Relapse outcomes in patients with multiple sclerosis treated with fingolimod: Subgroup analyses of three phase 3 fingolimod trials

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CONCLUSIONS

- **Across clinical trials, treatment once daily with fingolimod 0.5 mg consistently improved ARRs compared with placebo in patients with RRMS. This effect was observed irrespective of baseline demographic status, disease activity or disease severity**
- **Treatment with fingolimod was associated with significantly lower ARRs in all subgroups compared with IFNβ-1a IM, except in men and among patients older than 40 years. In the latter group, this lack of effect may be related to decreases in inflammatory disease activity**
- **The greatest improvements in ARR with fingolimod compared with placebo and IFNβ-1a were observed in younger patients, among individuals with active disease (based on magnetic resonance imaging and relapse parameters) at baseline**
- **In terms of relapse outcomes, these findings suggest that most benefit will be derived by patients with active disease who start fingolimod early in the disease course, but the findings also suggest that fingolimod treatment will benefit patients later in the disease course when they have already accrued disability**

INTRODUCTION

- Evidence from long-term studies suggests a correlation between relapse frequency early in the course of multiple sclerosis (MS) and long-term disability[1,2]
- Phase 3 clinical trials have shown that fingolimod significantly reduces annualized relapse rates (ARRs) compared with placebo (FREEDOMS and FREEDOMS II) and interferon (IFN) β-1a IM (TRANSFORMS) in patients with relapsing–remitting MS (RRMS)[3–5]
  - Analysis of the effects of fingolimod in predefined patient subgroups (defined according to age, sex, treatment history and baseline disease characteristics) showed that fingolimod reduced ARR compared with placebo and IFNβ-1a IM in most subgroups[6–8]
- This *post hoc* subgroup analysis of data pooled from FREEDOMS, FREEDOMS II and TRANSFORMS compared the treatment effect of fingolimod across a range of patient subgroups in a larger study population than is available in the individual studies

OBJECTIVE

- To evaluate the effects of fingolimod treatment on ARRs in subgroups of patients with RRMS

METHODS

Study designs and participants

- Patients included in the pooled data set were those randomized in FREEDOMS and FREEDOMS II to receive oral fingolimod 0.5 mg or placebo once daily for 2 years,[3,4] or those randomized in TRANSFORMS to receive oral fingolimod 0.5 mg once daily or IFNβ-1a IM 30 µg once weekly for 1 year[5]
- All three studies enrolled patients aged 18–55 years with RRMS (diagnosed in accordance with the 2005 revised McDonald criteria[9]) who had one or more confirmed relapses in the previous year or two or more in the previous 2 years, and had a score of 0–5.5 on the Expanded Disability Status Scale (EDSS)

Analyses

- Patient subgroups were predefined in the TRANSFORMS, FREEDOMS and FREEDOMS II study protocols[3–5] according to:
  - Sex
  - Age (≤40 years or >40 years)
  - Baseline number of gadolinium (Gd)-enhancing lesions (0 or >1)
  - Number of relapses in the 2 years before study entry (≤2 or ≥3)
  - Baseline disability (EDSS score 0–2.5 or ≥3)
- Modifications were made to some subgroup definitions after database lock to harmonize all three studies, to ensure adequate patient representation and to enable clinically meaningful comparisons
  - Owing to limited patient numbers in some of the predefined subgroups (0, 1, 2–3, 4–5 and >5 relapses), these were combined into two new groups (≤2 and ≥3 relapses)
  - The predefined EDSS score subgroups (≤3.5 and >3.5) were altered to define a group of less severely affected patients (0–2.5 and ≥3.0)
  - The age cut-off was raised from 37 years to 40 years among patients in FREEDOMS and FREEDOMS II for consistency with the predefined cut-off of 40 years in TRANSFORMS
  - For the Gd-enhancing lesion subgroups, the three predefined subgroups (0, 1–2 and ≥3 lesions) were reduced to two (0 or ≥1 lesion) in order to group patients with or without inflammation at baseline

Table 1. Patient disposition and study drug exposure (randomized population)

