Effect of oral fingolimod treatment on brain volume loss in patients with relapsing–remitting multiple sclerosis estimated using Bayesian methodology

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CONCLUSIONS

- **In the phase 3, placebo-controlled FREEDOMS II trial of fingolimod in patients with RRMS, estimates of PBVC obtained using Bayesian power prior methodology were consistent with previously reported results in phase 3 fingolimod studies**
- **Application of Bayesian methodology may improve estimates of treatment effects and their interpretability**

BACKGROUND

- Brain volume (BV) loss begins in the earliest stages of multiple sclerosis (MS) and continues throughout the disease course[1]
- In the 2-year, randomized, double-blind, phase 3 trials FREEDOMS and FREEDOMS II, fingolimod 0.5 mg/day was shown to have greater efficacy than placebo in reducing BV loss, as assessed by SIENA (structural image evaluation, using normalization, of atrophy) in patients with relapsing–remitting MS (RRMS)[2,3]
- Percentage BV change (PBVC), a BV parameter commonly reported in clinical trials of MS therapies, was calculated over the course of the primary studies[2,3]
- More sensitive estimates of the effect of fingolimod on PBVC may be obtained with Bayesian methodology, using prior evidence (FREEDOMS) to analyze FREEDOMS II data with probabilistic interpretation[4,5]

OBJECTIVE

- To estimate PBVC in patients with RRMS treated with fingolimod in FREEDOMS II using Bayesian power prior methodology

METHODS

Study designs and participants

- FREEDOMS and FREEDOMS II included patients aged 18–55 years with a diagnosis of RRMS defined using the 2005 revised McDonald criteria,[6] who experienced at least one confirmed relapse in the previous year or at least two in the previous 2 years and who had an Expanded Disability Status Scale (EDSS) score of 0–5.5 at enrollment
- Details of study designs and patient selection criteria have been previously published[2,3]

Analyses

- SIENA is a fully automated software package for estimating temporal BV change as assessed by magnetic resonance imaging.[7,8] SIENA-generated PBVCs were calculated from baseline to months 6, 12 and 24 in FREEDOMS and FREEDOMS II, and assessed by rank analysis of covariance (ANCOVA) with adjustment for study group, country and normalized BV at baseline
- Bayesian methodology was applied using historical data from FREEDOMS as the informative prior and appropriate prior distribution of model parameters, and the mean PBVC treatment difference between fingolimod 0.5 mg and placebo in FREEDOMS II was estimated
- The methodology inferred the posterior probability as a consequence of two antecedents: a prior probability and a likelihood function derived from a statistical model of the observed data

RESULTS

Study population

- Baseline demographics and disease characteristics were generally similar between studies and treatment groups, and were representative of an RRMS population with active disease[2,3] (**Table 1**)

Table 1. Patient baseline characteristics in FREEDOMS and FREEDOMS II

Characteristic	FREEDOMS (N=1272)		FREEDOMS II (N=1083)	
	Fingolimod 0.5 mg (n=425)	Placebo (n=418)	Fingolimod 0.5 mg (n=358)	Placebo (n=355)
Age, years	36.6 (8.77)	37.2 (8.60)	40.6 (8.39)	40.1 (8.42)
Women, n (%)	296 (69.6)	298 (71.3)	275 (76.8)	288 (81.1)
Time since onset of first symptom, years	8.0 (6.60)	8.1 (6.35)	10.4 (8.01)	10.6 (7.85)
Number of relapses in the previous year	1.5 (0.76)	1.4 (0.73)	1.4 (0.86)	1.5 (0.93)
Number of relapses in the previous 2 years	2.1 (1.13)	2.2 (1.19)	2.2 (1.38)	2.2 (1.49)
EDSS score	2.3 (1.29)	2.5 (1.29)	2.4 (1.33)	2.4 (1.31)
Patients free from Gd+ lesions, n (%)[a]	263 (62.0)	262 (63.0)	218 (61.1)	225 (63.6)
Number of Gd+ lesions	1.6 (5.57)	1.3 (2.93)	1.3 (3.37)	1.2 (3.23)
T2 lesion volume, mm³	6128 (7623)	6162 (7085)	5484 (8000)	5553 (7841)
Normalized BV, mL	1521 (83.16)	1512 (85.49)	1522 (82.49)	1526 (85.19)

