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Impact of Fingolimod Therapy on Magnetic Resonance Imaging Outcomes in Patients With Multiple Sclerosis

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Objective: To assess the impact of fingolimod (FTY720) therapy on magnetic resonance imaging measures of inflammatory activity and tissue damage in patients participating in a 2-year, placebo-controlled, phase 3 study.

Design: Patients with active relapsing-remitting multiple sclerosis were randomized to receive fingolimod, 0.5 mg; fingolimod, 1.25 mg; or placebo for 2 years. Standardized magnetic resonance imaging scans were obtained at months 0, 6, 12, and 24 and centrally evaluated for number and volume of T1 gadolinium-enhancing, T2 hyperintense, and T1 hypointense lesions and for percentage of brain volume change. Findings were compared across subgroups by treatment and baseline characteristics.

Setting: Worldwide, multicenter clinical trial.

Patients: Patients were part of the fingolimod FTY720 Research Evaluating Effects of Daily Oral Therapy in Multiple Sclerosis (FREEDOMS) clinical trial for relapsing-remitting multiple sclerosis (N = 1272).

Main Outcome Measures: We measured the effect of therapy on acute inflammatory activity, burden of disease, and irreversible loss of brain volume.

Results: Fingolimod therapy resulted in rapid and sustained reductions in inflammatory lesion activity as assessed by gadolinium-enhancing and new/newly enlarged T2 lesions after 6, 12, and 24 months of therapy ($P < .001$, all comparisons vs placebo). Changes in T2 hyperintense and T1 hypointense lesion volume also significantly favored fingolimod ($P < .05$, all comparisons). Fingolimod, 0.5 mg (licensed dose), significantly reduced brain volume loss during months 0 to 6, 0 to 12, 12 to 24, and 0 to 24 ($P < .05$, all comparisons) vs placebo, and subgroup analyses confirmed these effects over 2 years irrespective of the presence/absence of gadolinium-enhancing lesions, T2 lesion load, previous treatment status, or level of disability.

Conclusion: These results, coupled with the significant reductions in relapse rates and disability progression reported previously, support the positive impact on long-term disease evolution.

Trial Registration: clinicaltrials.gov Identifier: NCT00289978

Arch Neurol. 2012;69(10):1259-1269. Published online July 2, 2012. doi:10.1001/archneurol.2012.1051

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Group Information: The FREEDOMS Study Group Investigators are listed on page 1266.

With various disease-modifying therapies available to treat multiple sclerosis (MS), research efforts have turned toward finding effective treatments that not only reduce inflammation but also target neurodegeneration. Fingolimod (FTY720, GILENYA; Novartis Pharma AG) is the first in a new class of therapeutic compounds called the sphingosine 1–phosphate receptor (S1PR) modulators that was recently approved at 0.5 mg once daily for the treatment of relapsing MS. Modulation of S1PRs on lymphocytes by fingolimod retains circulating lymphocytes in the lymph nodes, thereby reducing the recirculation of autoreactive lymphocytes and preventing their infiltration into the central nervous system.[1-4] In addition, preclinical studies suggest that fingolimod limits demyelination and restores the function of neural cells.[1-3,5] In an in vivo model,[6] experimental autoimmune encephalomyelitis progression in mice required the presence of S1PR subtype 1 ($S1P_1$) on astrocytes. Experimental autoimmune encephalomyelitis scores and spinal cord demyelination/

Table 1. Baseline Demographic and Disease Characteristics of All 1272 Randomized Patients

