Improvement in relapse recovery with peginterferon beta-1a in patients with multiple sclerosis

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Abstract

Background: Subcutaneous peginterferon beta-1a every 2 weeks significantly affects clinical outcomes in patients with relapsing–remitting multiple sclerosis (RRMS).

Objectives: To explore relationships between relapses and worsening of disability in patients with RRMS, and assess the treatment effect of peginterferon beta-1a on relapse recovery.

Methods: Post-hoc analysis of the 2-year, randomized, double-blind, parallel-group, Phase 3 ADVANCE study. The severity of relapses, proportion of patients with relapses associated with residual disability (onset of 24-week confirmed disability progression (CDP) within 90 days following a relapse), and persistence of changes in Functional Systems Scores, were compared between treatment groups.

Results: Subcutaneous peginterferon beta-1a every 2 weeks significantly reduced the proportion of patients experiencing relapse associated with CDP over 2 years (6.6%, compared with 15.1% of patients who received placebo in Year 1; \( p = 0.02 \)). Reduction in relapses associated with residual disability was greater than the treatment effect on overall relapse rate, and occurred despite similar relapse severity across treatment groups.

Conclusions: The beneficial effect of peginterferon beta-1a on risk of CDP may be attributable to the combination of an overall reduction in the risk of relapses and improvement in recovery from relapses, thus limiting further disability progression.

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improvements across a range of relapse, disability, and magnetic resonance imaging (MRI) endpoints. We propose an examination of relapse recovery as part of an analysis of all available data on disability progression in the ADVANCE study, which permits us to explore relationships between relapses and disability, and a possible treatment effect of peginterferon beta-1a on relapse recovery.

**Materials and methods**

**Standard protocol approvals, registrations, and patient consents**

The ADVANCE study (ClinicalTrials.gov identifier NCT00906399) was approved by the Institutional Review Board at each site and was performed in accordance with the International Conference on Harmonization Guidelines for Good Clinical Practice and the Declaration of Helsinki. All patients provided written informed consent.

**Patients and study design**

The ADVANCE study design and methods have been described previously. Key inclusion criteria were RRMS, age 18–65 years, EDSS score 0–5, and ≥ 2 clinically documented relapses in the previous 3 years, with ≥ 1 occurring within the past 12 months. Patients were excluded if they received previous interferon treatment for MS for > 4 weeks or had discontinued < 6 months before baseline.

Patients were randomized (1:1:1) to receive double-blind SC injections with pre-filled syringes of placebo (administered every 2 weeks), peginterferon beta-1a 125 mcg every 2 weeks, or peginterferon beta-1a 125 mcg every 4 weeks (alternating injections of placebo and peginterferon beta-1a 125 mcg to maintain blinding), in the first year. For Year 2, patients receiving peginterferon beta-1a remained on the same dose frequency and patients receiving placebo were re-randomized to SC peginterferon beta-1a 125 mcg every 2 or 4 weeks (termed the “delayed treatment group”).

The primary endpoint was annualized relapse rate (ARR). Relapses were defined as neurologic symptoms not associated with fever or infection, lasting ≥ 24 hours, accompanied by new objective neurologic findings and validated by an Independent Neurology Evaluation Committee (INEC). Disability progression was evaluated using the EDSS, assessed at baseline and every 12 weeks thereafter. Confirmed disability progression (CDP) was defined as ≥ 1.0-point increase in EDSS score from a baseline score of ≥ 1.0, or ≥ 1.5-point increase from a baseline of 0.0, confirmed 12 or 24 weeks after onset. EDSS assessments were also performed within 5 days after onset of a suspected relapse, providing a measure of relapse severity.

