ADVANCE and ATTAIN, relapses were defined as new or recurrent neurologic symptoms not associated with fever or infection, lasting for ≥24 hours, accompanied by new objective neurologic findings, and separated from the onset of other confirmed relapses by ≥30 days; such relapses were confirmed by an independent neurologic evaluation committee (Calabresi et
al., 2014; Kieseier et al., 2015; Newsome et al., 2018). Relapses were not further categorized by severity.

Standardized neurological assessments, including Expanded Disability Status Scale (EDSS), were performed at screening, at baseline, and every 12 weeks thereafter, as well as at the time of suspected relapse (evaluated during unscheduled visits). For both studies, confirmed disability worsening (CDW) was defined as an increase in the EDSS score ≥1.0 point in patients with a baseline score ≥1.0 or an increase ≥1.5 points in patients with a baseline score of 0.0, confirmed after 12 and 24 weeks (ADVANCE) or 24 weeks (ATTAIN).

2.3.2 Radiologic assessments

NET2 lesions, Gd+ lesions, and T1 lesions were evaluated at baseline and in each study year by MRI scans. All MRI results were assessed at a centralized MRI reading center by an assessor blinded to treatment allocation. Methods for assessing conversion of NET2 or Gd+ lesions to persistent black holes (PBHs) and for assessing whole brain volume (WBV) have previously been published (Arnold et al., 2017a; Arnold et al., 2018a; Arnold et al., 2017b). Briefly, patients without black hole conversion were defined as those without conversion of baseline Gd+ or NET2 lesions to PBHs or with no Gd+ lesions at baseline, 24 weeks, or 48 weeks and no NET2 lesions at 24 weeks or 48 weeks (Arnold et al., 2018a; Arnold et al., 2017b). Additional MRI methods are summarized in the supplementary material.

2.4 Outcomes

Black hole conversion and change in WBV at year 2 were assessed from ADVANCE baseline. Change in WBV was additionally assessed after rebaselining at 6 months to adjust for apparent decrease in brain volume due to pseudoatrophy (Arnold et al., 2017a; Zivadinov et al., 2016).
Assessments of PBHs and WBV over study years 1–2 were conducted in ADVANCE ITT continuous- and delayed-treatment patients. The association of adjusted annualized relapse rate (ARR) and 12-week CDW over years 3–4 with black hole conversion status at year 2 was assessed in ADVANCE ITT patients with non-missing MRI measurements. MRI data for PBH and WBV assessments were not available beyond 2 years.

Overall NEDA, a composite measure of MS disease activity, was defined as clinical-NEDA (no relapses and no 24-week CDW) plus MRI-NEDA (no NET2 or new Gd+ lesions). NEDA outcomes over 4 years of treatment were analyzed year by year for newly diagnosed and non–newly diagnosed patients in the ATTAIN ITT population who had continuously been treated with peginterferon beta-1a Q2W beginning in ADVANCE (study year 1). NEDA assessments were not imputed and were performed using observed data only. Association of NEDA in years 1–2 with adjusted ARR in years 3–4 in the overall ATTAIN ITT population was assessed in all newly diagnosed and non–newly diagnosed patients to test whether early achievement of NEDA predicts longer-term outcomes, regardless of treatment received during year 1.

Safety outcomes (adverse events [AEs] and serious AEs [SAEs]) during the entire duration of ADVANCE and ATTAIN (up to nearly 6 years) were evaluated in the overall safety population, which included all patients who received either continuous or delayed treatment with peginterferon beta-1a Q2W.

Additional details of all outcome measures are provided in Supplementary Table S1.

### 2.5 Statistical analyses

Demographic and clinical characteristics of the newly diagnosed, non–newly diagnosed, and overall patient subgroups in the ADVANCE and ATTAIN ITT populations at the ADVANCE and ATTAIN study baselines were analyzed using descriptive statistics.
The conversion of NET2 lesions or new Gd+ lesions to PBHs in newly diagnosed and non–newly diagnosed patients was assessed using a negative binomial model to compare the conversion rates; chi-square tests were used to compare the proportion of patients with black hole conversion between the 2 groups. Associations between baseline variables and black hole conversion were assessed using a multivariate negative binomial regression model with treatment and all of the baseline variables included in the model.

Statistical analysis was conducted using SAS version 9.4. p values ≤0.05 were considered statistically significant.