	Fingolimod, 1.25 mg (n = 429)	Fingolimod, 0.5 mg (n = 425)	Placebo (n = 418)
Age, y			
Mean (SD)	37.4 (8.9)	36.6 (8.8)	37.2 (8.6)
Median (range)	38.0 (17-55)	36.0 (18-55)	37.0 (18-55)
Female, No. (%)	295 (68.8)	296 (69.6)	298 (71.3)
White, No. (%)	408 (95.1)	406 (95.5)	399 (95.5)
EDSS score			
Mean (SD)	2.4 (1.4)	2.3 (1.3)	2.5 (1.3)
Median (range)	2.0 (0-5.5)	2.0 (0-5.5)	2.0 (0-5.5)
Patients free from Gd-enhancing lesions, No. (%)	257 (60.6)	263 (62.0)	262 (63.0)
No. of Gd-enhancing lesions			
Mean (SD)	1.8 (4.7)	1.6 (5.6)	1.3 (2.9)
Median (range)	0 (0-50)	0 (0-84)	0 (0-26)
Volume of Gd-enhancing lesions, mm^3			
Mean (SD)	197 (604)	170 (601)	162 (421)
Median (range)	0 (0-6853)	0 (0-6850)	0 (0-2970)
Volume of T2 lesions, mm^3			
Mean (SD)	6829 (8491)	6128 (7623)	6162 (7085)
Median (range)	3557 (0-47 734)	3303 (0-47 148)	3416 (0-37 148)
Volume of T1 hypointense lesions, mm^3			
Mean (SD)	2114 (3220)	1898 (2854)	1962 (3131)
Median (range)	860 (0-25 886)	814 (0-22 378)	811 (0-20 956)
Normalized brain volume, cm^3			
Mean (SD)	1511 (86)	1521 (83)	1512 (85)
Median (range)	1515 (1217-1764)	1529 (1144-1734)	1515 (1230-1723)

Abbreviations: EDSS, Expanded Disability Status Scale; Gd, gadolinium.

neurodegeneration were strikingly reduced in mice lacking astrocytic $S1P_1$, suggesting a beneficial effect of functional $S1P_1$ antagonism in astrocytes, in addition to the known peripheral anti-inflammatory effects of fingolimod.[1]

Inflammatory pathology in MS can be visualized by counting gadolinium (Gd)-enhancing lesions on T1-weighted images[7] or new and enlarging T2 lesions on serial magnetic resonance imaging (MRI) scans. These lesions represent areas of recent inflammation and correlate with relapse rates in the short term.[8] The extent of hyperintense areas on T2-weighted images provides an indication of overall burden of disease (often referred to as T2 burden of disease),[9] although it lacks pathological specificity because areas of hyperintensity can represent acute inflammation and edema or demyelination, gliosis, and permanent axonal loss.[10]

Neurodegenerative pathology in MS can be assessed using other conventional MRI techniques: evaluation of T1 hypointense lesions in T1-weighted images and measures of brain volume, including change in volume over time. Chronic T1 hypointense lesions, also called "black holes," represent areas of severe demyelination, axonal injury, and matrix destruction.[10-13] Brain atrophy is the consequence of permanent neuroaxonal loss (a key pathological feature in MS progression) and can be observed during the earliest stages of MS.[14-16] It occurs at an accelerated rate compared with healthy individuals and is widely considered to be the main pathological substrate of irreversible disability.[7,15,17,18] Overall change in brain volume is considered to be among the best studied and most reliable in vivo measures of neurodegeneration, has a significant correlation with physical disability, and seems to be a stronger predictor of future disability than lesion-based MRI measures.[7,15,19] However, several factors must be considered when interpreting changes in brain volume. Brain volume loss per se is not specific for neuroaxonal loss (ie, neurodegeneration). The early, acute reductions in brain volume reported during the first few months with established anti-inflammatory MS therapies[20-22] may represent a reduction in inflammation-associated edema, a phenomenon described as pseudoatrophy.[17,23] Reduction in the rate of brain volume loss may therefore represent either an anti-inflammatory effect in the setting of inflammation and edema or another mechanism independent of inflammation as yet unidentified; such effects are not easily differentiated in human studies.

Herein, we report the MRI results of a randomized, placebo-controlled, phase 3 study of fingolimod in patients with relapsing-remitting MS, in which patients treated with fingolimod had significant reductions in annualized relapse rate and confirmed disability progression over 2 years, compared with placebo. The present analysis evaluated the effect of therapy on acute inflammatory activity, burden of disease, and irreversible loss of brain volume.