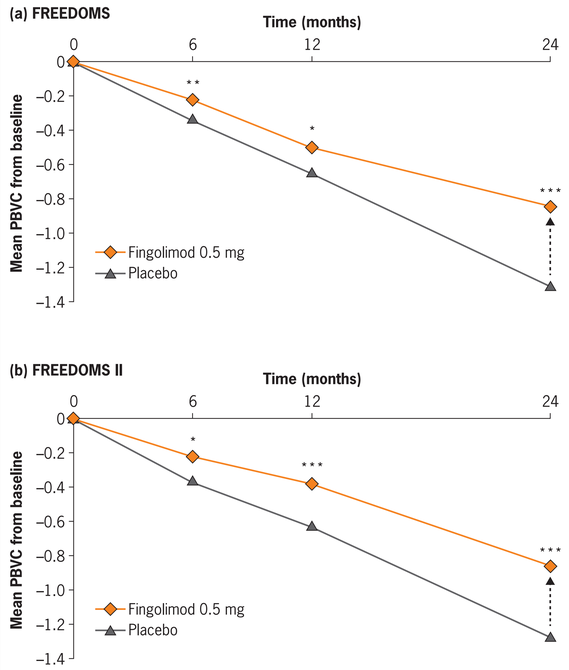
Data are mean (SD) unless stated otherwise
[a]FREEDOMS: fingolimod, n=424; placebo, n=416. FREEDOMS II: fingolimod, n=357; placebo, n=354
Gd+, gadolinium-enhancing

- There were proportionally more women in FREEDOMS II than in FREEDOMS and, on average, patients in FREEDOMS II were older at baseline than those in FREEDOMS[2,3]
- Patients in FREEDOMS II had a lower burden of disease (according to lesion number and volume) than those in FREEDOMS, even though a longer period had elapsed since they experienced their first MS symptom[2,3]

PBVC in FREEDOMS and FREEDOMS II

- The original analysis of FREEDOMS data demonstrated a significant positive treatment difference (p<0.001) in PBVC at 24 months between patients treated with fingolimod 0.5 mg (mean [SD] PBVC, −0.84% [1.31]) and those who received placebo (mean [SD] PBVC, −1.31% [1.50])[2] (**Figure 1a**)
- The original analysis of FREEDOMS II data also demonstrated a significant positive treatment difference (p<0.001) in PBVC at 24 months between patients treated with fingolimod 0.5 mg (mean [SD] PBVC, −0.86% [1.22]) and those who received placebo (mean [SD] PBVC, −1.28% [1.50])[3] (**Figure 1b**)

Figure 1. Effect of fingolimod therapy on BV loss in patients with RRMS in (a) FREEDOMS and (b) FREEDOMS II phase 3 trials[2,3]

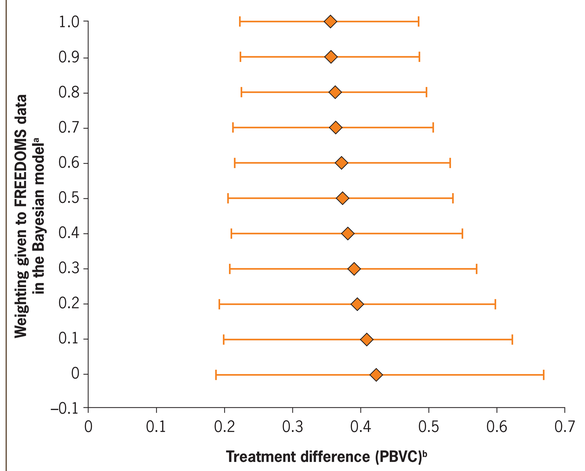


*p<0.05; **p<0.01; ***p<0.001
PBVC was assessed prospectively for all patients receiving fingolimod 0.5 mg or placebo
Dashed arrows indicate the positive treatment difference in PBVC at 24 months for patients treated with fingolimod relative to those receiving placebo
Differences in PBVC between patients receiving fingolimod and patients receiving placebo were assessed by two-sided ANCOVA with adjustment for study group, country and normalized BV at baseline

Analysis of PBVC using Bayesian methodology

- The Bayesian analysis of FREEDOMS II data with non-informative prior (zero weight given to FREEDOMS trial data) estimated a positive treatment difference in PBVC for patients treated with fingolimod relative to those who received placebo (mean [95% Bayesian credible interval (BCI)], 0.42% [0.19–0.67]) (**Figure 2**)
- Applying equal (1:1) weight to the likelihoods of prior (FREEDOMS) and current (FREEDOMS II) study data estimated a positive treatment difference in PBVC for fingolimod-treated patients relative to those receiving placebo (mean [95% BCI], 0.35% [0.22–0.48]) (**Figure 2**)
- Power priors weighted from 0.1 to 0.9 in increments of 0.1 were also explored

Figure 2. Mean (95% BCI) treatment difference between fingolimod 0.5 mg and placebo in PBVC from baseline to month 24 as a function of power prior weighting of FREEDOMS data in the Bayesian analysis of FREEDOMS II



[a]The weighting given to FREEDOMS data was increased in increments of 0.1 from 0 to 1.0, while the weighting given to FREEDOMS II data was fixed at 1.0 throughout
[b]Treatment difference was the positive effect on PBVC of fingolimod compared with placebo in patients with RRMS

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Disclosures

Guosheng Yin has nothing to disclose.

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