**Post-hoc analyses of relapse and disability endpoints**

Relapse recovery was assessed in terms of whether or not the relapse was followed by 24-week CDP. CDP was attributed to incomplete recovery from relapse if an INEC-confirmed relapse had occurred within 90 days prior to onset of CDP (Figure 1); relapses occurring after onset of CDP were excluded. Supporting analyses were performed using a 180-day window prior to onset of CDP to determine association between relapse and 24-week CDP, to verify that the main analysis did not exclude relapses occurring > 90 days prior to onset that contributed significantly to CDP.

Rates of incomplete recovery (relapses associated with subsequent 24-week CDP) over 1 year and over 2 years were compared for all randomized patients according to Year 1 treatment assignment: patients receiving continuous peginterferon beta-1a every 2 or 4 weeks were compared with the overall delayed treatment group (all patients originally randomized to receive placebo), using a Chi-square or Fisher’s exact test. In a set of supporting analyses, rates of incomplete recovery were assessed for patients who entered Year 2 according to Year 2 treatment assignment (continuous peginterferon beta-1a every 2 or 4 weeks or delayed peginterferon beta-1a every 2 or 4 weeks), using the peginterferon beta-1a every-4-weeks delayed treatment group, only, as the reference for comparison with all other groups, since overall exposure to

![Figure 1](image-url). Schema for percentage of relapses leading to CDP. Red arrow represents onset of CDP and blue arrows represent examples of patients with relapses associated or not associated with the CDP. CDP: confirmed disability progression.
peginterferon beta-1a was lowest in this group, providing a better proxy for a placebo group.

To further explore the relationship between relapses and CDP, the Prentice criteria, a set of four conditions determining the conditional independence of “true” and surrogate endpoints, were applied to assess whether relapses could serve as a surrogate for evaluating treatment effect on CDP. The criteria tested were that: treatment effect is significant for the “true” outcome (24-week CDP); treatment effect is significant for the surrogate marker (relapses); the true outcome is significantly correlated with the surrogate; the treatment effect on the true outcomes can be fully explained by the surrogate.

Changes in the individual Functional Systems Scores (FSS) comprising overall EDSS scores were examined in subgroups of patients with CDP due to incomplete relapse recovery and CDP without associated relapse, for the 24-week confirmation period that determined CDP. Simultaneous FSS worsening was defined as either a change of ≥1 point or of ≥2 points maintained for at least 24 weeks in the pyramidal, cerebellar, brainstem, sensory, bowel/bladder, visual or cerebral functional system, coinciding with 24-week CDP.

Results

Patients

A total of 1516 patients was enrolled between June 2009 and November 2011, of whom 1512 received randomized treatment with SC placebo (n = 500), SC peginterferon beta-1a 125 mcg every 2 weeks (n = 512), or SC peginterferon beta-1a 125 mcg every 4 weeks (n = 500) during Year 1 of the ADVANCE study. Demographics and baseline clinical characteristics have been published previously, and were similar across treatment groups. The mean duration of disease was 6.3–6.9 years, across groups; the mean number of relapses in the previous 3 years was 2.5–2.6. Overall, 17% of patients had received prior treatment for MS. 1332 patients entered Year 2 (438 each in the continuous peginterferon beta-1a every-2-weeks and every-4-weeks groups; 228 each in the delayed peginterferon beta-1a every-2-weeks and every-4-weeks groups). Patient disposition over 2 years is detailed elsewhere.

Relationship between relapse and confirmed disability progression

Among patients with at least 1 INEC-confirmed relapse (n = 121, 157, and 185 in the peginterferon beta-1a every-2-weeks, every-4-weeks, and combined delayed treatment groups, respectively), peginterferon beta-1a every 2 weeks significantly reduced the proportion with incomplete recovery (onset of 24-week CDP within 90 days) compared with delayed treatment, through 2 years of the ADVANCE study (6.6% vs. 15.1%; 56% reduction (p = 0.0237); Figure 2(a)). Among patients entering Year 2 of ADVANCE, continuous peginterferon beta-1a every 2 weeks provided a 70% reduction in relapses with incomplete recovery compared with delayed treatment with peginterferon beta-1a every