METHODS

FTY720 Research Evaluating Effects of Daily Oral Therapy in Multiple Sclerosis (FREEDOMS) was a randomized, double-blind, placebo-controlled, phase 3 trial involving 138 centers in 22 countries from January 2006 to July 2009.[24] It was conducted in accordance with the International Conference on Harmonization Guidelines for Good Clinical Practice[25] and the Declaration of Helsinki.[26] An independent steering committee

consisting of academic investigators collaborated with the sponsor (Novartis Pharma AG) to design the study and monitor its conduct. The protocol was approved by the institutional review board at each site and all patients gave written informed consent before any study-related procedures were performed.

PATIENTS

The study design and inclusion/exclusion criteria have been published previously,[24] in accordance with the CONSORT guidelines. Briefly, patients were randomly assigned (1:1:1 ratio) to once-daily fingolimod capsules, 0.5 mg or 1.25 mg, or matching placebo for 24 months.[24] Patients had to be aged 18 to 55 years with a diagnosis of MS according to the revised McDonald criteria,[27] a relapsing-remitting course, 1 or more documented relapses in the previous year (or 2 or more in the previous 2 years), and a score of 0 to 5.5 on the Expanded Disability Status Scale (EDSS).[28] Key exclusion criteria were relapse or corticosteroid treatment within 30 days before randomization, active infection, drug- or disease-induced immune suppression, or clinically significant systemic disease. Interferon beta or glatiramer acetate therapy had to have been stopped 3 months or more before randomization. Other previous therapies had to have been discontinued for 6 months or more before randomization. Patients were also excluded if they were unable to undergo MRI scans, including those with claustrophobia or a history of severe hypersensitivity to Gd–diethylenetriamine pentaacetic acid.

MRI PROCEDURES

Standardized MRI scans were obtained at screening and at 6, 12, and 24 months and were analyzed centrally at the Medical Image Analysis Center at the University Hospital in Basel, Switzerland. The central reader checked scans for completeness and quality, after which all scans were analyzed by trained technicians and reviewed by radiologists, all of whom were unaware of study-group assignments. Details of MRI assessments are provided in the eAppendix (http://www.archneurol.com).

At each study visit, T1-weighted images, before and after administration of contrast medium (single dose of 0.1 mmol/kg intravenously), and T2-weighted images (T2 and proton density) were obtained according to a standardized imaging protocol (eTable) at certified sites. Investigators were requested to avoid carrying out MRI scans within 30 days of initiation of steroid treatment.

Lesions were identified and marked by radiologists or specially trained personnel on the digital images following a standardized operating procedure. In case of doubt, lesions were discussed in consensus reading sessions. Once lesions were identified, volume calculations were performed by other specially trained technicians (mean intratechnician variability of 3.02% within the MS MRI team at the Medical Image Analysis Center) using an interactive segmentation program developed on the Amira platform (Mercury Computer Systems GmbH). After lesions were marked and segmented, these processes were reviewed and approved by a radiologist.

Percentage of brain volume change (PBVC) between baseline and each postbaseline scan was calculated using the SIENA software included in the Functional Magnetic Resonance Imaging of the Brain software library (FMRIB Analysis Group, Oxford University). At baseline, the single-point SIENA cross-sectional counterpart, SIENAX, was used to estimate the normalized brain volume.

Table 2. Inflammatory Lesion Activity on Magnetic Resonance Imaging as Assessed by New/Newly Enlarged T2 and Gd-Enhancing Lesions (Intent-to-Treat Population)

