Pegylated interferon beta-1a for relapsing-remitting multiple sclerosis (ADVANCE): a randomised, phase 3, double-blind study

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Summary

Background Subcutaneous pegylated interferon (peginterferon) beta-1a is being developed for treatment of relapsing multiple sclerosis, with less frequent dosing than currently available first-line injectable treatments. We assessed the safety and efficacy of peginterferon beta-1a after 48 weeks of treatment in the placebo-controlled phase of the ADVANCE trial, a study of patients with relapsing-remitting multiple sclerosis.

Methods We did this 2-year, double-blind, parallel group, phase 3 study, with a placebo-controlled design for the first 48 weeks, at 183 sites in 26 countries. Patients with relapsing-remitting multiple sclerosis (age 18–65 years, with Expanded Disability Status Scale score ≤5) were randomly assigned (1:1:1) via an interactive voice response or web system, and stratified by site, to placebo or subcutaneous peginterferon beta-1a 125 μg once every 2 weeks or every 4 weeks. The primary endpoint was annualised relapse rate at 48 weeks. This trial is registered with ClinicalTrials.gov, number NCT00906399.

Findings We screened 1936 patients and enrolled 1516, of whom 1512 were randomly assigned (500 to placebo, 512 to peginterferon every 2 weeks, 500 to peginterferon every 4 weeks); 1332 (88%) patients completed 48 weeks of treatment. Adjusted annualised relapse rates were 0·397 (95% CI 0·328–0·481) in the placebo group versus 0·256 (0·206–0·318) in the every 2 weeks group and 0·288 (0·234–0·355) in the every 4 weeks group (rate ratio for every 2 weeks group 0·644, 95% CI 0·500–0·831, p=0·0007; rate ratio for the every 4 weeks group 0·725, 95% CI 0·565–0·930, p=0·0114). 417 (83%) patients taking placebo, 481 (94%) patients taking peginterferon every 2 weeks, and 472 (94%) patients taking peginterferon every 4 weeks reported adverse events including relapses. The most common adverse events associated with peginterferon beta-1a were injection site reactions, influenza-like symptoms, pyrexia, and headache. 76 (15%) patients taking placebo, 55 (11%) patients taking study drug every 2 weeks, and 71 (14%) patients taking study drug every 4 weeks reported serious adverse events; relapse, pneumonia, and urinary tract infection were the most common.

Interpretation After 48 weeks, peginterferon beta-1a significantly reduced relapse rate compared with placebo. The drug might be an effective treatment for relapsing-remitting multiple sclerosis with less frequent administration than available treatments.

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See Online for appendix

Introduction

Interferon beta treatments have been approved for relapsing multiple sclerosis for more than 20 years[1] and are considered safe and effective. However, as small proteins, interferon betas are rapidly cleared by the kidneys or degraded and so need to be given often,[2] from once per week to every other day. The need for frequent administration can be a barrier to treatment for multiple sclerosis[3] and, along with injection-associated adverse events, it can negatively affect adherence.[4–6]

Pegylated interferon (peginterferon) beta-1a was developed by the attachment of a polyethylene glycol side-chain to the parent interferon molecule,[7] a process known as pegylation. Pegylation changes the pharmacokinetic and pharmacodynamic profile of interferon alfa and several other drugs approved for chronic conditions,[2,8,9] while maintaining safety and tolerability and reducing immunogenicity.[10,11] Two studies[12] established that subcutaneous peginterferon beta-1a has a prolonged half-life and increased systemic exposure (area under the curve and peak concentration) compared with intramuscular interferon beta-1a. These studies confirmed the potential for using less frequent subcutaneous dosing intervals of peginterferon beta-1a, without attenuating the biological or pharmacodynamic properties associated with existing interferon treatments for multiple sclerosis.

Here we report primary results from the first 48 weeks (placebo-controlled period) of the 2-year, phase 3, ADVANCE study assessing the efficacy and safety of peginterferon beta-1a administered every 2 weeks or every 4 weeks for patients with relapsing-remitting multiple sclerosis.

Methods

Study design and participants

We did this randomised, double-blind, placebo-controlled phase 3 trial at 183 neurology practices—including

hospitals, academic medical centres, and private practices—in 26 countries. Key eligibility criteria were a diagnosis of relapsing-remitting multiple sclerosis as defined by the McDonald criteria,[13] age 18–65 years, a score of 0–5 on the Expanded Disability Status Scale (which ranges from 0 to 10, with higher scores indicating greater disability),[14] and at least two clinically documented relapses in the previous 3 years, with at least one having occurred within the past 12 months. Key exclusion criteria were progressive forms of multiple sclerosis, pre-specified laboratory abnormalities, and previous treatment with interferon for multiple sclerosis for more than 4 weeks or discontinuation less than 6 months before baseline (see appendix for full details of exclusion criteria).

The protocol was approved by the institutional review board at each site and the study was done according to International Conference on Harmonization Guidelines for Good Clinical Practice and the Declaration of Helsinki.[15,16] Every patient provided written informed consent before entering the study.

Randomisation and masking

Patients were enrolled by investigators at each site and randomly assigned (1:1:1) to receive subcutaneous injections with pre-filled syringes of placebo, peginterferon beta-1a at a dose of 125 μg once every 2 weeks, or peginterferon beta-1a 125 μg once every 4 weeks. Randomisation was done by a centralised interactive voice response and web system, stratified by site. Placebo was a matched diluent, given with a matched pre-filled syringe. Patients received either study drug or placebo every 2 weeks to maintain masking; those assigned to receive study drug every 4 weeks received alternate injections of placebo and peginterferon beta-1a every 2 weeks. Participants assigned to receive peginterferon beta-1a underwent dose escalation over the first 4 weeks to mitigate influenza-like symptoms (starting dose 63 μg; 94 μg at week 2; target dose 125 μg at week 4 and thereafter). At the end of 48 weeks, patients in the placebo group were randomly re-assigned to peginterferon beta-1a 125 μg every 2 weeks or 4 weeks. All patients were masked to treatment until the end of year 2. All study management and site personnel, investigators, and patients were masked to treatment assignment. Each site had separate examining and treating neurologists, thereby maintaining rater masking for all treatment groups.