Figure 2. Proportion of patients experiencing relapses with incomplete recovery (onset of 24-week CDP within 90 days following relapse) over 2 years: (a) all patients with relapse, by Year 1 treatment assignment; (b) all patients with relapse who entered Year 2, by Year 2 treatment assignment.
In Year 1 of ADVANCE, peginterferon beta-1a every 2 weeks significantly reduced the proportion with incomplete recovery (onset of 24-week CDP within 90 days) compared with placebo (5.6% vs. 16.7%; 66% reduction; \(p = 0.0135\); see Supplementary Figure 1 online).

While there were fewer relapses in peginterferon beta-1a groups, peginterferon beta-1a did not appear to modify severity of relapses when they did occur. Among patients experiencing relapse in Year 1, 69% each in the placebo and peginterferon beta-1a every-4-weeks groups, and 66% in the peginterferon beta-1a every-2-weeks group, had a relapse with \(\geq 1\)-point increase in EDSS score at assessment \(\leq 5\) days after onset of symptoms compared with the last assessment prior to the relapse.

Considering the relationship between disability progression and relapse in terms of the proportion of cases of CDP that followed a relapse, approximately half of patients experiencing 24-week CDP in the delayed treatment over two years had experienced a relapse within 90 days prior to onset of CDP (and therefore CDP was considered to be a residual effect of relapse), whereas CDP was attributable to incomplete recovery from relapse in only approximately one-quarter of patients with 24-week CDP in the peginterferon beta-1a every-2-weeks group (Table 1).

A sensitivity analysis that used a 180-day window to determine association between 24-week CDP and relapse provided highly consistent results to those obtained based on the 90-day window (per Figure 1). Furthermore, results over 1 year or over 2 years were consistent with reduction in relapses with incomplete recovery for peginterferon beta-1a every 2 weeks versus placebo in Year 1 (see Supplementary Table 1 online).

Relapses were not a surrogate marker for CDP according to the Prentice criteria. The first three criteria were met. However, the treatment effect of peginterferon beta-1a on 24-week CDP remained significant after adjusting for relapses (coefficient for treatment effect \(-0.6126\); \(p = 0.0323\)) so the fourth criterion failed, indicating a treatment effect of peginterferon beta-1a on CDP beyond its treatment effect of reducing the occurrence of relapses.

Table 1. Proportions of patients with 24-week CDP, with/without associated relapse, over 2 years.

| Characteristic, n (%) | Delayed treatment | Peginterferon beta-1a |
|-----------------------|------------------|----------------------|
|                       | Placebo (overall delayed treatment group; \(n = 500\)) | Peginterferon beta-1a every 2 weeks (\(n = 512\)) | Peginterferon beta-1a every 4 weeks (\(n = 500\)) |
|                       | 24-week CDP      | 34 (6.6)            | 52 (10.4)            |
|                       | 29 (5.8)         | 26 (5.1)            | 29 (5.8)            |
|                       | 8 (1.6) \(p = 0.0005\) vs. delayed treatment | 23 (4.6) \(p = 0.47\) vs. delayed treatment |
|                       | Due to incomplete recovery from relapse |                       |                       |
|                       | 28 (5.6)         |                       |                       |

CDP = confirmed disability progression.
**Worsening in individual functional systems in patients with 24-week CDP**

Among patients with 24-week CDP due to incomplete recovery from relapse, 86% had worsening of ≥1 point in ≥1 FSS, and 43% had worsening of ≥2 points in ≥1 FSS. Among patients with 24-week CDP independent of relapse, similar proportions of patients had FSS worsening by ≥1 or ≥2 points (89% and 34%, respectively). FSS worsening occurred most frequently in the pyramidal domain, in both subgroups of patients with 24-week CDP (see Supplementary Figure 2 online).