### 2.6 Standard protocol approvals, registrations, and patient consents

The ADVANCE and ATTAIN protocols were approved by the institutional review board at each site, and the studies were conducted according to International Conference on Harmonisation Guidelines for Good Clinical Practice and the Declaration of Helsinki. All patients provided written informed consent before entering the studies.

### 3 RESULTS

#### 3.1 Patients and analysis populations

The ADVANCE ITT population included 512 continuously treated patients (newly diagnosed: n=231; non–newly diagnosed: n=281) and 500 delayed-treatment patients (newly diagnosed: n=229; non–newly diagnosed: n=271; Table 1).

The ATTAIN ITT population included 376 continuously treated patients. Of these, 180 were newly diagnosed and 196 were non–newly diagnosed. The delayed-treatment group in the
ATTAIN ITT population included 346 patients, of whom 163 were newly diagnosed and 183 were non–newly diagnosed (Table 2).

As shown in Tables 1 and 2, baseline demographic and disease characteristics of newly diagnosed and non–newly diagnosed patients in both the ADVANCE and ATTAIN ITT populations were generally well balanced, although newly diagnosed patients could be distinguished from corresponding non–newly diagnosed patients by shorter mean times since MS symptom onset and MS diagnosis.

### 3.2 Black hole conversion

Conversion of NET2 or Gd+ lesions to PBHs was assessed over 2 years in newly diagnosed and non–newly diagnosed patients in the ADVANCE ITT population. For both of these subgroups, fewer PBHs developed from NET2 lesions at 2 years in patients treated continuously with peginterferon beta-1a Q2W than in delayed-treatment patients (p<0.0001 for both; Fig. 1A). Similarly, for both newly diagnosed and non–newly diagnosed subgroups, fewer PBHs developed at 96 weeks from Gd+ lesions in continuous-treatment patients than delayed-treatment patients (P<0.0001 for both; Fig. 1B).

### 3.3 Association of black hole conversion with clinical outcomes

The association of black hole conversion status with clinical outcomes in study years 1–2 was assessed in all newly diagnosed and non–newly diagnosed ADVANCE ITT patients. Adjusted ARR over 2 years was significantly lower in both newly diagnosed and non–newly diagnosed patients who did not exhibit conversion of NET2 or Gd+ lesions to PBHs compared with those with black hole conversion (newly diagnosed: p=0.0109; non–newly diagnosed: p=0.0044; Fig. 2A). Over the same period, the proportion of patients with 12-week CDW was numerically lower
in newly diagnosed patients without than with black hole conversion ($p=0.2787$) and significantly lower in non–newly diagnosed patients without than with black hole conversion ($p=0.0045$; Fig. 2B).

### 3.4 Brain volume

From ADVANCE baseline to study year 2, the percentage change (decrease) in WBV was numerically less in newly diagnosed and non–newly diagnosed ADVANCE ITT patients continuously treated with peginterferon beta-1a than in those who received delayed treatment (Fig. 3A). The percentage change in WBV from 6 months, after rebaselining to adjust for pseudoatrophy (Zivadinov et al., 2016), to study year 2 was significantly less for both continuously treated cohorts compared with delayed-treatment patients (newly diagnosed: $p=0.042$; non–newly diagnosed: $p=0.0041$; Fig. 3B).

### 3.5 Sustained overall NEDA in patients treated with peginterferon beta-1a

Overall NEDA, a composite measure of clinical-NEDA, defined as no relapses and no 24-week CDW (further defined as an increase in EDSS score of $\geq 1.0$ point in patients with a baseline score of $\geq 1.0$ or an increase of $\geq 1.5$ points in patients with a baseline score of $0.0$, confirmed after 24 weeks), and MRI-NEDA, defined as no Gd+ lesions and no NET2 lesions, was assessed over 4 years in newly diagnosed and non–newly diagnosed patients in the ATTAIN ITT population who received continuous treatment with peginterferon beta-1a Q2W starting in study year 1. In year 1, significantly greater proportions of both newly diagnosed and non–newly diagnosed patients treated with peginterferon beta-1a Q2W than with placebo achieved overall NEDA (newly diagnosed: $p=0.0010$; non–newly diagnosed: $p<0.0001$; Fig. 4). During study year 2, the proportions of newly diagnosed and non–newly diagnosed patients achieving overall
NEDA increased 1.9-fold to 53.9% and 1.3-fold to 54.6%, respectively, and these increases were sustained in years 3–4. Results for clinical-NEDA and MRI-NEDA were similar (Supplementary Fig. S2).