	Fingolimod, 1.25 mg (n = 429)	Fingolimod, 0.5 mg (n = 425)	Placebo (n = 418)
No. of New/Newly Enlarged T2 Lesions			
Months 0-6			
Patients with data, No.	392	408	394
Mean (SD)	1.1 (2.5)	1.0 (2.6)	3.6 (7.9)
Median (range)	0 (0-27)	0 (0-28)	1.0 (0-96)
P value vs placebo[a]	<.001	<.001	. . .
Months 0-12			
Patients with data, No.	378	401	367
Mean (SD)	1.5 (3.2)	1.6 (4.5)	5.5 (8.0)
Median (range)	0 (0-28)	0 (0-63)	3 (0-78)
P value vs placebo[a]	<.001	<.001	. . .
Months 13-24			
Patients with data, No.	338	371	340
Mean (SD)	1.1 (3.6)	0.9 (3.3)	4.3 (7.9)
Median (range)	0 (0-32)	0 (0-44)	2 (0-69)
P value vs placebo[a]	<.001	<.001	. . .
Months 0-24			
Patients with data, No.	337[b]	370[b]	339[b]
Mean (SD)	2.5 (5.5)	2.5 (7.2)	9.8 (13.2)
Median (range)	0 (0-41)	0 (0-107)	5 (0-99)
P value vs placebo[a]	<.001	<.001	. . .
Gd-Enhancing Lesion Outcomes			
Gd-enhancing lesion count			
Month 6			
Patients with data, No.	388	403	373
Mean (SD)	0.3 (1.1)	0.2 (0.8)	1.3 (3.4)
Median (range)	0 (0-12)	0 (0-13)	0 (0-43)
P value vs placebo[b]	<.001	<.001	. . .
Month 12			
Patients with data, No.	376	394	356
Mean (SD)	0.3 (1.0)	0.2 (1.4)	1.1 (2.2)
Median (range)	0 (0-11)	0 (0-21)	0 (0-19)
P value vs placebo[b]	<.001	<.001	. . .
Month 24			
Patients with data, No.	343	369	332
Mean (SD)	0.2 (1.1)	0.2 (0.8)	1.1 (2.4)
Median (range)	0 (0-11)	0 (0-8)	0 (0-21)
P value vs placebo[b]	<.001	<.001	. . .
Volume of Gd-enhancing lesions, mm^3			
Month 6			
Patients with data, No.	388	403	373
Mean (SD)	35 (151)	26 (153)	142 (415)
Median (range)	0 (0-1545)	0 (0-2538)	0 (0-5233)
P value vs placebo[a]	<.001	<.001	. . .
Month 12			
Patients with data, No.	376	394	356
Mean (SD)	46 (246)	39 (276)	135 (340)
Median (range)	0 (0-3511)	0 (0-5070)	0 (0-2215)
P value vs placebo[a]	<.001	<.001	. . .
Month 24			
Patients with data, No.	343	369	332
Mean (SD)	29 (152)	39 (245)	149 (439)
Median (range)	0 (0-1940)	0 (0-3943)	0 (0-4395)
P value vs placebo[a]	<.001	<.001	. . .

Abbreviations: ellipses, not applicable; Gd, gadolinium.
[a] Negative binomial model adjusted for treatment and country.
[b] Includes patients who had completed to month 24 and had a follow-up visit thereafter.

STATISTICAL ANALYSES

All efficacy analyses, including MRI analyses (all prospectively defined secondary end points), were evaluated in the intent-to-treat population, which comprised all randomized patients. Additionally, patients needed to have evaluable MRI scans to be included in the MRI analyses. All between-group differences were

Table 3. Magnetic Resonance Imaging Outcomes for Volume of T2 Lesions and T1 Hypointense Lesions (Intent-to-Treat Population)[a]