Study procedures

We did standardised neurological assessments, including the Expanded Disability Status Scale, at screening, at baseline, every 12 weeks, and at the time of suspected relapse (evaluated during unscheduled visits). Patients had MRI scans at screening and at weeks 24 and 48, and were assessed at a central MRI reading centre by an assessor masked to treatment allocation.

Relapse was defined as new or recurrent neurological symptoms not associated with fever or infection, lasting for at least 24 h, accompanied by new objective neurological findings confirmed by the independent neurological evaluation committee (appendix), and separated from the onset of other confirmed relapses by at least 30 days. Disability progression was defined as an increase of Expanded Disability Status Scale score of at least 1·0 point for patients with a baseline score of 1·0 or more, or an increase of at least 1·5 points for patients with a baseline score of 0, confirmed after 12 weeks (appendix). We assessed neutralising antibodies before participants were given peginterferon beta-1a at the baseline visit (including participants who had previously had interferon treatment).

Outcomes

The primary endpoint was annualised relapse rate at week 48, based on number of relapses. Secondary efficacy endpoints were the number of new or newly enlarging hyperintense lesions on T2-weighted images (relative to baseline MRI), proportion of patients who relapsed, and proportion of patients with disability progression at 48 weeks. Tertiary prespecified MRI endpoints at 48 weeks were the number of gadolinium-enhancing lesions, new T1 hypointense lesions, and new active lesions (sum of gadolinium-enhancing plus non-enhancing new or newly enlarging T2 hyperintense lesions), the volume of new or newly enlarging T2 hyperintense, gadolinium-enhancing, and T1 hypointense lesions, brain atrophy, and magnetisation transfer ratio.

Statistical analysis

The first 48 weeks of the study (the placebo-controlled period) were completed on Oct 24, 2012. On this date, the trial was ongoing because not all patients had completed the full 2-year period. We did all efficacy analyses for the intention-to-treat population (all randomly assigned patients who received study treatment). Statistical tests were two-sided, with an overall type 1 error rate of 0·05. We estimated that a sample size of 500 participants per group was needed to provide 85% power to detect a 32% reduction in annualised relapse rate with study drug compared with placebo,[17,18] assuming an annualised relapse rate of roughly 0·40 for placebo and 10% drop-out.

We used a sequential (closed) testing procedure to control for overall type 1 error because of multiple comparisons, with the every 2 weeks group versus the placebo group first, followed by the every 4 weeks group versus the placebo group, and with the ordering of primary and secondary endpoints; each comparison was only considered significant if the preceding comparison had a p value of less than 0·05 (appendix). We analysed annualised relapse rate (total number of relapses divided by patient-years in the study, excluding data obtained after patients switched to alternative multiple sclerosis drugs) with a negative binomial regression model adjusted for baseline Expanded Disability Status Scale

	Placebo group (n=500)	Peginterferon beta-1a 125 µg every 2 weeks group (n=512)	Peginterferon beta-1a 125 µg every 4 weeks group (n=500)
Age (years)	36·3 (9·7)	36·9 (9·8)	36·4 (9·9)
Women	358 (72%)	361 (71%)	352 (70%)
White ethnic origin	412 (82%)	416 (81%)	409 (82%)
Geographic region			
India	56 (11%)	58 (11%)	56 (11%)
North America	17 (3%)	19 (4%)	16 (3%)
Western Europe	38 (8%)	41 (8%)	39 (8%)
Eastern Europe	354 (71%)	355 (69%)	355 (71%)
Rest of the world	35 (7%)	39 (8%)	34 (7%)
Time since first multiple sclerosis symptoms (years)	6·3 (6·3)	6·9 (6·6)	6·5 (6·1)
Time since multiple sclerosis diagnosis (years)	3·5 (4·6)	4·0 (5·1)	3·4 (4·4)
Relapses within the previous 3 years	2·6 (1·00)	2·6 (0·99)	2·5 (0·77)
Relapses within the previous 12 months	1·6 (0·67)	1·6 (0·67)	1·5 (0·62)
EDSS score	2·44 (1·18)	2·47 (1.26)	2·48 (1·24)
<4	432 (86%)	423 (83%)	413 (83%)
≥4	68 (14%)	89 (17%)	87 (17%)
Patients without gadolinium-enhancing lesions	296 (59%)	334 (65%)	297 (59%)
Number of gadolinium-enhancing lesions	1·6 (3·8)	1·2 (3·4)	1·8 (5·4)
Number of T2 lesions	50·6 (35·7)	48·7 (36·8)	51·4 (36·0)
Previous treatment*			
Glatiramer acetate	24 (5%)	27 (5%)	28 (6%)
Interferon beta-1b	6 (1%)	8 (2%)	5 (1%)
Interferon beta-1a	5 (1%)	4 (<1%)	6 (1%)
Other	58 (12%)	56 (11%)	58 (11%)

Data are mean (SD) or n (%). EDSS=Expanded Disability Status Scale. Peginterferon=pegylated interferon. *Patients who had taken more than one drug were counted more than once: the total number of patients who had previously been treated was 260 (17%).