	Placebo (n=773)	IFNβ-1a IM (n=435)	Fingolimod 0.5 mg (n=1214)
Completed study, n (%)	587 (75.9)	386 (88.7)	1039 (85.6)
On study drug	535 (69.2)	380 (87.4)	972 (80.1)
Off study drug	52 (6.7)	6 (1.4)	67 (5.5)
Discontinued from the study, n (%)	186 (24.1)	49 (11.3)	175 (14.4)
Abnormal laboratory value	3 (0.4)	1 (0.2)	29 (2.4)
Abnormal test procedure	2 (0.3)	3 (0.7)	6 (0.5)
Administrative problem	5 (0.6)	7 (1.6)	5 (0.4)
Adverse event	34 (4.4)	9 (2.1)	44 (3.6)
Death	2 (0.3)	0	0
Lost to follow-up	28 (3.6)	4 (0.9)	19 (1.6)
Protocol violation	6 (0.8)	2 (0.5)	7 (0.6)
Consent withdrawn	63 (8.2)	16 (3.7)	50 (4.1)
Condition no longer required study drug	1 (0.1)	0	0
Unsatisfactory therapeutic effect	42 (5.4)	7 (1.6)	15 (1.2)
Drug exposure, days[a]			
Mean (SD)	596 (223)	337 (81)	517 (221)
Median (interquartile range)	719 (497–731)	361 (351–370)	576 (363–723)
Drug exposure, patient-years[b]	1261	398	1716

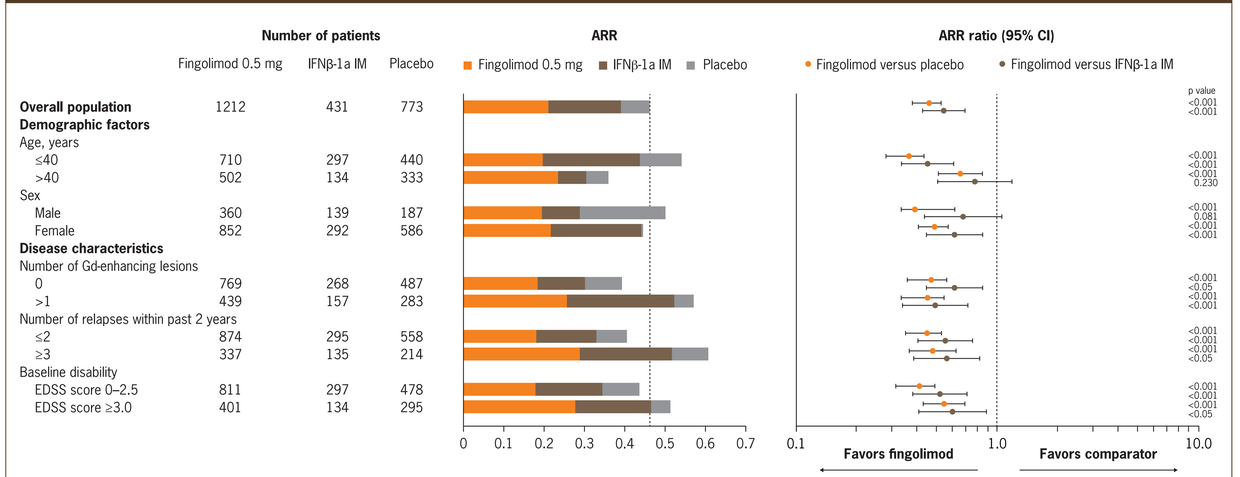
[a]Number of days on study drug
[b]Patient-years calculated as the sum of the number of days on study drug for all patients in the group divided by 365.25 days

Table 2. Baseline demographics, disease characteristics and patient characteristics (randomized population)