	Fingolimod, 1.25 mg (n = 429)	Fingolimod, 0.5 mg (n = 425)	Placebo (n = 418)
T2 Lesion Load			
Absolute change in T2 lesion volume from baseline to month 12, mm^3			
Patients with data, No.	375	401	365
Mean (SD)	−108 (1856)	−153 (1972)	526 (1559)
Median (range)	−40 (−12 850 to 17 282)	−20 (−26 046 to 17 628)	152 (−7119 to 10 775)
P value vs placebo[b]	<.001	<.001	. . .
Absolute change in T2 lesion volume from baseline to month 24, mm^3			
Patients with data, No.	345	372	342
Mean (SD)	−96 (2167)	−24 (2360)	1045 (2716)
Median (range)	−60 (−15 253 to 17 508)	−42 (−27 657 to 22 893)	357 (−5142 to 33 170)
P value vs placebo	<.001	<.001	. . .
Percentage of change in T2 lesion volume from baseline to month 12, mm^3			
Patients with data, No.	373	397	361
Mean (SD)	2.7 (38.1)	3.4 (35.2)	18.7 (80.5)
Median (range)	−2.2 (−71 to 381)	−0.8 (−100 to 279)	3.9 (−62 to 1098)
P value vs placebo[b]	<.001	<.001	. . .
Percentage of change in T2 lesion volume from baseline to month 24, mm^3			
Patients with data, No.	343	368	339
Mean (SD)	1.6 (30.7)	10.6 (103.5)	33.8 (106.9)
Median (range)	−3.1 (−68 to 221)	−1.7 (−100 to 1829)	8.6 (−85 to 1379)
P value vs placebo	<.001	<.001	. . .
T1 Hypointense Lesion Load			
Absolute change in T1 hypointense lesion volume from baseline to month 24, mm^3			
Patients with data, No.	343	372	340
Mean (SD)	30 (674)	33 (536)	173 (690)
Median (range)	0 (−2403 to 7811)	0 (−4913 to 3462)	2.9 (−3440 to 5857)
P value vs placebo	<.001	.008	. . .
Percentage of change in T1 hypointense lesion volume from baseline to month 24, mm^3			
Patients with data, No.	317	346	305
Mean (SD)	12.2 (85.5)	8.8 (76.3)	50.7 (388.3)
Median (range)	−0.2 (−100 to 888)	0.0 (−100 to 1037)	1.6 (−100 to 5285)
P value vs placebo	.02	.01	. . .

Abbreviation: ellipses, not applicable.
[a] *P* values calculated using rank analysis of covariance adjusted for treatment, country, and volume of corresponding lesions at baseline.
[b] *P* values based on descriptive statistics.

assessed in a pairwise manner and missing data were not imputed. Between-group differences in the numbers of new/newly enlarged T2 lesions were assessed using a negative binomial model adjusted for treatment and country. Rank analysis of covariance adjusted for treatment, country, and baseline number or volume of Gd-enhancing lesions was used to assess between-group differences in the number or volume of Gd-enhancing lesions, respectively. The proportions of patients who were free from Gd-enhancing T1 lesions or new inflammatory activity (Gd-enhancing lesions and new/newly enlarged T2 lesions) were analyzed using a logistic regression model adjusted for treatment, country, and baseline number of Gd-enhancing T1 lesions. The proportions of patients who were free from new/newly enlarged T2 lesions were analyzed using a logistic regression model adjusted for treatment and country (no baseline T2 counts were performed). Absolute and percentage of changes from baseline in the total volume of T2 lesions or T1 hypointense lesions were assessed by rank analysis of covariance adjusted for treatment, country, and corresponding baseline lesion volume (T2 or T1 hypointense volume, respectively). Between-group differences in PBVC were assessed using rank analysis of covariance adjusted for treatment, baseline normalized brain volume, and region. Post hoc subgroup analyses were performed to assess PBVC according to baseline treatment status (treatment-naive or previously treated), EDSS score (0-3.5 points or >3.5 points), Gd-enhancing lesion status (present or absent), or T2 lesion vol-

ume (≤3300 mm^3 or >3300 mm^3); details of these analyses are provided in the eAppendix. No adjustment for multiple analyses was performed for the secondary or post hoc analyses.

RESULTS

STUDY POPULATION

Baseline patient demographics and MRI characteristics were broadly similar across treatment groups (**Table 1**); although baseline MRI parameters for the fingolimod, 1.25 mg, group were slightly worse than fingolimod, 0.5 mg, and placebo, these differences were not clinically meaningful. In total, 1033 of 1272 patients (81.2%) completed the 24-month study, with 945 individuals (74.3%) still receiving the assigned study drug.[24] The number of evaluable MRI scans at baseline and months 6, 12, and 24 are reported in **Tables 1**, **2**, and **3** for each of the assessed MRI outcomes. Across treatment groups, evaluable MRI scans and brain volume data were available in 98.6% to 99.8% of patients at baseline, 89.2% to 96.0% at month 6, 85.2% to 94.4% at month 12, and 77.9% to 87.5% of individuals at month 24. Reasons for missing scans were not collected. As stated in the "Methods" section, no adjustment was made for multiple analyses.

