Brain volume change by quartile and disability progression in multiple sclerosis: a 4-year analysis of the phase 3 FREEDOMS trial and its extension

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CONCLUSIONS

- **In FREEDOMS and its extension, the quartile of patients with the most brain volume loss at month 24 had the highest on-study risk of reaching milestone EDSS scores and the highest on-study rates of confirmed disability progression**
- **MS disease activity and severity at baseline in FREEDOMS were predictive of brain volume stability up to month 24**
- **These findings support the clinical relevance of brain volume changes in the long-term evolution of MS and the need to reduce brain volume loss as early as possible in the disease course**

INTRODUCTION

- Accelerated brain volume loss (BVL) occurs throughout the course of multiple sclerosis (MS) and is evident from the earliest stages[1]
- The estimated mean rate of BVL in patients with relapsing–remitting MS (RRMS) is in the range of 0.5–1.35% per year, which is considerably higher than the age-related rate of BVL in the general population (0.1–0.3% per year)[1]
- Both focal and diffuse damage in grey and white matter contribute to MS progression,[2] and BVL is increasingly recognized as a measure that captures these pathologies[1–3]
- In MS, BVL correlates with and predicts future disability, in terms of both physical and cognitive decline[4,5]
- In the 2-year, phase 3 FREEDOMS trial, fingolimod reduced BVL in patients with RRMS by approximately one-third compared with placebo[6]
- Patients who were randomized to placebo during FREEDOMS and switched to fingolimod in the FREEDOMS extension also benefited in terms of reduced BVL during the extension study[7]

OBJECTIVES

- To investigate whether BVL at month 24 is associated with and is predictive of disability progression in FREEDOMS and its extension

METHODS

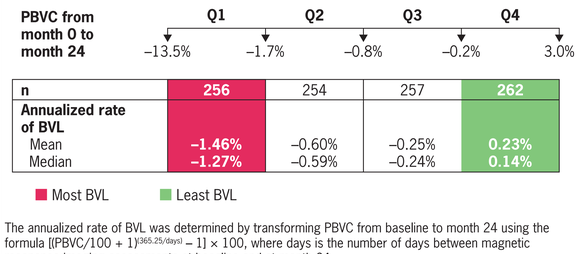
Study design and participants

- In FREEDOMS, patients with RRMS were randomized to receive fingolimod 0.5 mg, fingolimod 1.25 mg or placebo for 24 months.[6] Patients completing FREEDOMS were eligible to enter the extension on the same dose of fingolimod, and those taking placebo were re-randomized to fingolimod 0.5 mg or 1.25 mg. All patients receiving fingolimod 1.25 mg were subsequently switched to fingolimod 0.5 mg[7]
- This analysis included all patients who were randomized and received at least one dose of study medication during both FREEDOMS and its extension

Analyses

- Percentage brain volume change (PBVC) from baseline to month 24 was estimated using 'structural image evaluation, using normalization, of atrophy' (SIENA)
- Patients were categorized by quartile at month 24, based on PBVC from baseline, and quartile 4 (Q4) was used as the reference category in subsequent analyses
- The annualized rate of BVL was determined by transforming PBVC using the formula $[(PBVC/100 + 1)^{(365.25/days)} - 1] \times 100$, where 'days' is the number of days between magnetic resonance imaging assessments made at baseline and at month 24 (**Figure 1**)

Figure 1. Annualized rate of BVL in FREEDOMS, by PBVC quartile



The annualized rate of BVL was determined by transforming PBVC from baseline to month 24 using the formula $[(PBVC/100 + 1)^{(365.25/days)} - 1] \times 100$, where days is the number of days between magnetic resonance imaging assessments at baseline and at month 24
BVL, brain volume loss; PBVC, percentage brain volume change; Q, quartile

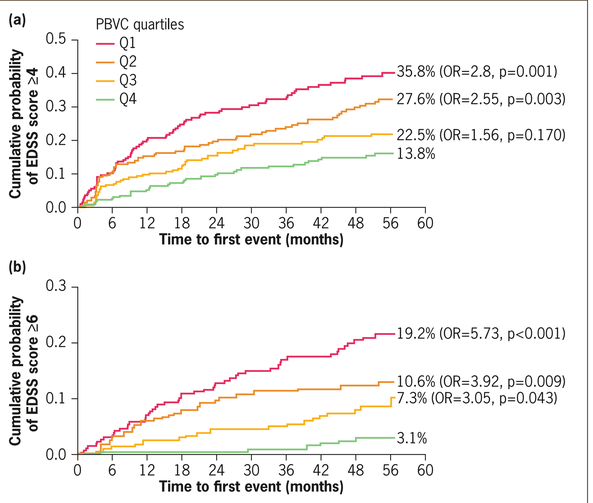
Table 1. Baseline characteristics by PBVC quartile and association with brain volume stability