Table 1: **Baseline characteristics**

score (<4 *vs* ≥4), baseline relapse rate (number of relapses in 3 years before study entry divided by 3), and age (<40 *vs* ≥40 years). We used negative binomial regression to analyse new or newly enlarging hyperintense lesions on T2-weighted images (adjusted for baseline number of T2 lesions) and new active lesions (adjusted for baseline number of gadolinium-enhancing lesions). We used multiple logit regression to analyse the number of gadolinium-enhancing and new T1-hypointense lesions (adjusted for baseline number of respective lesions). We used ANCOVA to analyse lesion volumes (adjusted for respective baseline lesion volumes), brain atrophy (adjusted for baseline normal brain volume) and magnetisation transfer ratio (adjusted for baseline normal appearing brain tissue magnetisation transfer ratio). We used a Cox proportional hazards model to analyse time to first clinical relapse (adjusted for baseline Expanded Disability Status Scale score, age, baseline relapse rate, and baseline gadolinium-enhancing lesions) and time to first disability progression (adjusted for baseline Expanded Disability Status Scale score and age). We summarised safety data with descriptive statistics for all patients who received at least one dose of study drug, excluding data obtained after patients switched to alternative multiple sclerosis drugs. We did sensitivity analyses to assess the effect of the data collected after patients switched to alternative multiple sclerosis drugs and patient withdrawal.

This trial is registered with ClinicalTrials.gov, number NCT00906399.

Role of the funding source

Biogen Idec collected, analysed, and contributed to the interpretation of the data. The first draft was written by PAC and Biogen Idec funded support and coordination for revisions and the preparation of tables and figures. SL, YZ, AS, SH, and AD were employed by the funder during the study and preparation of the report. All authors participated in the decision to publish the paper and had full access to all study data. The corresponding author had final responsibility for the decision to submit for publication.

Results

We recruited patients between June, 2009, and November, 2011. We screened 1936 patients and randomly assigned 1516, of whom 1512 received at least one dose of study drug and were included in the intention-to-treat population (500 received placebo, 512 received peginterferon beta-1a every 2 weeks, 500 received

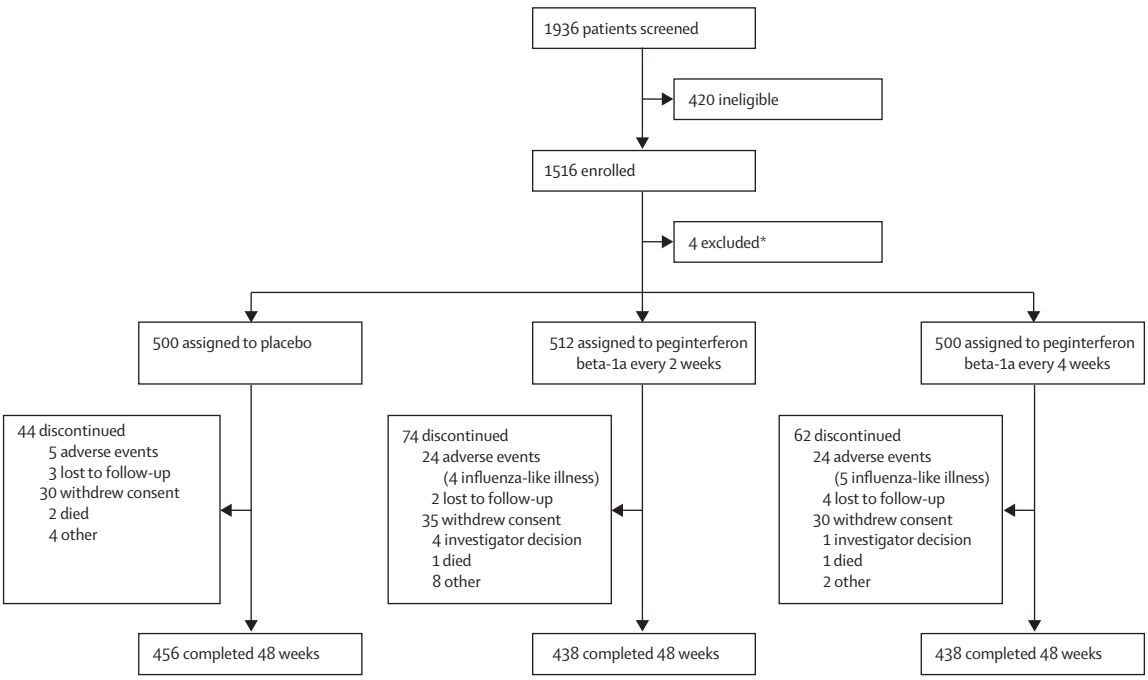


Figure 1: **Trial profile**
One patient in the every 2 weeks group discontinued study treatment but remained in the study for follow-up. Peginterferon=pegylated interferon. *Three randomised in error (violation of inclusion or exclusion criteria) and one had an adverse event after randomisation but before treatment rendering them ineligible for treatment.

	Placebo group (n=500)	Peginterferon beta-1a 125 µg every 2 weeks group (n=512)	Peginterferon beta-1a 125 µg every 4 weeks group (n=500)
Annualised relapse rate at 48 weeks			
Annualised relapse rate (95% CI)*	0·397 (0·328–0·481)	0·256 (0·206–0·318)	0·288 (0·234–0·355)
Rate ratio (*vs* placebo; 95% CI)	..	0·644 (0·500–0·831)	0·725 (0·565–0·930)
p value (*vs* placebo)	..	0·0007	0·0114
Proportion of patients with a relapse at 48 weeks			
n	142	90	105
Estimated proportion relapsed (SE)	0·291 (0·0206)	0·187 (0·0178)	0·222 (0·0191)
Hazard ratio *vs* placebo (95% CI)†	..	0·61 (0·47–0·80)	0·74 (0·57–0·95)
p value (*vs* placebo)†	..	0·0003	0·02
Disability progression at 48 weeks‡			
n	50	31	31
Estimated proportion with disability progression (SE)	0·105 (0·0142)	0·068 (0·0119)	0·068 (0·0119)
Hazard ratio *vs* placebo (95% CI)§	..	0·62 (0·40–0·97)	0·62 (0·40–0·97)
p value (*vs* placebo)§	..	0·0383	0·0380
New or newly enlarging T2-weighted hyperintense lesions at 48 weeks¶‖			
Number of patients evaluated	476	457	462
Adjusted mean number of lesions (95% CI)**	10·9 (9·6–12·5)	3·6 (3·1–4·2)	7·9 (6·9–9·0)
Lesion mean ratio (95% CI)**	..	0·33 (0·27–0·40)	0·72 (0·60–0·87)
p value (*vs* placebo)**	..	<0·0001	0·0008

