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Peginterferon beta-1a may improve recovery following relapses in the ADVANCE relapsing-remitting multiple sclerosis study

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INTRODUCTION

- Peginterferon beta-1a, a pegylated form of interferon beta-1a, is a new investigational drug in clinical development as a subcutaneous (SC) treatment for relapsing remitting multiple sclerosis (RRMS) that requires less frequent dosing than currently-available injectable therapies.
  - Covalently attaching one or more polyethylene glycol (PEG) molecules, or pegylation, is a process used to increase the half-life and reduce the immunogenicity of drugs by increasing molecular size, shielding the molecule, and improving chemical stability.[1]
  - Phase 1 data have demonstrated that peginterferon beta-1a has a longer half-life and increased exposure (area under the curve and peak concentration) compared with non-pegylated interferon beta-1a.[2]
- In the phase 3 ADVANCE study, SC peginterferon beta-1a (125 µg) administered every 2 weeks (Q2W) or every 4 weeks (Q4W) significantly reduced the risk of 12-week confirmed disability progression (38% reduction in both dosing arms) and annualized relapse rate (ARR; reduction of 36% and 28%, respectively) after 1 year compared to placebo.
- Data from the placebo arms of other studies of patients with RRMS show
  - Subsequent confirmed disability progression is associated with approximately 20-30% of reported relapses.
  - Approximately half of patients with confirmed disability progression do not experience associated relapses.
- Thus, treatment effects other than a reduction in ARR may contribute to the reduced risk of disability progression with peginterferon beta-1a in the ADVANCE study.

OBJECTIVE

- To determine whether peginterferon beta-1a improves recovery following relapses versus placebo in patients with RRMS.
- To examine the relationship between change in individual functional systems scores (FSS) during a relapse and following confirmed disability progression

METHODS

Study design

- ADVANCE is a 2-year, multicenter, randomized, double-blind, parallel-group, Phase 3 study with a 1-year placebo-controlled period (NCT00906399).
- During Year 1 of the study patients were randomized (1:1:1) to self-administered SC injections of placebo or peginterferon beta-1a 125 µg Q2W or Q4W.
  - All subjects were to self-administer an injection every 2 weeks; subjects randomized to Q4W self-administered alternating injections of peginterferon beta-1a 125 µg and placebo to maintain blinding.

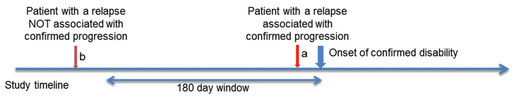
Patients

- Key inclusion criteria:
  - Men and women aged 18–65 years
  - Confirmed diagnosis of RRMS (McDonald criteria 1–4)
  - Expanded Disability Status Scale (EDSS) score ≤5.0
  - ≥2 relapses within the last 3 years, including ≥1 relapse in the 12 months prior to randomization.
- Key exclusion criteria
  - Primary progressive, secondary progressive, or progressive relapsing MS
  - Prior interferon treatment exceeding 4 weeks or within <6 months prior to baseline.

Study endpoints and assessments

- The current post-hoc analyses were conducted using data from ADVANCE to assess the impact of peginterferon beta-1a on recovery from relapses as well as the relationship between change in individual FSS during a relapse and confirmed disability progression.
- Relapses were defined as new or recurrent neurologic symptoms not associated with fever or infection, lasting at least 24 hours, and accompanied by new objective neurological findings upon examination by the examining neurologist.
- Disability progression due to incomplete recovery following relapse was defined as onset of 12-week confirmed disability progression (increase in EDSS score of ≥1.0 from a baseline score of ≥1.0 or ≥1.5 from a baseline score of 0.0) within 180 days of a relapse that occurred prior to the onset of disability progression (Figure 1).
  - Relapses occurring after onset of confirmed disability progression were excluded (all other relapses were included).
- Simultaneous worsening of FSS was defined as a ≥1- and ≥2-point change in FSS caused by a relapse, with the same FSS worsening contributing to the confirmed disability progression based on the increase of EDSS scores.