**Discussion**

In the ADVANCE study, continuous treatment with peginterferon beta-1a 125 mcg every 2 weeks over 2 years reduced the proportion of relapses associated with residual disability by more than half, compared with delayed treatment (placebo in the first year of the study), indicating a positive treatment effect of peginterferon beta-1a on relapse recovery. The effect on residual disability was in fact greater than the effect of peginterferon beta-1a on overall relapse rate in the ADVANCE study, i.e. 37% reduction in ARR over 2 years with peginterferon beta-1a every 2 weeks compared with delayed treatment, and in the overall study population (regardless of relapse status) there was >70% reduction in relapses with incomplete recovery (see Supplementary Figure 3 online). It does not appear to be the case that peginterferon beta-1a simply reduced relapse severity, and thereby lessened the likelihood of residual deficits, since similar proportions of patients in each treatment group had relapses with ≥1-point increase in EDSS score. Despite this apparent lack of treatment effect on relapse severity clinically, treatment might be associated with improved recovery due to some effect on the initial forming lesion(s). More plausibly, later events involving recovery could be effected. Alternatively, if treatment creates a modification in the overall process of cumulative residual disability, the apparent effects of each superimposed attack may be modified.

Among patients with 24-week CDP, overall reduction in risk of 24-week CDP in the peginterferon beta-1a every-2-weeks group was largely driven by reduction in CDP resulting from relapses with incomplete recovery. This may be attributable, in part, to a reduction in total number of relapses in the peginterferon beta-1a group; however, our analysis indicates that improved recovery when relapse does occur was also a factor. Indeed, we found that relapses were not a surrogate marker for CDP in the ADVANCE study, whereas relapses with incomplete recovery were, according to the Prentice criteria. Given the apparent little difference between treatment groups in rates of CDP independent of relapse, we suggest that relapse recovery accounts for this differential treatment effect. Much of the CDP seen in this trial did occur free from relapse, as reported in a few other trials looking at phenotypes of worsening patients, suggesting a role for understanding clinical phenotypes in drug development.

A sensitivity analysis showed that rates of association between relapse and CDP were very similar when the window for determining that association was extended from 90 to 180 days. This confirms that our analysis was not likely to have underestimated the contribution of relapses to CDP. In fact, the vast majority (57/59 (97%)) of cases of incomplete relapse recovery had onset of 24-week CDP within 14 days. Therefore, it appears that our results reflect residual disability related to relapse (and conversely, relapse recovery when relapse is not followed by CDP) rather than simply fluctuation in EDSS scores over time. Furthermore, the majority of patients with CDP had simultaneous worsening in one or more FSS during the confirmation period for 24-week CDP. This helps support our assumption that recorded changes in CDP were due to the protocol-defined relapses, rather than impairment fluctuating across multiple domains. The functional system most commonly affected was the pyramidal system. Prior studies of FSS have shown that motor system involvement (pyramidal and cerebellar scores) are likely paramount in worsening patients in the mid-range of EDSS scores, so recovery in these domains could be an important factor in determining whether relapse leads to CDP. However, there may be inherent difficulties in using the EDSS for measuring motor system problems due to relapse without recovery, given the sensitivity of this scale.

The ADVANCE population appears to be representative of MS trial populations, in terms of relapse recovery independent of treatment effect, as residual disability in the placebo group was highly consistent with that in two recent trials of dimethyl fumarate, DEFINE and CONFIRM; approximately 20% of patients in the placebo groups in each of these trials had onset of 12-week CDP within 180 days following relapse (see Supplementary Table 1). This is also similar to a previous analysis of pooled data from placebo groups from several trials, in which 28% of patients were found to have a residual deficit of ≥1 EDSS point an average of 64 days after...
exacerbation. Our findings can be viewed in the context of different MS phenotypes described by recently proposed terminology defining active disease as relapse, progression of disability, or new MRI activity. Worsening disease is defined as documented increase in relapse frequency or disability. Some but not all relapses result in worsening (incomplete recovery). Assessment of relapse recovery was highlighted in this consensus report as an area for future research.

