Effect of Fingolimod on Brain Atrophy: MRI Data From Phase 3 Studies

Douglas R. Jeffery, MD,[1] Jeffrey A. Cohen, MD,[2] Xiangyi Meng, PhD,[3] Ron Hashmonay, MD[3]

[1]Advance Neurology and Pain, Cornerstone Healthcare, Advance, NC; [2]Mellen Center, Cleveland Clinic Foundation, Cleveland, OH; [3]Novartis Pharmaceuticals Corporation, East Hanover, NJ

CONCLUSIONS

- **Brain atrophy (as measured by PBVC) was reduced in fingolimod-treated patients compared with controls, regardless of baseline factors.**
  - **The treatment effect was evident with the first postbaseline scan (month 6) in both FREEDOMS studies.**
  - **The treatment effect was evident in patients with and without Gd-enhancing lesions at baseline.**
- **Baseline T2 lesion volume and presence of Gd-enhancing lesions significantly predicted PBVC over the course of the studies.**
- **On-study brain volume loss correlated with new T2 lesion formation and worsening disability.**
- **Fingolimod is the only approved MS treatment that provided a consistent and significant treatment effect on PBVC across all phase 3 studies compared with placebo or IFNβ-1a IM.**

INTRODUCTION

- Brain volume loss (a measure of brain atrophy) is used to assess neurodegeneration and provides a means to evaluate neuroprotection in clinical trials.[1]
  - In patients with MS, brain atrophy occurs at ~5–10 times the rate of that observed in healthy individuals (decrease of 0.5%–1% vs 0.1%–0.3% per year, respectively) and begins early in the disease.[1,2]
- Brain atrophy correlates significantly with physical disability and cognitive dysfunction in patients with MS,[3,4] and when observed during the first 2 years of a clinical trial, is predictive of future disability.[5]
  - Brain atrophy may be a stronger predictor of disability than MRI lesion-load measures.[5]
- In clinical trials, several of the currently available disease-modifying therapies either had no effect on brain atrophy vs placebo or had effects that were delayed until the second year of therapy **(Table 1)**.
- Fingolimod, a first-in-class sphingosine 1-phosphate receptor modulator, was the first oral therapy approved in the United States and more than 60 other countries for treatment of relapsing multiple sclerosis (MS),[a] and was evaluated in three phase 3 clinical trials.

Table 1. Effects of approved therapies on brain atrophy in relapsing-remitting MS

	Significant reduction in brain atrophy vs placebo		
Therapy	0–1 year	1–2 years	0–≈2 years
IFNβ-1a IM[7]	X	√	X
IFNβ-1a SC*[8]	–	–	X
IFNβ-1b[9,10]	–	–	–
Glatiramer acetate[11]	X	√†	–
Natalizumab[12]	X	√	X
Teriflunomide[13]	–	–	X
BG-12[14]	–	–	√

IFN=interferon; IM=intramuscular; SC=subcutaneous.
–=Data not reported/available; X=no significant effect; √=significant effect.
**Vs glatiramer acetate. Brain atrophy results not available for placebo-controlled trials.*
†*Significant effect at 9–18 months.*

OBJECTIVE

- To assess the magnitude of treatment effect of fingolimod (0.5 mg/d) vs placebo or interferon (IFN) β-1a intramuscular (IM) on brain volume in three phase 3 trials in patients with relapsing-remitting MS

[a]*The approved indication may vary from country to country. In the United States, it is approved for the treatment of patients with relapsing forms of MS. In the EU, fingolimod is approved for treatment of patients with highly active relapsing-remitting MS.*

METHODS

Study Design

- FREEDOMS and FREEDOMS II were double-blind, randomized, multicenter, placebo-controlled, parallel-group studies comparing once-daily fingolimod 0.5 mg, fingolimod 1.25 mg, and placebo over 24 months.
- TRANSFORMS was a double-blind, randomized, multicenter, double-dummy, parallel-group study comparing once-daily fingolimod 0.5 mg, fingolimod 1.25 mg, and once-weekly IFNβ-1a IM 30 μg over 12 months.
- Eligible patients were adults aged 18–55 years diagnosed with relapsing-remitting MS according to the 2005 revised McDonald criteria,[6] with an Expanded Disability Status Scale score 0–5.5 and ≥1 relapse in the previous year or ≥2 in the previous 2 years.

MRI Assessments

- Magnetic resonance imaging (MRI) scans were obtained at baseline, 6, 12, and 24 months (FREEDOMS and FREEDOMS II) or at baseline and 12 months (TRANSFORMS).
- Scans were analyzed by a blinded central reader at the MS MRI Evaluation Centre, University Hospital, Basel, Switzerland (FREEDOMS and FREEDOMS II) or at the Image Analysis Centre, VU University Medical Center, Amsterdam, Netherlands (TRANSFORMS).
- Structural Image Evaluation using Normalization of Atrophy (SIENA) was used to assess changes in brain volume.
  - Baseline brain volume was measured using a cross-sectional method (SIENAX).
  - SIENA estimates the percentage brain volume change (PBVC) between 2 input images of the same individual obtained at 2 different time points.
    - Analysis programs strip the non-brain tissue from the 2 images, register each brain image (skulls are used to hold the scaling constant), and analyze the PBVC between the 2 time points.

Analysis

- Brain volume analysis was predefined.
  - PBVC across treatment groups was compared using the Wilcoxon rank sum test (TRANSFORMS) or rank analysis of covariance adjusted for treatment, region, and baseline normalized brain volume (FREEDOMS and FREEDOMS II).
- Pearson correlation coefficients were calculated to determine correlation between clinical factors.
- Predictors of PBVC were identified using a multiple regression model with treatment as factor and T2 volume and number of gadolinium (Gd)–enhancing lesions at baseline as predictive variables.