### 3.6 Association of overall NEDA with clinical outcomes

The relationship between achieving overall NEDA in the first 2 years of the study and longer-term clinical outcomes was evaluated by examining adjusted ARRs in study years 3 and 4 in newly diagnosed and non–newly diagnosed ATTAIN ITT population patients. Adjusted ARRs in years 3 and 4 were significantly lower in newly diagnosed and non–newly diagnosed patients who achieved overall NEDA in study years 1–2 than in those who did not (newly diagnosed: \( p=0.0003 \); non–newly diagnosed: \( p=0.0001 \); Fig. 5). Results were similar for patients who achieved clinical- or MRI-NEDA in years 1–2 (Supplementary Fig. S3).

### 3.7 Safety

Safety was assessed over the entire duration of the combined study (nearly 6 years) and included 344 newly diagnosed and 396 non–newly diagnosed ATTAIN ITT patients who received either continuous or delayed treatment with peginterferon beta-1a Q2W. AEs were reported by 330 newly diagnosed patients (96%) and 381 non–newly diagnosed patients (96%), with injection site erythema (235 patients [68%] and 240 patients [61%], respectively) and influenza-like illness (203 patients [59%] and 214 [54%], respectively) the most frequently reported AEs (Table 3). Over the duration of the combined study, similar proportions of newly diagnosed patients (25 of 344 [7%]) and non–newly diagnosed patients (43 of 396 [11%]) discontinued treatment due to an AE (Table 3).
SAEs were reported by 72 newly diagnosed patients (21%) and 101 non–newly diagnosed patients (26%), with MS relapse (42 patients [12%] and 62 patients [16%], respectively) the most frequently reported SAE. These results are consistent with the safety analyses on the overall ADVANCE/ATTAIN patient population (Newsome et al., 2018).

4 DISCUSSION

This study extends previously reported efficacy results for peginterferon beta-1a (Arnold et al., 2017a; Arnold et al., 2018b; Calabresi et al., 2014; Kieseier et al., 2015; Newsome et al., 2018) to patients newly diagnosed and non–newly diagnosed with RRMS and demonstrates that early and continuous treatment provides sustained improvements in radiological and clinical outcomes, including composite NEDA outcomes, in these patients. Safety outcomes in these patient subgroups were also consistent with findings for the overall patient populations from ADVANCE and ATTAIN (Arnold et al., 2017a; Arnold et al., 2014; Arnold et al., 2018b; Calabresi et al., 2014; Kieseier et al., 2015; Newsome et al., 2018).

Brain atrophy and cognitive impairment, presumably due to inflammatory demyelination, occur early in the MS disease process, even in the absence of other evidence of disease activity (De Stefano et al., 2010; Gold et al., 2010). Therefore, current clinical practice recommendations for RRMS include early intervention with well-tolerated DMTs (Gold et al., 2010; Goodin and Bates, 2009; Kavaliunas et al., 2017; Montalban et al., 2018; Rae-Grant et al., 2018). Benefits of early DMT use include minimizing further inflammatory axonal damage, slowing disease progression, reducing the risk of relapse and the number of MRI lesions, preserving brain volume and cognitive functioning, and delaying irreversible disability (Goodin and Bates, 2009; Montalban et al., 2018). A meta-analysis of DMT use and treatment outcomes in patients with RRMS demonstrated an association between earlier treatment and larger treatment effects (Signori et al., 2015). A more recent study of Swedish patients with MS demonstrated that the risk of
progression to EDSS $\geq 4.0$ increased by 5% for each year of delayed treatment start (Kavaliunas et al., 2017). In this study, both newly diagnosed and non–newly diagnosed patients who received continuous peginterferon beta-1a were less likely to develop PBHs from NET2 or Gd+ lesions at 96 weeks than corresponding delayed treatment patients who did not start treatment until year 2 of ADVANCE. Newly diagnosed and non–newly diagnosed patients who did not develop PBHs from NET2 or from Gd+ lesions had less clinical disease activity over 96 weeks than patients who did develop PBHs, consistent with observations in the overall ADVANCE population (Arnold et al., 2017b) and with the idea that evolution of PBHs may be a useful marker of therapeutic outcomes in patients with RRMS (Sahraian et al., 2010). Our observation that continuously treated newly diagnosed and non–newly diagnosed ADVANCE ITT patients exhibited significantly less percentage decrease in WBV than their delayed-treatment counterparts after rebaselining at 6 months is consistent with previously published findings in the overall ADVANCE patient cohort (Arnold et al., 2017a) and additionally supports the rationale for early treatment intervention.