This analysis highlights the relevance of relapse recovery as a useful additional measure of treatment effect. Relapses with incomplete versus complete recovery may be a more appropriate endpoint than relapse rate for MS clinical trials, in recognition that quality may be more relevant than quantity of relapses in predicting clinical outcomes, as overall relapse frequency after the first few years of MS may be a poor predictor of long-term outcome. A previous analysis of patient-reported outcomes in ADVANCE showed that CDP due to incomplete relapse recovery was an important factor in driving the negative impact of MS on health-related quality of life, having a greater impact than CDP independent of relapse, or relapses that did not lead to CDP, further highlighting the value of improving relapse recovery.

Early analyses suggest that effects on relapse recovery may help to differentiate treatment options. In our current analysis of ADVANCE data, peginterferon beta-1a demonstrated potential to improve relapse recovery, whereas analysis of MSCRG study data, using the same method to test Prentice criteria, indicated that intramuscular interferon beta-1a had no effect on CDP beyond that explained by reduction in relapse rate. An effect on outcome after relapse has been demonstrated for some other treatments; however, mechanisms may differ as none have demonstrated recovery in the way that peginterferon beta-1a improved recovery in this study. In the AFFIRM study, a significantly lower proportion of patients on natalizumab had residual EDSS worsening following relapse, compared with placebo. This coincided with a significant reduction in relapse severity with natalizumab compared with placebo, suggesting that the effect on relapse recovery was driven by a “protective” effect against severe relapses, whereas in ADVANCE peginterferon beta-1a improved relapse recovery rates despite similar relapse severity across groups. In a post-hoc analysis of the TEMSO study, teriflunomide reduced the rate of relapses with sequelae, but this did not appear to be attributable to improved relapse recovery since the risk of sequelae per relapse was found not to be modified by treatment. However, caution should be exercised in attempting to compare treatment effects on relapse recovery, since the assessments described above are based on post-hoc analyses and all used different definitions for recovery/residual effects. Further study of treatment effects on relapse recovery, ideally recorded as a pre-specified endpoint and assessed using standardized definitions, could provide valuable information to help guide treatment decisions. Longer-term data may also permit more thorough analysis of the relationship between relapse recovery and long-term disability, as this has only been the subject of a few long-term studies.

In conclusion, the effect of peginterferon beta-1a on risk of CDP may be attributable to improvement in recovery from relapses, as well as an overall reduction in risk of relapses, thus limiting further disability progression. Although our positive findings are modest, and the underlying reasons for this association remain unclear, models for studying this effect are new and we believe will be valuable going forward, particularly in drug development.

Declaration of conflicting interests
T.F. Scott has received research support from Biogen and Novartis, and has received honoraria for participation in scientific advisory boards and speaking for Biogen, Genzyme, Teva Neurosciences, Accorda Therapeutics, and Novartis.

B.C. Kieseier has received personal compensation for activities with Bayer Schering, Biogen, Merck Serono, Novartis, Roche, Sanofi-Aventis, and Teva Neurosciences as a lecturer, and research support from Bayer Schering, Biogen, Merck Serono, and Teva Neurosciences. He was not affiliated to Biogen at the time of study conduct and data analysis, but is now an employee and stock holder of Biogen.