EDSS=Expanded Disability Status Scale. Peginterferon=pegylated interferon. *Based on negative binomial regression; adjusted for baseline EDSS (<4 *vs* ≥4), baseline relapse rate, and age (<40 *vs* ≥40). †Based on Cox proportional hazards model, adjusted for baseline EDSS (<4 *vs* ≥4), age (<40 *vs* ≥40), baseline relapse rate, and baseline gadolinium-enhancing lesions (presence *vs* absence). ‡Defined as ≥1·0 point increase on the EDSS from a baseline EDSS ≥1·0 sustained for 12 weeks or at least a 1·5 point increase on the EDSS from a baseline EDSS of 0 sustained for 12 weeks. §Based on Cox proportional hazards model, adjusted for baseline EDSS and age (<40 *vs* ≥40 years). ¶Intention-to-treat population with at least one post-baseline lesion on MRI scan. ‖Data after patients switched to alternative multiple sclerosis drugs were deemed missing; all missing data were imputed on the basis of previous visit data assuming a constant rate of lesion development. 18 participants in the placebo group, 23 in the every 4 weeks group, and 18 in the every 2 weeks group had imputed data. **Based on negative binomial regression analysis, adjusted for region and baseline T2 lesion number.

Table 2: **Primary and secondary clinical and MRI results**

peginterferon beta-1a every 4 weeks; table 1, figure 1). Four patients did not receive any treatment (figure 1). Baseline demographic and disease characteristics were similar between treatment groups (table 1). 260 (17%) of 1512 patients in the intention-to-treat population had previously received treatment for multiple sclerosis, and this proportion was consistent across treatment groups (table 1). 1332 (88%) of 1512 participants completed the first year of the study (figure 1). Treatment compliance (number of doses a patient received divided by the number they were expected to have) was greater than 99% in each treatment group. The proportion of patients who discontinued study treatment or withdrew in the first 48 weeks was slightly lower in the placebo group compared with the intervention groups, as a result of differences in adverse events (figure 1). Withdrawal of consent was the most common reason for discontinuing study treatment and occurred in similar proportions across groups (figure 1). The appendix shows additional demographic information.

Relapses were significantly less frequent in patients taking peginterferon beta-1a than in those taking placebo. At week 48, the adjusted annualised relapse rate was 0·397 relapses per patient-year (95% CI 0·328–0·481) in the placebo group, 0·256 (0·206–0·318) in the every 2 weeks group, and 0·288 (0·234–0·355) in the every 4 weeks group. The rate ratio for peginterferon every 2 weeks versus placebo was 0·644 (95% CI 0·500–0·831; p=0·0007) and the rate ratio for peginterferon every 4 weeks compared with placebo was 0·725 (95% CI 0·565–0·930; p=0·0114; table 2). The Kaplan-Meier estimate of the proportion of patients with a relapse at 48 weeks was 0·291 (SE 0·0206) in the placebo group, 0·187 (0·0178) in the every 2 weeks group, and 0·222 (0·0191) in the every 4 weeks group (figure 2). Hazard ratios show significant reductions in risk of relapse after treatment with study drug relative to placebo (table 2).

The proportion of patients who had had 12 weeks of sustained disability progression at 48 weeks was 0·105 (SE 0·0142) in the placebo group and 0·068 (0·0119) in both intervention groups (figure 3). Hazard ratios show that peginterferon beta-1a significantly reduced the risk of progression of disability (table 2).

Patients treated with peginterferon beta-1a had fewer new or newly enlarging hyperintense lesions on T2-weighted images at 48 weeks than did patients in the placebo group (table 2); these lesions were also significantly smaller for those patients taking study drug compared with those taking placebo (p<0·0001; appendix). Patients in the every 2 weeks group had significantly fewer and smaller new T1 hypointense and gadolinium-enhancing lesions, and significantly fewer new active lesions, compared with patients in the placebo group (all p<0·0001; appendix). Patients in the every 4 weeks group had fewer new active lesions and smaller T2 and gadolinium-enhancing lesions compared with those in the placebo group (all p<0·0001; appendix). We reported fewer T1 hypointense and gadolinium-enhancing lesions, with peginterferon