The composite outcome NEDA has been proposed as a measure of treatment response in clinical trial settings and real-world clinical practice (Giovannoni et al., 2017; Kappos et al., 2016; Parks et al., 2017). In the NEDA results presented here, significantly greater proportions of newly diagnosed patients treated continuously with peginterferon beta-1a Q2W than with placebo achieved clinical-NEDA, MRI-NEDA, and overall NEDA in year 1, and approximately half of newly diagnosed patients achieved overall NEDA during each of the years 2–4. The predictive value of NEDA on long-term disease outcomes has been suggested by some studies (Goodin et al., 2019; Rotstein et al., 2015) but has not been firmly established (Cree et al., 2016). In our study, achievement of clinical-, MRI-, and overall NEDA in years 1–2 was significantly associated with lower ARR in years 3–4 in both newly diagnosed and non–newly diagnosed patients (with the exception of MRI-NEDA in non–newly diagnosed patients), which
is consistent with a previous analysis in the overall ATTAIN patient population (Arnold et al., 2018b). The association of ARR in study years 3–4 with early achievement of NEDA observed here supports the hypothesis that NEDA is predictive of positive long-term clinical outcomes and further suggests that a treat-to-target approach may be appropriate for newly diagnosed RRMS patients (Parks et al., 2017).

Interpretation of the results of this study is limited by several factors, including the post hoc nature of the analyses. Moreover, ATTAIN was an open-label extension of ADVANCE, and outcomes may have been affected by patient self-selection bias. Finally, as MS is a chronic disease, longer-term studies, including studies in real-world patient populations, are needed to evaluate the effects of peginterferon beta-1a.

Several observations suggest that these results may be generalizable to a broader population of peginterferon beta-1a patients. Overall, the subgroup analyses of ADVANCE and ATTAIN described here are consistent with previous reports of peginterferon beta-1a efficacy and safety (Arnold et al., 2014; Calabresi et al., 2014; Kieseier et al., 2015; Newsome et al., 2018). The black hole conversion and NEDA results observed in the newly diagnosed and non–newly diagnosed subgroups are consistent with those reported for the overall ADVANCE (Arnold et al., 2017a; Arnold et al., 2017b) and ATTAIN (Arnold et al., 2018b) patient populations, respectively.

In summary, these results demonstrate that newly diagnosed patients with RRMS experienced clinical and radiologic benefits, as measured by achievement of NEDA, the absence of black hole conversion, and decreased WBV loss, from earlier treatment with peginterferon beta-1a Q2W. While guidelines for optimal treatment for newly diagnosed MS patients are evolving, injectable therapies with well-studied benefit-risk profiles, such as peginterferon beta-1a, remain an appropriate therapeutic choice for many of these patients (Corboy et al., 2018). Early initiation of peginterferon beta-1a appears to be an effective treatment option for patients with RRMS, including newly diagnosed, treatment-naive patients, who may experience additional
benefits from early treatment initiation. Clinical and radiologic benefits from continuous versus delayed peginterferon beta-1a treatment were also observed in non–newly diagnosed patients, suggesting that these patients, who had a disease duration prior to initiating peginterferon beta-1a approximately 6 years longer than newly diagnosed patients, can also experience sustained treatment benefits from peginterferon beta-1a.

CRediT Statement

Scott D. Newsome: Conceptualization, Methodology, Investigation, Writing - Review & Editing, Supervision
Thomas F. Scott: Conceptualization, Methodology, Investigation, Writing - Review & Editing, Supervision
Douglas L. Arnold: Conceptualization, Methodology, Investigation, Writing - Review & Editing, Supervision
Arman Altincatal: Formal analysis, Data Curation, Writing - Review & Editing
Maria L. Naylor: Conceptualization, Methodology, Investigation, Writing - Review & Editing, Supervision

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CONFLICT OF INTEREST STATEMENT

SDN has received consulting fees for scientific advisory boards from Biogen, Bristol Myers Squibb, EMD Serono, Genentech, Greenwich Biosciences, and Novartis and has served as an advisor for Autobahn and BioIncept and a clinical adjudication committee member for a MedDay clinical trial; his institution has received research funding from Biogen, Genentech, the National Multiple Sclerosis Society, the Patient-Centered Outcomes Institute, and the US Department of Defense.