	Placebo (n=773)	IFNβ-1a IM (n=435)	Fingolimod 0.5 mg (n=1214)
Baseline demographic factors			
Age, years	38.6 (8.6)	36.0 (8.3)	37.8 (8.9)
Sex, female, n (%)	586 (75.8)	295 (67.8)	853 (70.3)
Baseline disease characteristics			
Time since diagnosis, years	5.7 (5.5)	4.9 (5.4)	5.2 (5.3)
Number of relapses within past year	1.5 (0.8)	1.5 (0.8)	1.5 (1.0)
Number of relapses within past 2 years	2.2 (1.3)	2.3 (1.2)	2.2 (1.7)
EDSS score	2.5 (1.3)	2.2 (1.3)	2.3 (1.3)
Number of Gd-enhancing lesions at baseline	1.2 (3.1)	1.1 (2.8)	1.3 (4.1)
Treatment history			
Treatment-naïve, n (%)	345 (44.6)	190 (43.7)	531 (43.7)
Previous MS treatment, n (%)			
Glatiramer acetate	190 (24.6)	67 (15.4)	228 (18.8)
IFNβ-1a SC	143 (18.5)	72 (16.6)	236 (19.4)
IFNβ-1a IM	185 (23.9)	118 (27.1)	313 (25.8)
IFNβ-1b SC	120 (15.5)	69 (15.9)	173 (14.3)
Natalizumab	25 (3.2)	1 (0.2)	25 (2.1)
Other	79 (10.2)	16 (3.7)	87 (7.2)

All values are presented as mean (SD) unless otherwise stated

Figure 1. ARRs in patient subgroups defined by baseline demographics and disease characteristics (intention-to-treat population)



ARR values for different treatment groups are superimposed in the histogram

- Subgroup analyses were performed on the intention-to-treat populations pooled from all three trials
- ARRs were obtained using a negative binomial regression model with study, treatment, subgroup and treatment-by-subgroup as explanatory variables
- 95% CIs are presented and p values indicate the statistical significance of treatment differences; p values were hypothesis generated only and no adjustments were made for multiple comparisons

RESULTS

Study population

- In total, 2416 patients were included in the pooled analysis: 1212 in the fingolimod 0.5 mg group, 773 in the placebo group and 431 in the IFNβ-1a IM group. **Table 1** presents patient disposition and study drug exposure
- Baseline demographics and disease characteristics were similar across treatment groups (**Table 2**). Overall, more than two-thirds of patients (71.4%) were women and approximately 59% were younger than 40 years

Annualized relapse rates

- Compared with placebo, fingolimod 0.5 mg was associated with significantly lower ARRs across all patient subgroups, with relative reductions of up to 64% (**Figure 1**)
- The greatest relative reduction in ARR seen with fingolimod 0.5 mg versus placebo occurred in patients aged ≤40 years (64%; p<0.001); the smallest reduction was seen in patients aged >40 years (35%; p<0.001)
- Compared with IFNβ-1a IM, reductions in ARR of up to 55% were observed with fingolimod 0.5 mg, with the greatest effects observed in women (51%; p<0.001) and younger patients (55%; p<0.001) (**Figure 1**)
- Fingolimod did not significantly reduce ARRs in patients aged >40 years (23%; p=0.230) or in men (33%; p=0.081) versus IFNβ-1a IM
- ARRs were lower with fingolimod in patients with active disease (>1 Gd-enhancing lesions, ≥3.0 relapses in the previous 2 years) at baseline, with relative reductions in ARR of 46–55% compared with placebo, and 40–51% compared with IFNβ-1a IM

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Disclosures

Tobias Derfuss serves on scientific advisory boards for Novartis Pharmaceuticals, Merck Serono, Biogen Idec, Genzyme, GeNeuro, Mitsubishi Pharma, Teva Pharmaceuticals and Bayer Schering Pharma; has received funding for travel and/or speaker honoraria from Biogen Idec, Genzyme, Novartis, Merck Serono and Bayer Schering Pharma; and receives research support from Biogen Idec, Novartis Pharmaceuticals, the European Union, the Swiss National Foundation and the Swiss MS Society. **Daniel Ontaneda** has received research support from the US National Institutes of Health and the US National Multiple Sclerosis Society; and has received consulting or speaker fees from Acorda Therapeutics, Biogen Idec, Genzyme, Mallinckrodt Pharmaceuticals and Teva Pharmaceuticals. **Jacqueline Nicholas** has received research support from the US National Multiple Sclerosis Society, Biogen Idec, the US National Institutes of Health, Actelion Pharmaceuticals, Mallinckrodt Pharmaceuticals, Roche and Novartis; and has received consulting fees from Biogen Idec, Genzyme, Novartis and Vindico Medical Education. **Xiangyi Meng** and **Kathleen Hawker** are employees and stock holders of Novartis Pharmaceuticals Corporation.

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