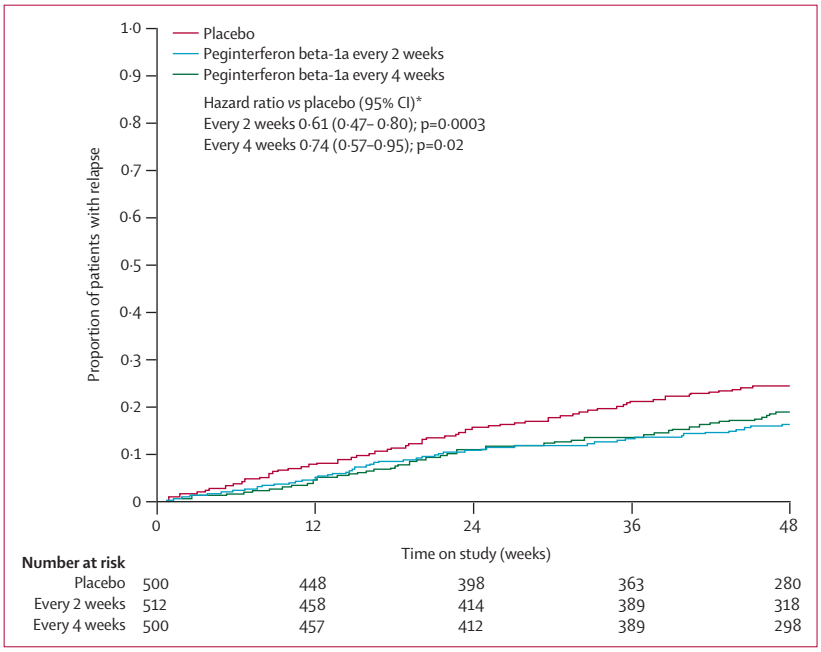


Figure 2: **Time to first relapse over 48 weeks**
Peginterferon=pegylated interferon. *Based on Cox proportional hazards model, adjusted for baseline Expanded Disability Status Scale score (<4 *vs* ≥4), age (<40 *vs* ≥40), baseline relapse rate, and baseline gadolinium-enhancing lesions (presence *vs* absence).

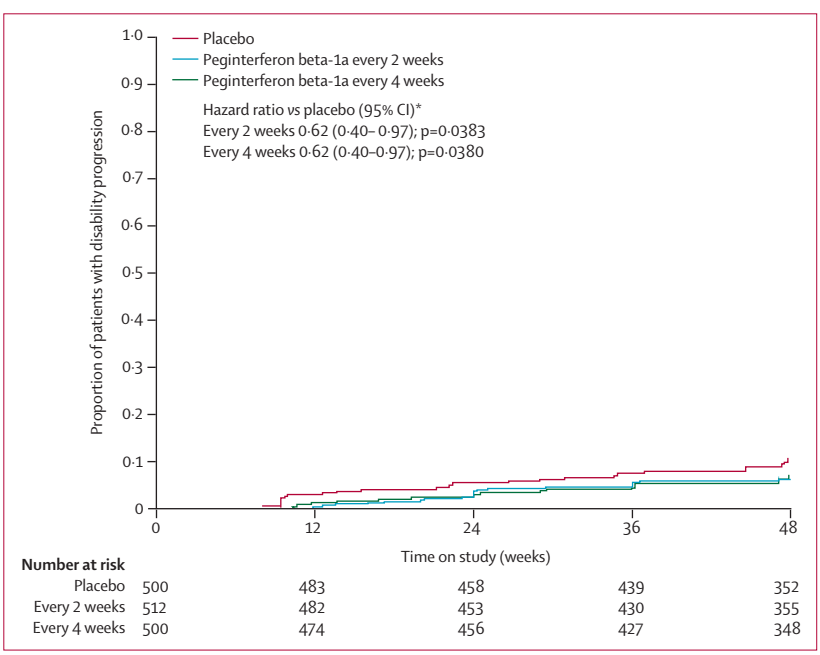


Figure 3: **Time to disability progression over 48 weeks**
Disability progression defined as ≥1·0 point increase on the Expanded Disability Status Scale from a baseline score of ≥1·0 sustained for 12 weeks or at least a 1·5 point increase from a baseline score of 0 sustained for 12 weeks. Peginterferon=pegylated interferon. *Based on Cox proportional hazards model, adjusted for baseline Expanded Disability Status Scale score (<4 *vs* ≥4) and age (<40 *vs* ≥40).

	Placebo group (n=500)	Peginterferon beta-1a every 2 weeks group (n=512)	Peginterferon beta-1a every 4 weeks group (n=500)
Any adverse event	417 (83%)	481 (94%)	472 (94%)
Any adverse event (excluding multiple sclerosis relapse)	394 (79%)	477 (93%)	469 (94%)
Most common adverse events (≥10% in any treatment group)			
Injection site erythema	33 (7%)	315 (62%)	282 (56%)
Influenza-like illness	63 (13%)	239 (47%)	234 (47%)
Pyrexia	76 (15%)	228 (45%)	218 (44%)
Headache	165 (33%)	224 (44%)	204 (41%)
Multiple sclerosis relapse	159 (32%)	96 (19%)	111 (22%)
Myalgia	30 (6%)	97 (19%)	97 (19%)
Chills	23 (5%)	88 (17%)	92 (18%)
Injection-site pain	15 (3%)	77 (15%)	67 (13%)
Asthenia	38 (8%)	68 (13%)	70 (14%)
Back pain	57 (11%)	61 (12%)	64 (13%)
Injection-site pruritus	6 (1%)	68 (13%)	56 (11%)
Nasopharyngitis	77 (15%)	53 (10%)	69 (14%)
Arthralgia	35 (7%)	57 (11%)	54 (11%)
Fatigue	49 (10%)	51 (10%)	55 (11%)
Pain in extremity	49 (10%)	44 (9%)	54 (11%)
Adverse events related to study treatment	266 (53%)	459 (90%)	449 (90%)
Adverse events leading to discontinuation	7 (1%)	25 (5%)	24 (5%)
Influenza-like illness leading to discontinuation (≥1% in any active treatment group)	0	4 (<1%)	8 (2%)
Any serious adverse events	76 (15%)	55 (11%)	71 (14%)
Any serious adverse event (excluding multiple sclerosis relapse)	23 (5%)	24 (5%)	26 (5%)
Most common serious adverse events (≥two patients)			
Multiple sclerosis relapse	57 (11%)	35 (7%)	47 (9%)
Infection			
Dengue fever	0	1 (<1%)	1 (<1%)
Pneumonia	1 (<1%)	0	2 (<1%)
Urinary tract infection	1 (<1%)	0	2 (<1%)
Other (including intervertebral disc disorder, paraparesis)	0	2 (<1%)	2 (<1%)
Severe adverse events*	53 (11%)	90 (18%)	82 (16%)
Deaths	2 (<1%)†	1 (<1%)‡	1 (<1%)§

Data are number of patients (%). Peginterferon=pegylated interferon. *Defined as symptoms that cause severe discomfort, incapacitation, or significant effect on patient's daily life; severity could cause cessation of study treatment, treatment for symptoms, or admission to hospital. †One sudden death of unknown cause, one subarachnoid haemorrhage. ‡Cause unknown. §Septic shock.