TFS has received payments for research activities, advisory boards, promotional speaking, and consulting from Biogen, Genentech, Genzyme, Novartis, and Teva Neuroscience.

DLA has received personal fees for consulting from Acorda, Albert Charitable Trust, Biogen, Celgene, F. Hoffmann-La Roche, Frequency Therapeutics, GeNeuro, MedDay, MedImmune, Merck Serono, Mitsubishi, Novartis, Receptos, and Sanofi; grants from Biogen and Novartis; and personal fees from Wave Life Science. He also has an equity interest in NeuroRx Research.

AA and MLN are former employees of and may hold stock in Biogen.

REFERENCES


Table 1. Baseline demographic and disease characteristics of newly diagnosed and non–newly diagnosed patients in the ADVANCE ITT population

<table>
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<tr>
<th>Characteristic</th>
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<th>Non–newly diagnosed patients</th>
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<tbody>
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<td>Continuous treatment</td>
<td>Placebo/Delayed treatment</td>
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<td></td>
<td>(n=231)(^a)</td>
<td>(n=229)(^b)</td>
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<td>Time since MS diagnosis, mean (SD)</td>
<td>0.5 (0.5)</td>
<td>0.5 (0.5)</td>
</tr>
<tr>
<td>Relapses in prior year, mean (SD)</td>
<td>1.7 (0.7)</td>
<td>1.7 (0.6)</td>
</tr>
<tr>
<td>EDSS score, mean (SD)</td>
<td>2.06 (1.14)</td>
<td>2.08 (1.08)</td>
</tr>
<tr>
<td>&lt;4.0, n (%)</td>
<td>210 (91)</td>
<td>212 (93)</td>
</tr>
<tr>
<td>≥4.0, n (%)</td>
<td>21 (9)</td>
<td>17 (7)</td>
</tr>
<tr>
<td>Patients without Gd+ lesions, n (%)</td>
<td>151 (65)</td>
<td>138 (60)</td>
</tr>
<tr>
<td>No. of Gd+ lesions, mean (SD)</td>
<td>1.3 (4.2)</td>
<td>1.7 (4.2)</td>
</tr>
<tr>
<td>No. of T2 lesions, mean (SD)</td>
<td>42.5 (33.1)</td>
<td>47.3 (36.1)</td>
</tr>
</tbody>
</table>

EDSS=Expanded Disability Status Scale; Gd+=gadolinium enhancing; MS=multiple sclerosis; SD=standard deviation.

\(^a\)Continuous-treatment patients were randomized to receive peginterferon Q2W beginning in study year 1.