Figure 1. Schema for percentage of relapses leading to confirmed disability progression



The percentage of patients with a relapse that leads to confirmed disability progression = a/(a+b)%

RESULTS

Patients

- Overall, 1512 patients were randomized and received placebo (n=500), peginterferon beta-1a 125 µg Q2W (n=512), or peginterferon beta-1a 125 µg Q4W (n=500).
- Patient demographics and baseline disease characteristics were generally similar between treatment groups (Table 1).

Recovery following relapses

- Of 112 patients who had disability progression, 55 experienced confirmed disability progression associated with relapses and 57 patients experienced confirmed disability progression not associated with relapses (numerically lower proportion of patients on peginterferon beta-1a versus placebo).
- Degree of relapse severity was not different between groups.
  - Proportion of relapses with an EDSS increase >1 during relapse was approximately 60% across all arms.

Table 1: Baseline demographic and clinical characteristics

Characteristic	Placebo (n=500)	Peginterferon beta-1a 125 µg Q4W (n=500)	Peginterferon beta-1a 125 µg Q2W (n=512)
Age, y	36.3 (9.74)	36.4 (9.87)	36.9 (9.79)
Gender, % female	72	70	71
Race, % Caucasian	82	82	81
Geographic regions, %			
India	11	11	11
North America	3	3	4
Western Europe	8	8	8
Eastern Europe	71	71	69
Rest of World	7	7	8
Duration since first MS symptoms, y	6.3 (6.28)	6.5 (6.07)	6.9 (6.61)
Relapses within the previous 12 months	1.6 (0.67)	1.5 (0.62)	1.6 (0.67)
EDSS score	2.44 (1.18)	2.48 (1.24)	2.47 (1.26)
EDSS <4, %	86	83	83
EDSS ≥4, %	14	17	17
Number of T2 lesions	50.6 (35.7)	51.4 (36.0)	48.7 (36.8)
Number of Gd+ lesions	1.6 (3.81)	1.8 (5.38)	1.2 (3.44)
Prior medication, n (%)			
Glatiramer acetate	24 (5)	28 (6)	27 (5)
IFN beta-1b	6 (1)	5 (1)	8 (2)
IFN beta-1a	5 (1)	6 (1)	4 (<1)

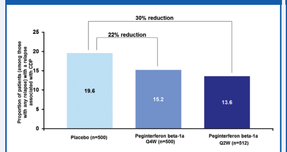
Data presented as mean (standard deviation) unless otherwise stated. EDSS=Expanded Disability Status Scale; Gd+=gadolinium enhancing; MS=multiple sclerosis; Q2W=every 2 weeks; Q4W=every 4 weeks

- Baseline EDSS scores were similar for patients who experienced confirmed disability progression with and without an associated relapse (mean of 2.3 for both groups).
- Relapses were observed in 88 (17%) patients in the Q2W group, 105 (21%) patients in the Q4W group, and 138 (28%) patients in the placebo group.
- Among patients who experienced relapses, 12 (13.6%) patients in the Q2W group, 16 (15.2%) patients in the Q4W group, and 27 (19.6%) patients in the placebo group experienced confirmed disability progression associated with a relapse.
  - Thus, peginterferon beta-1a Q2W and Q4W were associated with relative reductions in risk of progression following any relapse of 30% and 22% compared with placebo, respectively (Figure 2a).
- Peginterferon beta-1a Q2W and Q4W reduced the proportion of patients experiencing confirmed disability progression due to incomplete recovery following a relapse versus placebo by 56% (p=0.012) and 41% (p=0.086), respectively (Figure 2b).
- 85% of these patients had their most recent relapses within 14 days of onset of disability progression.