Table 3: **Adverse events, serious adverse events, discontinuations, and deaths**

beta-1a every 4 weeks compared with placebo, but differences were not statistically significant (appendix). We noted no significant differences for whole brain volume between groups (appendix). Mean percentage decrease in magnetisation transfer ratio was significantly lower for patients in the every 2 weeks group, compared with those in the placebo group (p=0·0438); we recorded no statistically significant difference when comparing those treated with peginterferon every 4 weeks with those treated with placebo (p=0·6873; appendix). In sensitivity analyses, the effect sizes for the primary outcomes were generally consistent with those of the primary analyses (appendix).

The overall incidence of adverse events including relapses was lower in the placebo group compared with the intervention groups and similar between the two peginterferon beta-1a dosing regimens (417 [83%] of 500 in the placebo group, 481 [94%] of 512 in the every 2 weeks group, 472 [94%] of 500 in the every 4 weeks group; table 3).

The adverse events that were more than 2% more common in the peginterferon beta-1a groups than in the placebo group were injection-site reactions, influenza-like illness, pyrexia, and headache. Adverse events deemed related to study treatment by the investigator were more common in the intervention groups than in the placebo group (table 3). The most commonly

reported treatment-related adverse events were injection-site reactions, influenza-like illness, and headache. The incidence of adverse events that led to discontinuation of study treatment was higher in the intervention groups than the placebo group (table 3). Influenza-like illness was the most common adverse event leading to treatment discontinuation in the peginterferon beta-1a groups (table 3). Most adverse events were of mild or moderate severity. Severe adverse events were reported by 53 (11%) of 500 patients in the placebo group, 90 (18%) of 512 in the every 2 weeks group, and 82 (16%) of 500 in the every 4 weeks group.

The incidence of serious adverse events was similar in each group (table 3). Relapse was the most common serious adverse event overall (table 3). Other serious adverse events included pneumonia and urinary tract infection (table 3). We noted no significant trends related to treatment or dose for incidence of infections or serious infections. By 48 weeks, four patients had died (one of sudden death of unknown cause in the placebo group, one of subarachnoid haemorrhage in the placebo group, one of unknown cause in the every 2 weeks group, and one of septic shock in the every 4 weeks group). None of the deaths were deemed related to study treatment.

A greater proportion of patients in the intervention groups had reductions of haematological parameters and increased liver enzymes compared with patients in the placebo group (appendix). However, most were not clinically significant and did not result in discontinuation of treatment. We recorded decreases in white blood cell counts of less than $3{\cdot}0\times10^9$ cells per L in 34 (7%) patients in the every 2 weeks group, 21 (4%) in the every 4 weeks group, and five (1%) receiving placebo; mean counts remained within normal limits for patients treated with peginterferon beta-1a. Most increases in hepatic aminotransferase concentrations were less than three-times the upper limit of normal. We noted increases of alanine aminotransferase greater than five-times the upper limit of normal for five (1%) patients in the placebo group, 12 (2%) patients in the every 2 weeks group, and nine (2%) in the every 4 weeks group. Equivalent proportions for aspartate aminotransferase were three (1%) of 500 versus three (1%) of 512 versus four (1%) of 500. There were no clinically meaningful differences between groups for other clinical or laboratory assessments. The development of neutralising antibodies to interferon beta-1a was low and generally transient, with similar results for placebo group (n=2; <1%), the every 2 weeks group (n=4; <1%), and the every 4 weeks group (n=2; <1%).

Discussion

Our findings show that, for patients with relapsing-remitting multiple sclerosis, subcutaneous peginterferon beta-1a 125 μg administered every 2 weeks significantly reduced annualised relapse rate at 48 weeks, relapses and the risk of disability progression over 48 weeks, the number of T2 lesions at 48 weeks, and several tertiary MRI measures (including smaller and fewer gadolinium-enhancing lesions), compared with placebo. Administration every 2 weeks had greater treatment effects than did administration every 4 weeks in terms of reduction in annualised relapse rate and several MRI measures, although a direct comparison was not done. The safety profile of peginterferon beta-1a was similar between the two regimens and adverse events were consistent with those of established interferon beta treatments for relapsing multiple sclerosis.[17,18,28,29] Injection-site reactions and influenza-like symptoms were the most commonly reported. We also recorded reductions in haematological parameters and increases in liver enzymes, which are known side effects of interferon beta treatments.

Multiple sclerosis has a complex pathogenesis involving inflammation, demyelination, and axonal damage.[19–21] Relapses signify an acute worsening of neurological function that greatly impairs quality of life[22] and are thought to be associated with the development of residual deficits,[23] making their reduction an important therapeutic goal.

Lesions detected on T2-weighted sequences and gadolinium-enhancing lesions represent a range of histopathological multiple sclerosis events and denote the presence of active inflammation. T2-weighted lesions can accumulate over time, making the total number and volume of T2-weighted lesions important indicators of the accumulated burden of focal inflammatory disease. These measures can predict future relapses and clinical disability.[24–26] Our results for atrophy are not surprising, in view of the short duration of treatment and the potential effect of pseudoatrophy (shrinkage of the brain after cessation of inflammation) during the first year of treatment.[27] An assessment of brain atrophy and changes in magnetisation transfer ratio will be done at year 2 of the ADVANCE study.