\(^b\)Placebo/Delayed-treatment patients were randomized to placebo in study year 1 and received peginterferon beta-1a Q2W or Q4W in study year 2.
Table 2. Baseline demographic and disease characteristics of newly diagnosed and non–newly diagnosed patients in the ATTAIN ITT population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Newly diagnosed patients</th>
<th>Non–newly diagnosed patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Continuous treatment</td>
<td>Placebo/Delayed treatment</td>
</tr>
<tr>
<td></td>
<td>(n=180)a</td>
<td>(n=163)b</td>
</tr>
<tr>
<td>Age at enrollment in ADVANCE, mean (SD), y</td>
<td>34.6 (9.5)</td>
<td>34.9 (9.6)</td>
</tr>
<tr>
<td>&lt;40, n (%)</td>
<td>131 (73)</td>
<td>110 (67.5)</td>
</tr>
<tr>
<td>≥40, n (%)</td>
<td>49 (27)</td>
<td>53 (32.5)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>124 (69)</td>
<td>115 (70.6)</td>
</tr>
<tr>
<td>White ethnic origin, n (%)</td>
<td>159 (88)</td>
<td>145 (89.0)</td>
</tr>
<tr>
<td>Time since first MS symptoms, mean (SD), y</td>
<td>3.6 (3.8)</td>
<td>3.3 (4.8)</td>
</tr>
<tr>
<td>Time since MS diagnosis, mean (SD), y</td>
<td>0.5 (0.5)</td>
<td>0.5 (0.5)</td>
</tr>
<tr>
<td>Relapses in prior year, mean (SD)</td>
<td>1.7 (0.7)</td>
<td>1.7 (0.6)</td>
</tr>
<tr>
<td>EDSS score, mean (SD)</td>
<td>2.0 (1.1)</td>
<td>2.1 (1.1)</td>
</tr>
<tr>
<td>&lt;4.0, n (%)</td>
<td>165 (92)</td>
<td>150 (92.0)</td>
</tr>
<tr>
<td>≥4.0, n (%)</td>
<td>15 (8)</td>
<td>13 (8)</td>
</tr>
<tr>
<td>Patients without Gd+ lesions, n (%)</td>
<td>121 (67)</td>
<td>99 (61)</td>
</tr>
<tr>
<td>No. of Gd+ lesions, mean (SD)</td>
<td>1.4 (4.4)</td>
<td>1.5 (3.3)</td>
</tr>
<tr>
<td>No. of T2 lesions, mean (SD)</td>
<td>43.6 (34.1)</td>
<td>45.9 (34.5)</td>
</tr>
</tbody>
</table>

EDSS=Expanded Disability Status Scale; Gd+=gadolinium enhancing; MS=multiple sclerosis; SD=standard deviation.

aContinuous-treatment patients received peginterferon Q2W beginning in study year 1 and at least one dose of peginterferon beta-1a Q2W in study years 3–4.

bPlacebo/Delayed-treatment patients received placebo in study year 1, peginterferon beta-1a Q2W or Q4W beginning in study year 2, and at least one dose of peginterferon beta-1a in study years 3–4.

cData available for 182 patients.
Table 3. AEs, SAEs, and severe AEs in ATTAIN patients continuously treated with peginterferon beta-1a Q2W

<table>
<thead>
<tr>
<th>Event, n (%)</th>
<th>Newly diagnosed patients (n=344)</th>
<th>Non–newly diagnosed patients (n=396)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>330 (96)</td>
<td>381 (96)</td>
</tr>
<tr>
<td>Injection site erythema</td>
<td>235 (68)</td>
<td>240 (61)</td>
</tr>
<tr>
<td>Influenza-like illness</td>
<td>203 (59)</td>
<td>214 (54)</td>
</tr>
<tr>
<td>Headache</td>
<td>152 (44)</td>
<td>187 (47)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>136 (40)</td>
<td>202 (51)</td>
</tr>
<tr>
<td>MS relapse</td>
<td>113 (33)</td>
<td>134 (34)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>78 (23)</td>
<td>83 (21)</td>
</tr>
<tr>
<td>Injection site pain</td>
<td>74 (22)</td>
<td>62 (16)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>62 (18)</td>
<td>57 (14)</td>
</tr>
<tr>
<td>Chills</td>
<td>62 (18)</td>
<td>81 (20)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>62 (18)</td>
<td>54 (14)</td>
</tr>
<tr>
<td>Injection site pruritus</td>
<td>60 (17)</td>
<td>55 (14)</td>
</tr>
<tr>
<td>Back pain</td>
<td>50 (15)</td>
<td>67 (17)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>47 (14)</td>
<td>58 (15)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>47 (14)</td>
<td>68 (17)</td>
</tr>
<tr>
<td>Nausea</td>
<td>48 (14)</td>
<td>45 (11)</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>45 (13)</td>
<td>57 (14)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>41 (12)</td>
<td>58 (15)</td>
</tr>
<tr>
<td>Upper respiratory tract Infection</td>
<td>34 (10)</td>
<td>39 (10)</td>
</tr>
<tr>
<td>Depression</td>
<td>36 (10)</td>
<td>30 (8)</td>
</tr>
<tr>
<td>Any AE leading to study discontinuation</td>
<td>25 (7)</td>
<td>43 (11)</td>
</tr>
<tr>
<td>Any SAE</td>
<td>72 (21)</td>
<td>101 (26)</td>
</tr>
</tbody>
</table>

Safety population includes all patients in the ATTAIN analysis population who received peginterferon beta-1a Q2W at any point in the study. AEs reported by ≥10% of patients are shown. Patients were counted only once within each system organ class/preferred term.