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References
1. Langer-Gould A, Popat RA, Huang SM, et al. Clinical and demographic predictors of long-term disability in patients with relapsing-remitting multiple sclerosis: a systematic review. Arch Neurol 2006; 63: 1686–1691.
2. Scott TF. Are we studying MS relapses in the right way? Mult Scler Relat Disord 2013; 2: 2–3.
3. Skoog B, Tedeholm H, Runmarker B, et al. Continuous prediction of secondary progression in the individual course of multiple sclerosis. Mult Scler Relat Disord 2014; 3: 584–592.
4. Lublin FD, Baier M and Cutter G. Effect of relapses on development of residual deficit in multiple sclerosis. Neurology 2003; 61: 1528–1532.
5. Hirst C, Ingram G, Pearson O, et al. Contribution of relapses to disability in multiple sclerosis. J Neurol 2008; 255: 280–287.
6. O’Connor PW, Lublin FD, Wolinsky JS, et al. Teriflunomide reduces relapse-related neurological sequelae, hospitalizations and steroid use. J Neurol 2013; 260: 2472–2480.
7. Lublin FD, Cutter G, Giovannoni G, et al. Natalizumab reduces relapse clinical severity and improves relapse recovery in MS. Mult Scler Relat Disord 2014; 3: 705–711.
8. Calabresi PA, Kieseier BC, Arnold DL, et al.; on behalf of the ADVANCE Study Investigators. Pegylated interferon β-1a for relapsing-remitting multiple sclerosis (ADVANCE): a randomised, phase 3, double-blind study. Lancet Neurol 2014; 13: 657–665.
9. 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.
10. Biogen. Plegridy® (package insert). Cambridge, MA: Biogen, 2014.
11. Polman CH, Reingold SC, Edan G, et al. Diagnostic criteria for multiple sclerosis: 2005 revisions to the ‘McDonald Criteria’. Ann Neurol 2005; 58: 840–846.
12. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology 1983; 33: 1444–1452.
13. Berger VW. Does the Prentice criterion validate surrogate endpoints? Stat Med 2004; 23: 1571–1578.
14. Scott TF, You X and Mann MK. Incomplete relapse recovery and sustained disability progression in multiple sclerosis. In: Fifth cooperative meeting of the Consortium of Multiple Sclerosis Centers and Americas Committee for Treatment and Research in Multiple Sclerosis, Orlando, FL, 29 May–1 June 2013.
15. Sorman MP, Vollmer TL, Comi G, et al. Laquinimod effect on confirmed disability progression: minimal mediation by relapse or T2 lesions reduction. In: Meeting of the European Committee for Treatment and Research in Multiple Sclerosis, Boston, MA, 10–13 September 2014.
16. Scott TF, You X and Foulds P. Functional system scores provide a window into disease activity occurring during a multiple sclerosis treatment trial. Neurol Res 2011; 33: 549–552.
17. Gold R, Kappos L, Arnold DL, et al.; on behalf of the DEFINE Study Investigators. Placebo-controlled phase 3 study of oral BG-12 for relapsing multiple sclerosis. N Engl J Med 2012; 367: 1098–1107.
18. Fox RJ, Miller DH, Phillips JT, et al.; on behalf of the CONFIRM Study Investigators. Placebo-controlled phase 3 study of oral BG-12 or glatiramer in multiple sclerosis. N Engl J Med 2012; 367: 1087–1097.
19. Lublin FD, Reingold SC, Cohen JA, et al. Defining the clinical course of multiple sclerosis: the 2013 revisions. Neurology 2014; 83: 278–286.
20. Scalfari A, Neuhaus A, Degenhardt A, et al. The natural history of multiple sclerosis: a geographically based study 10: relapses and long-term disability. Brain 2010; 133: 1914–1929.
21. Newsome SD, Guo S, Altincatal A, et al. Impact of peginterferon beta-1a and disease factors on quality of
life in multiple sclerosis. *Mult Scler Relat Disord* 2015; 4: 350–357.

22. You X, Scott T, Shang S, et al. Evaluation of relapses as a surrogate marker for confirmed disability progression in relapsing-remitting multiple sclerosis patients treated with peginterferon beta-1a using the Prentice criteria. In: *First congress of the European Association of Neurology*, Berlin, Germany, 20–23 June 2015.

23. Scott TF, Getting EJ, Hackett CT, et al. Specific clinical phenotypes in relapsing multiple sclerosis: the impact of relapses on long-term outcomes. *Mult Scler Relat Disord* 2016; 5: 1–6.