Panel: Research in context

Systematic review

We searched PubMed on Aug 8, 2013, for "multiple sclerosis" (MESH) AND placebo, limited to randomised controlled clinical trials, with no date or language restrictions. We selected phase 3 studies of first-line injection monotherapies for multiple sclerosis (we excluded secondary and primary progressive multiple sclerosis studies), identifying six placebo-controlled studies: two of interferon beta-1b (subcutaneous),[28,30] two of interferon beta-1a (intramuscular),[17] one of interferon beta-1a (subcutaneous),[18] and one of glatiramer acetate (subcutaneous).[29]

Interpretation

Our clinical and MRI findings are generally consistent with those from studies of other interferon beta treatments. However, because ADVANCE did not include an active comparator, comparisons with existing treatments were not possible. Presently available interferon beta treatments require injections up to several times per week. Data from our study suggest that peginterferon beta-1a has the potential to offer similar efficacy and safety as other interferon beta treatments with the added benefit of reduced frequency of administration.

Our data are consistent with previously reported clinical and MRI effects of available first-line interferon beta treatments (eg, a 29–34% reduction in the rate of clinical relapses, a 12–37% reduction in the risk of disability progression, and a reduction in new T2 lesions in 2-year trials; panel).[17,18,28–30] However, because ADVANCE did not include an active comparator, a formal assessment of the efficacy of peginterferon beta-1a compared with existing treatments is not possible. Also, the designs of studies of multiple sclerosis vary. We assessed the primary endpoint at 48 weeks whereas others were traditional 2-year studies. Other studies[17,18,28–30] tended to be smaller than ours, with the number of patients ranging from 251 to 560. Our study also had a relatively low number of previously treated patients (despite moderate disease activity).

Despite the efficacy of interferon beta treatment, many patients with relapsing-remitting multiple sclerosis remain untreated.[24] Presently available interferon beta treatments require injections once to four times each week and patients with active disease might choose not to be treated because of concerns about the need for frequent injections. Peginterferon beta-1a, with its less frequent dosing regimen, could address some of the factors that lead to avoidance of treatment or poor adherence, while still providing clinical benefits expected from approved interferon beta therapies.[31] Because we present results for only 1 year, the long-term efficacy of peginterferon beta-1a is still not fully understood. However, in other studies of interferon for multiple sclerosis, annualised relapse rate at 1 year was predictive of results at 2 years.[17,18,28] Additional data from the completed 2-year study will provide further insight into the longer-term efficacy and safety of peginterferon beta-1a.

Contributors

PAC coordinated the study and chaired the steering committee and wrote the first draft. SH and AD designed the study, analysed and interpreted data, and wrote the report. SL and YZ designed the study and analysed and interpreted data. BCK, DLA, and LJB were members of the steering committee and interpreted data. AB and JP were members of the steering committee, investigators of the study, enrolled patients, and interpreted results. AS designed the study and collected and interpreted data. The advisory committee and independent data and safety monitoring committee (appendix) collaborated with the sponsor to develop the protocol and monitor the study. Data were collected by investigators and analysed by the sponsor. All authors had access to the data, participated in steering committee meetings, were involved in interpretation or presentation of the data, reviewed and revised the initial draft and subsequent versions of the report, and approved the submitted version.

Declaration of interests

PAC has received grants and research support from Biogen Idec, Abbott, Vertex, Novartis, and Bayer, and consulting fees from Abbott, Vaccinex, and Vertex. BCK has received grants and research support from Bayer Schering, Biogen Idec, Genzyme, Merck Serono, Novartis, Roche, Sanofi-Aventis, Talecris, and Teva Neurosciences, and consulting fees from Bayer Schering, Biogen Idec, Genzyme, Merck Serono, Novartis, Roche, Sanofi-Aventis, Talecris, and Teva Neurosciences. DLA has received grant and research support from Bayer Healthcare and consulting fees from Bayer Healthcare, Biogen Idec, EMD Serono, Genentech, Genzyme, GlaxoSmithKline, NeuroRx Research, Novartis, Roche, Merck Serono, and Teva. LJB has received consulting fees from Biogen Idec, Questcor, and Novartis. AB has received consulting fees from Schering, Merck Serono, Teva, Novartis, Biogen Idec, Nycomed, and Genzyme. JP has received consulting fees from Allergan, Bayer Schering Pharma, Biogen Idec, Genzyme, Merck Serono, Novartis, Sanofi, and Teva; non-profit foundation support from ARSEP; academic research support from PHRC; and unconditional research support from Bayer Schering Pharma, Biogen Idec, BristolMyers-Squibb, GlaxoSmithKline, Merck Serono, Novartis, Peptimmune, Roche, Sanofi, Teva, and Wyeth. SL, YZ, AS, SH and AD are employees of Biogen Idec.

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References

1 Nikfar S, Rahimi R, Abdollahi M. A meta-analysis of the efficacy and tolerability of interferon-beta in multiple sclerosis, overall and by drug and disease type. *Clin Ther* 2010; **32:** 1871–88.

2 Jain A, Jain SK. PEGylation: an approach for drug delivery. A review. *Crit Rev Ther Drug Carrier Syst* 2008; **25:** 403–47.

3 Menzin J, Caon C, Nichols C, White LA, Friedman M, Pill MW. Narrative review of the literature on adherence to disease-modifying therapies among patients with multiple sclerosis. *J Manag Care Pharm* 2013; **19:** S24–40.