RESULTS

Baseline Brain Volume Correlation With Disease Characteristics

- The study population included 3665 participants in FREEDOMS (n=1272), FREEDOMS II (n=1083), and TRANSFORMS (n=1280).
- Brain volume at baseline correlated with age, MS duration, disability, and MRI lesion burden **(Table 2)**.

Table 2. Correlation of baseline brain volume with demographic and clinical characteristics

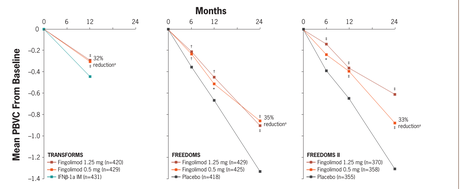
	Pearson correlation coefficient		
	FREEDOMS N=1272	FREEDOMS II N=1083	TRANSFORMS N=1280
Correlation* of normalized brain volume with			
Age	–0.42	–0.44	–0.34
Duration of MS	–0.38	–0.35	–0.28
EDSS	–0.35	–0.28	–0.21
MSFC	0.40	0.34	0.20
T1 lesion volume	–0.41	–0.36	–0.39
T2 lesion volume	–0.44	–0.37	–0.35

EDSS=Expanded Disability Status Scale; MS=multiple sclerosis; MSFC=Multiple Sclerosis Functional Composite.
**P<0.0001 for all correlations.*

Treatment Effects: PBVC

- Fingolimod significantly reduced brain volume loss over 1 year compared with IFNβ-1a IM and over 2 years compared with placebo **(Figure 1)**.
  - Significant reductions vs placebo were observed after 6 months of treatment.

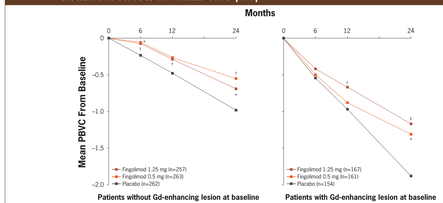
Figure 1. PBVC in TRANSFORMS, FREEDOMS, and FREEDOMS II (ITT)



IFN=interferon; IM=intramuscular; ITT=intent to treat; PBVC=percentage brain volume change.
†*Fingolimod 0.5 mg vs IFNβ-1a IM or placebo.*
**P<0.05, †P<0.01, ‡P<0.001.*

- Fingolimod significantly reduced PBVC at 12 and 24 months compared with placebo in patients with and without Gd-enhancing lesions at baseline **(Figure 2)**.
  - Reductions in PBVC were greater in patients with Gd-enhancing lesions at baseline.
  - Comparable results were observed in FREEDOMS II and TRANSFORMS (not shown).

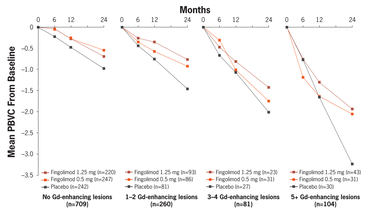
Figure 2. Effect of absence or presence of Gd-enhancing lesions at baseline on PBVC treatment effects in FREEDOMS (ITT)



Gd=gadolinium; ITT=intent to treat; PBVC=percentage brain volume change.
Findings were similar in FREEDOMS II (24 months) and TRANSFORMS (12 months).
**P<0.05, †P<0.01, ‡P<0.001 vs placebo (rank analysis of covariance adjusted for treatment region and baseline normalized brain volume).*

- The magnitude of effect of fingolimod on PBVC increased with increasing Gd-enhancing lesion burden **(Figure 3)**.

Figure 3. Effect of number of Gd-enhancing lesions at baseline on PBVC treatment effects in FREEDOMS

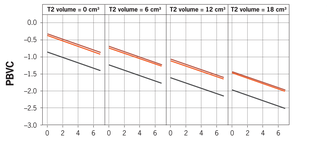


Gd=gadolinium; PBVC=percentage brain volume change.
Findings were similar in FREEDOMS II (24 months) and TRANSFORMS (12 months).

- Baseline T2 lesion volume and number of baseline Gd-enhancing lesions were significant, independent predictors of PBVC across treatment arms **(Figure 4)**.

Figure 4. Association of baseline T2 lesion volume, baseline number of Gd-enhancing lesions and PBVC

	FREEDOMS N=1272	FREEDOMS II N=1083	TRANSFORMS N=1280
Explained variance, R^2	48%*	38%*	27%*



Gd=gadolinium; ITT=intent to treat; PBVC=percentage brain volume change.
Data shown are from FREEDOMS. Findings were similar in FREEDOMS II (24 months) and TRANSFORMS (12 months).
**P<0.001 vs placebo. P values calculated using multiple regression model with treatment as factor and T2 volume and number of Gd-enhancing lesions at baseline as predictive variables.*

- On-study PBVC correlated with new T2 lesion formation and worsening disability **(Table 3)**.

Table 3. Correlation of on-study brain volume loss with new T2 lesion formation and worsening of disability measures

	Pearson correlation coefficient		
	FREEDOMS N=1272 (baseline–month 24)	FREEDOMS II N=1083 (baseline–month 24)	TRANSFORMS N=1280 (baseline–month 12)
Correlation of PBVC with			
ΔT2 lesion volume	–0.17†	–0.10*	0.03
ΔT2 lesion number	–0.29†	–0.17†	–0.26†
ΔEDSS score	–0.11†	–0.03	–0.03
ΔMSFC score	0.13†	0.09*	0.01

EDSS=Expanded Disability Status Scale; MSFC=Multiple Sclerosis Functional Composite; PBVC=percentage brain volume change.
**P<0.05.*
†*P<0.001.*

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