Characteristic	PBVC quartile Q1 (n=256)	Q2 (n=254)	Q3 (n=257)	Q4 (n=262)	OR for prediction of brain volume stability[a]	p value
Age, years	37.7 (8.9)	37.1 (8.6)	36.9 (8.6)	36.6 (8.6)	0.99	0.171
Women, n (%)	191 (74.6)	186 (73.2)	178 (69.3)	180 (68.7)	1.34	0.137
Time from first symptom, years	7.9 (6.4)	8.2 (6.6)	8.5 (6.8)	7.7 (6.4)	0.99	0.727
Number of relapses in the previous 2 years	2.3 (1.3)	2.2 (1.3)	2.1 (1.1)	2.0 (1.1)	0.82	0.011
EDSS score	2.7 (1.3)	2.3 (1.3)	2.3 (1.2)	2.1 (1.2)	0.69	<0.001
MSFC z-score	–0.21 (0.75)	0.09 (0.55)	0.13 (0.53)	0.16 (0.57)	2.45	<0.001
Gd+ lesion count	3.1 (5.6)	1.3 (3.1)	0.6 (1.1)	0.6 (1.3)	0.71	<0.001
T1 hypointense lesion volume, mm^3	3584 (4208)	1899 (3002)	1529 (2331)	996 (1873)	0.68	<0.001
T2 lesion volume, mm^3	11 266 (10 215)	5988 (6697)	4424 (5363)	3316 (4371)	0.83	<0.001
Normalized brain volume, cm^3	1484 (87.1)	1522 (80.0)	1527 (78.5)	1535 (80.1)	1.01	<0.001

Data are mean (standard deviation) unless otherwise stated
[a]Brain volume stability is defined as a PBVC within Q4
For each variable, ORs compare Q1 and Q4 and are derived from individual regression models, with the respective variable as predictor; patients categorized in Q2 or Q3 were excluded from this analysis
For continuous variables, the OR corresponds to a unit increase in the variable. For the one categorical variable, women were the reference category; therefore an OR>1 implies a higher chance of brain volume stability among men than women
EDSS, Expanded Disability Status Scale; Gd+, gadolinium-enhancing; MSFC, Multiple Sclerosis Functional Composite; OR, odds ratio; PBVC, percentage brain volume change; Q, quartile

- Baseline patient characteristics, and the following parameters at months 24 and 48, were also determined and analyzed by PBVC quartile at month 24
  - Proportion of patients with Expanded Disability Status Scale (EDSS) score ≥4.0 or ≥6.0 at any time post-baseline
  - Time to EDSS score ≥4.0 and ≥6.0, determined using Kaplan–Meier analysis
    - Odds ratios (ORs) and p values were derived from a logistic regression of EDSS score ≥4.0 or ≥6.0 on PBVC quartile and baseline EDSS score
  - 3-month and 6-month confirmed disability progression (CDP), defined as an increase in EDSS score of ≥1.0 if baseline EDSS score was ≤5.0 or an increase of ≥0.5 if baseline EDSS score was ≥5.5
    - ORs and p values were derived from a logistic regression of CDP on PBVC quartile and baseline EDSS score
  - Mean changes from baseline in EDSS score and MS Functional Composite (MSFC) z-score
    - p values were obtained from a rank analysis of covariance model using PBVC quartile and baseline EDSS score as covariates

Figure 2. Time to reach (a) EDSS score ≥4 and (b) EDSS score ≥6 in FREEDOMS and its extension, by PBVC quartile



p values are for comparison with Q4
EDSS, Expanded Disability Status Scale; OR, odds ratio; PBVC, percentage brain volume change; Q, quartile

RESULTS

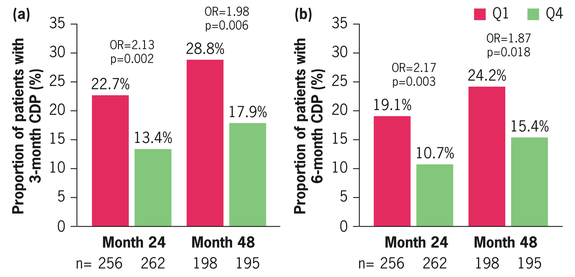
Study population

- In total, 1029 patients were included in the analysis; baseline characteristics by PBVC quartile are shown in **Table 1**
- At baseline, compared with patients in Q4 (least BVL), those in Q1 (most BVL) had:
  - More relapses in the previous 2 years
  - Greater levels of disability (higher mean EDSS score and lower mean MSFC z-score)
  - More active inflammatory disease (more gadolinium-enhancing lesions)
  - More brain tissue damage (greater T1-hypointense and T2 lesion volumes)

BVL and disability progression

- Patients with the most BVL at 24 months had the greatest risk of reaching EDSS score ≥4.0 and ≥6.0 during the study (**Figure 2**)

Figure 3. In FREEDOMS and its extension, (a) 3-month CDP and (b) 6-month CDP, for PBVC Q1 and Q4



p values are for comparison of Q1 and Q4
CDP, confirmed disability progression; OR, odds ratio; PBVC, percentage brain volume change; Q, quartile

Figure 4. Mean change from baseline in (a) EDSS score and (b) MSFC z-score in FREEDOMS and its extension, by PBVC quartile

p values are for comparison with Q4
EDSS, Expanded Disability Status Scale; MSFC, Multiple Sclerosis Functional Composite; PBVC, percentage brain volume change; Q, quartile

- At month 24, 30.3% of patients in Q1 and 11.4% of patients in Q4 reached EDSS score ≥4.0 (OR, 3.29; p<0.001), and at month 48, 35.8% and 13.8% of patients, respectively, reached EDSS score ≥4.0 (OR, 2.80; p=0.001)
- At month 24, 14.8% of patients in Q1 and 1.1% of patients in Q4 reached EDSS score ≥6.0 (OR, 11.85; p<0.001), and at month 48, 19.2% and 3.1% of patients, respectively, reached EDSS score ≥6.0 (OR, 5.73; p<0.001)
- Patients with the most BVL at 24 months also had the greatest risk of 3-month or 6-month CDP during the study (**Figure 3**)
- Higher rates of BVL at 24 months were generally associated with greater increases in EDSS score and decreases in MSFC z-score during the study than were lower rates of BVL (**Figure 4**)

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Disclosures

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