4 Patti F. Optimizing the benefit of multiple sclerosis therapy: the importance of treatment adherence. *Patient Prefer Adher* 2010; **4:** 1–9.

5 Beer K, Muller M, Hew-Winzeler AM, et al. The prevalence of injection-site reactions with disease-modifying therapies and their effect on adherence in patients with multiple sclerosis: an observational study. *BMC Neurol* 2011; **11:** 144.

6 Mohr DC, Boudewyn AC, Likosky W, Levine E, Goodkin DE. Injectable medication for the treatment of multiple sclerosis: the influence of self-efficacy expectations and injection anxiety on adherence and ability to self-inject. *Ann Behav Med* 2001; **23:** 125–32.

7 Baker DP, Lin EY, Lin K, et al. N-terminally PEGylated human interferon-beta-1a with improved pharmacokinetic properties and in vivo efficacy in a melanoma angiogenesis model. *Bioconjug Chem* 2006; **17:** 179–88.

8 Bailon P, Won CY. PEG-modified biopharmaceuticals. *Expert Opin Drug Deliv* 2009; **6:** 1–16.

9 Kieseier BC, Calabresi PA. PEGylation of interferon-beta-1a: a promising strategy in multiple sclerosis. *CNS Drugs* 2012; **26:** 205–14.

10 Gaberc-Porekar V, Zore I, Podobnik B, Menart V. Obstacles and pitfalls in the PEGylation of therapeutic proteins. *Curr Opin Drug Discov Devel* 2008; **11:** 242–50.

11 Thomas T, Foster G. Nanomedicines in the treatment of chronic hepatitis C--focus on pegylated interferon alpha-2a. *Int J Nanomedicine* 2007; **2:** 19–24.

12 Hu X, Miller L, Richman S, et al. A novel PEGylated interferon beta-1a for multiple sclerosis: safety, pharmacology, and biology. *J Clin Pharmacol* 2012; **52:** 798–808.

13 Polman CH, Reingold SC, Edan G, et al. Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald Criteria". *Ann Neurol* 2005; **58:** 840–46.

14 Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology* 1983; **33:** 1444–52.

15 International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH harmonized tripartite guideline — guideline for good clinical practice: E6(R1). www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6_R1/Step4/E6_R1__Guideline pdf (accessed Sept 10, 2013).

16 Declaration of Helsinki — ethical principles for medical research involving human subjects. http://www.wma.net/en/30publications/10policies/b3/ (accessed Sept 10, 2013).

17 Jacobs LD, Cookfair DL, Rudick RA, et al. Intramuscular interferon beta-1a for disease progression in relapsing multiple sclerosis. The Multiple Sclerosis Collaborative Research Group (MSCRG). *Ann Neurol* 1996; **39:** 285–94.

18 Ebers GC, PRISMS (Prevention of Relapses and Disability by Interferon beta-1a Subcutaneously in Multiple Sclerosis) Study Group. Randomised double-blind placebo-controlled study of interferon beta-1a in relapsing/remitting multiple sclerosis. *Lancet* 1998; **352:** 1498–504.

19 Silber E, Sharief MK. Axonal degeneration in the pathogenesis of multiple sclerosis. *J Neurol Sci* 1999; **170:** 11–18.

20 Frohman EM, Racke MK, Raine CS. Multiple sclerosis-the plaque and its pathogenesis. *N Engl J Med* 2006; **354:** 942–55.

21 Bjartmar C, Trapp BD. Axonal and neuronal degeneration in multiple sclerosis: mechanisms and functional consequences. *Curr Opin Neurol* 2001; **14:** 271–78.

22 Putzki N, Fischer J, Gottwald K, et al. Quality of life in 1000 patients with early relapsing-remitting multiple sclerosis. *Eur J Neurol* 2009; **16:** 713–20.

23 Lublin FD, Baier M, Cutter G. Effect of relapses on development of residual deficit in multiple sclerosis. *Neurology* 2003; **61:** 1528–32.

24 Rudick RA, Lee JC, Simon J, Ransohoff RM, Fisher E. Defining interferon beta response status in multiple sclerosis patients. *Ann Neurol* 2004; **56:** 548–55.

25 Prosperini L, Gallo V, Petsas N, Borriello G, Pozzilli C. One-year MRI scan predicts clinical response to interferon beta in multiple sclerosis. *Eur J Neurol* 2009; **16:** 1202–09.

26 Fisniku LK, Brex PA, Altmann DR, et al. Disability and T2 MRI lesions: a 20-year follow-up of patients with relapse onset of multiple sclerosis. *Brain* 2008; **131:** 808–17.

27 Vidal-Jordana A, Sastre-Garriga J, Perez-Miralles F, et al. Early brain pseudoatrophy while on natalizumab therapy is due to white matter volume changes. *Mult Scler* 2013; **19:** 1175–81.

28 IFNB MS Study Group. Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. I. Clinical results of a multicenter, randomized, double-blind, placebo-controlled trial. The IFNB Multiple Sclerosis Study Group. *Neurology* 1993; **43:** 655–61.

29 Johnson KP, Brooks BR, Cohen JA, et al. Copolymer 1 reduces relapse rate and improves disability in relapsing-remitting multiple sclerosis: results of a phase III multicenter, double-blind placebo-controlled trial. The Copolymer 1 Multiple Sclerosis Study Group. *Neurology* 1995; **45:** 1268–76.

30 Paty DW, Li DK. Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. II. MRI analysis results of a multicenter, randomized, double-blind, placebo-controlled trial. UBC MS/MRI Study Group and the IFNB Multiple Sclerosis Study Group. *Neurology* 1993; **43:** 662–67.

31 Lugaresi A. Addressing the need for increased adherence to multiple sclerosis therapy: can delivery technology enhance patient motivation? *Expert Opin Drug Deliv* 2009; **6:** 995–1002.