AE=adverse event; SAE=serious adverse event.
FIGURE LEGENDS
Fig. 1. Number of PBHs at study year 2 that developed from (A) NET2 lesions and (B) Gd+ lesions in newly diagnosed and non–newly diagnosed patients. Patients with non-missing MRI (A) T2 or (B) Gd+ measurements at weeks 24, 48, and 96. \( p \) values based on negative binomial regression, adjusted for baseline age (\( \geq 40 \) vs <40), sex, baseline EDSS score, and the number of baseline Gd+ lesions. Continuously treated patients received peginterferon beta-1a Q2W beginning in study year 1. Delayed-treatment patients received placebo in study year 1 and peginterferon beta-1a Q2W or Q4W in study year 2. CI=confidence interval; EDSS=Expanded Disability Status Scale; Gd+=gadolinium enhancing; MRI=magnetic resonance imaging; NET2=new or newly enlarging T2; PBH=persistent black hole.
Fig. 2. (A) Adjusted ARR and (B) 12-week CDW in newly diagnosed and non–newly diagnosed patients without and with black hole conversion. ADVANCE ITT patients with non-missing MRI measurements at 96 weeks (2 years). No black hole conversion includes patients without black hole conversion of baseline Gd+ or NET2 lesions, and patients with no Gd+ lesions at baseline, 24 weeks, and 48 weeks and no NET2 lesions at 24 weeks and 48 weeks. (A) CIs and p values estimated with negative binomial regression including year 1 randomized treatment, black hole conversion status, and their interaction, with adjustment for baseline EDSS score (<4.0 vs ≥4.0), baseline age (≥40 vs <40), and the number of Gd+ lesions at baseline. (B) CIs and p values estimated with Cox proportional hazards including year 1 randomized treatment, black hole conversion status, and their interaction, with adjustment for baseline EDSS score (<4.0 vs ≥4.0), baseline age (≥40 vs <40), and the number of Gd+ lesions at baseline. ARR=annualized relapse rate; CDW=confirmed disability worsening; CI=confidence interval; EDSS=Expanded Disability Status Scale; Gd+=gadolinium enhancing; HR=hazard ratio; ITT=intent to treat; MRI=magnetic resonance imaging; NET2=new or newly enlarging T2.
Fig. 3. Mean percentage change in whole brain volume from (A) ADVANCE baseline to study year 2 and (B) 6 months to study year 2 in newly diagnosed and non–newly diagnosed patients. Whole brain volume changes were assessed in ADVANCE ITT patients. For panel (B), patients were rebaselined at 6 months. SD=standard deviation.
**Fig. 4.** Yearly rates of overall NEDA in combined study years 1–4 in (A) newly diagnosed and (B) non–newly diagnosed patients. Overall NEDA in newly diagnosed and non–newly diagnosed patients with assessments who received placebo in study year 1 or peginterferon beta-1a Q2W in study years 1–4 (continuous treatment). Overall NEDA=no relapses, no 24-week CDW, no Gd+ lesions, and NET2 lesions. *p* values for peginterferon beta-1 Q2W groups vs corresponding placebo groups at 1 year based on logistic regression. CDW=confirmed disability worsening; Gd+=gadolinium enhancing; NEDA=no evidence of disease activity; NET2=new or newly enlarging T2; Q2W=every 2 weeks.

**Fig. 5.** Adjusted ARR in years 3–4 by overall NEDA status in years 1–2 years in newly diagnosed and non–newly diagnosed patients. Patients with overall NEDA achieved NEDA status for all measurements with no missing data; patients without overall NEDA had evidence of disease activity in ≥1 measurement. Patient population includes placebo, peginterferon beta-1a Q2W, and peginterferon beta-1a Q4W treatment groups from the ATTAIN ITT patient population. Adjusted annualized relapse
rates and $p$ values are based on negative binomial regression with adjustment for overall NEDA status during years 1–2; ADVANCE baseline Expanded Disability Status Scale score (<4.0 vs ≥4.0); ADVANCE baseline relapse rate; and ADVANCE baseline age (<40 vs ≥40 years). ARR=annualized relapse rate; CI=confidence interval; NEDA=no evidence of disease activity; Q2W=every 2 weeks; Q4W=every 4 weeks.