Relapse outcomes in patients with multiple sclerosis according to disease duration

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CONCLUSIONS

- **Across clinical trials, treatment with fingolimod 0.5 mg consistently reduced ARRs compared with placebo and IFNβ-1a IM in patients with RRMS**
- **Fingolimod 0.5 mg demonstrated consistent efficacy benefits over placebo and IFNβ-1a IM irrespective of time since onset of first symptom or duration of previous treatment, with the exception of patients in the IFNβ-1a IM subgroup previously treated for 1 year or less**
- **The greatest improvements in ARR with fingolimod 0.5 mg compared with placebo and IFNβ-1a IM were seen in patients with disease duration of less than 3 years**
- **These findings provide insight into the long-term outcomes of patients with relapsing forms of MS who are receiving DMTs, and suggest that starting fingolimod treatment early is likely to be particularly beneficial**

INTRODUCTION

- Higher annualized relapse rates (ARRs) early in the course of MS have been shown to correlate with poorer outcomes, including long-term disability[1,2]
- In phase 3 clinical trials, fingolimod significantly reduced ARRs in patients with relapsing–remitting multiple sclerosis (RRMS) compared with placebo (FREEDOMS and FREEDOMS II) and with interferon (IFN) β-1a IM (TRANSFORMS)[3–5]
- Pooling data from FREEDOMS, FREEDOMS II and TRANSFORMS provided a larger study population than was available from the individual studies for *post hoc* analyses of the efficacy of fingolimod in subgroups with varying duration of either disease or previous exposure to DMTs
  - Analyses of patient subgroups (predefined by age, sex, treatment history and baseline disease characteristics) are provided in poster DX18
  - Subgroup analyses based on treatment history are provided in poster DX60

OBJECTIVES

- To report the effects of oral fingolimod treatment on ARRs in patients with RRMS according to duration of disease and duration of previous treatment with DMTs

METHODS

Study designs and participants

- Patients included in the pooled analyses had been randomized to receive oral fingolimod 0.5 mg or placebo once daily for 2 years (in FREEDOMS and FREEDOMS II)[6,7] or to receive oral fingolimod 0.5 mg once daily or IFNβ-1a IM 30 µg once weekly for 1 year (in TRANSFORMS)[8]
- In the three studies, patients (aged 18–55 years) had been diagnosed with RRMS in accordance with the 2005 revised McDonald criteria[9], 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 defined according to:
  - Time since onset of first MS symptom (≥3 versus <3 years before randomization)
  - Number of years of previous treatment received (0, ≤1, >1–3, and >3 years before randomization)
- 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 analyses: 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**)

Annualized relapse rates

- In patients with less than 3 years since onset of first symptom, fingolimod 0.5 mg significantly reduced ARR by 69% (p<0.001) versus placebo and by 50% (p=0.002) versus IFNβ-1a IM (**Figure 1**)
- In patients with 3 or more years since onset of first symptom, reductions in ARR with fingolimod 0.5 mg were 49% (p<0.001) versus placebo and 46% (p<0.001) versus IFNβ-1a IM
- Fingolimod 0.5 mg significantly reduced ARR in patients with 0, >1–3 and >3 years of treatment before randomization compared with placebo and IFNβ-1a IM, but not in patients in the IFNβ-1a IM group previously treated for 1 year or less (relative reduction: 35%, [p=0.108])

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

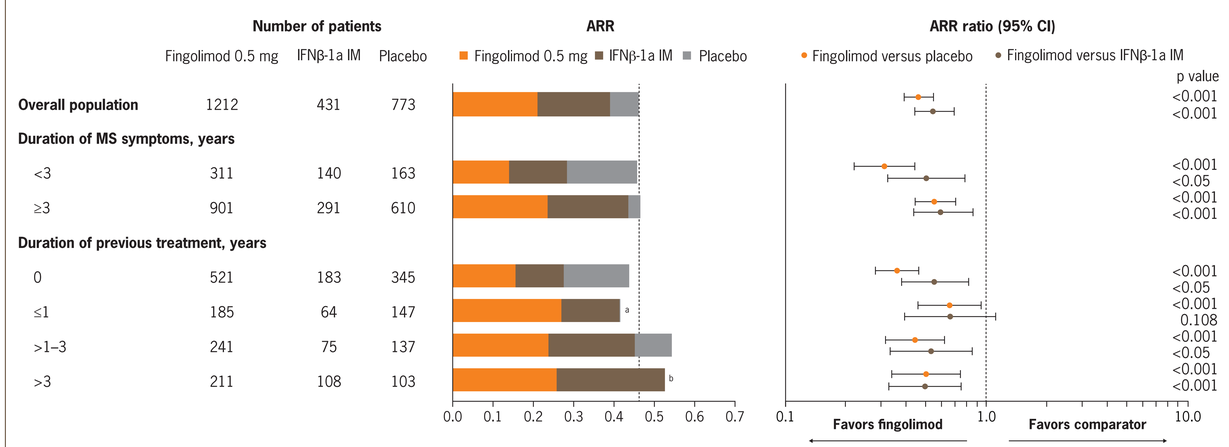
[a]Number of days on study drug
[b]Patient-years calculated as the sum of the number of days on study drug for all patients in the group divided by 365.25 days

Table 2. Baseline demographics 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,[a] 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
[a]Treatment-naïve patients were defined as those who had not previously received any drugs for the treatment of MS, according to MS history case report forms

Figure 1. ARRs in patient subgroups defined by duration of disease and duration of previous treatment (intention-to-treat population)



ARRs for different treatment groups in the histogram are superimposed
[a]ARRs were 0.414 for the IFNβ-1a IM group and 0.416 for the placebo group. Only the IFNβ-1a IM ARR is displayed
[b]ARR was 0.547 for the IFNβ1a IM group and 0.527 for the placebo group. Only the IFNβ-1a IM ARR is displayed

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