Relationship between overall FSS and confirmed disability progression

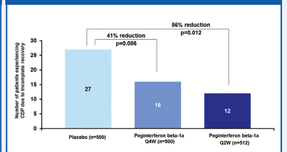
- Among patients who had confirmed disability progression due to incomplete recovery from relapses, approximately 90% and 39% had ≥1 FSS that had simultaneous worsening of ≥1.0 and ≥2.0 along with disability progression, respectively.
  - In 87% (41/47) of the patients who had ≥1 FSS with simultaneous worsening of ≥1.0 point along with disability progression, the associated relapse occurred within 14 days before the onset of disability progression (Table 2).
  - In 40% (19/47) of the patients who had ≥1 FSS with simultaneous worsening of ≥2.0 point along with disability progression, the associated relapse occurred within 14 days before the onset of disability progression (Table 2).
  - Simultaneous FSS worsening of ≥1 point or ≥2 points along with disability progression occurred most frequently in the pyramidal domain (Table 3).

Figure 2a: Proportion of patients with a relapse associated with confirmed disability progression



CDP = confirmed disability progression

Figure 2b: Number of patients experiencing confirmed disability progression due to incomplete recovery



CDP = confirmed disability progression

Table 2: Distribution of number of simultaneously worsening FSS among patients with confirmed EDSS progression (n=47)

	Number of worsening FSS						Any worsening FSS
	0	1	2	3	4	5	
FSS worsening by ≥1.0, n (%)	6 (12.8)	12 (25.5)	15 (31.9)	8 (17.0)	4 (8.5)	2 (4.3)	41 (87.2)
FSS worsening by ≥2.0, n (%)	28 (59.6)	16 (34.0)	3 (6.4)	0	0	0	19 (40.4)

EDSS=Expanded Disability Status Scale; FSS=Functional System Score.

Seven patients who had confirmed EDSS progression were excluded due to >14 days between the most recent relapse and the starting date of EDSS progression; 1 patient who had confirmed EDSS progression was excluded due to missing FSS information from ADVANCE Year 1 dataset.

Table 3: Patients with 12-week EDSS progression (n=47) with or without simultaneous worsening on individual FSS

	FSS						
FSS worsening ≥1.0	**Visual**	**Sensory**	**Brainstem**	**Bowel & Bladder**	**Pyramidal**	**Cerebral**	**Cerebellar**
EDSS progression with simultaneous FSS worsening, n (%)	9 (19.1)	18 (38.3)	9 (19.1)	7 (14.9)	26 (55.3)	7 (14.9)	16 (34.0)
FSS worsening ≥2.0							
EDSS progression with simultaneous FSS worsening, n (%)	2 (4.3)	6 (12.8)	1 (2.1)	1 (2.1)	8 (17.0)	0	8 (4.5)

EDSS=Expanded Disability Status Scale; FSS=Functional System Score.

Seven patients who had confirmed EDSS progression were excluded due to >14 days between the most recent relapse and the starting date of EDSS progression; 1 patient who had confirmed EDSS progression was excluded due to missing FSS information from ADVANCE Year 1 dataset.

CONCLUSIONS

- Approximately half of patients with confirmed disability progression in Year 1 of ADVANCE had an associated relapse.
- Approximately half of patients with confirmed disability progression in Year 1 did not have an associated relapse, adding further evidence that disability progression in RRMS patients is only partly explained by accumulation of disability due to relapses.
- Peginterferon beta-1a Q2W significantly reduced the percentage of patients who experienced confirmed disability progression due to incomplete recovery from a relapse by 56% compared to placebo.
- The effect of peginterferon beta-1a on risk of disability progression associated with relapses may be attributable to the combination of an overall reduction in risk of relapses and improvement in recovery from relapses.
- Simultaneous worsening of pyramidal FSS accounted for the majority of confirmed disability progression caused by relapses.
- These results, along with efficacy for clinical endpoints,[3] support peginterferon beta-1a as a potential effective treatment option for patients with RRMS, with the benefit of less frequent SC administration.

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DISCLOSURES

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