INFLAMMATORY LESION ACTIVITY

Both fingolimod doses reduced the number of new/newly enlarged T2 lesions over 24 months compared with placebo ($P < .001$); the reductions were significant by month 6 and remained so during the 24-month study ($P < .001$ for all comparisons of fingolimod vs placebo) (Table 2). Patients treated with either dose of fingolimod also had fewer Gd-enhancing lesions and lower Gd-enhancing lesion volumes at each postbaseline MRI assessment than patients treated with placebo ($P < .001$ for all comparisons).

More patients receiving fingolimod than those receiving placebo were free from new/newly enlarged T2 lesions, Gd-enhancing lesions, or both (ie, free of new inflammatory activity) at all assessments throughout the study ($P < .001$) (**Figure 1**).

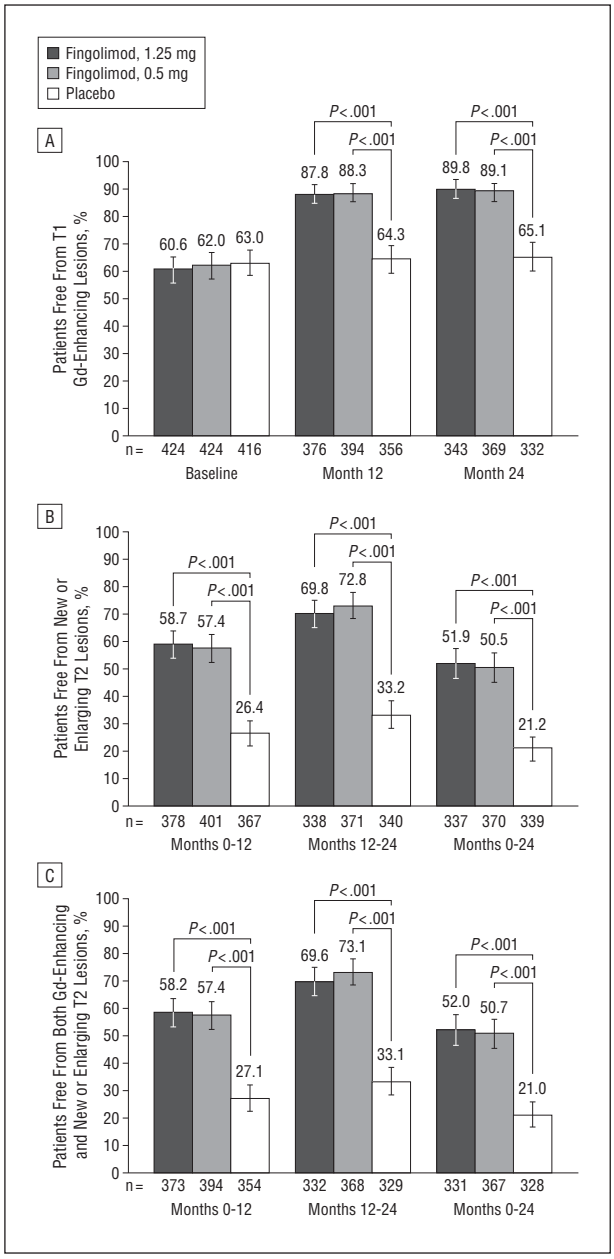


Figure 1. New or inflammatory lesion activity over time. Lesions were assessed by the proportions of patients free from gadolinium (Gd)-enhancing lesions (A), new or enlarging T2 lesions (B), and both Gd-enhancing and new/newly enlarged T2 lesions (intent-to-treat population) (C). Data are percentage (number of patients with evaluable magnetic resonance imaging [MRI] scans) of patients free from lesions in the intent-to-treat population and 95% confidence intervals are based on the binomial distribution using equal-tailed tests. In part A, *P* values were determined using a logistic regression model adjusted for treatment, country, and baseline Gd-enhancing lesion count. In part B, *P* values were determined using a logistic regression model adjusted for treatment and country. In part C, *P* values were determined using a logistic regression model adjusted for treatment, country, and baseline Gd-enhancing lesion count.

T2 BURDEN OF DISEASE

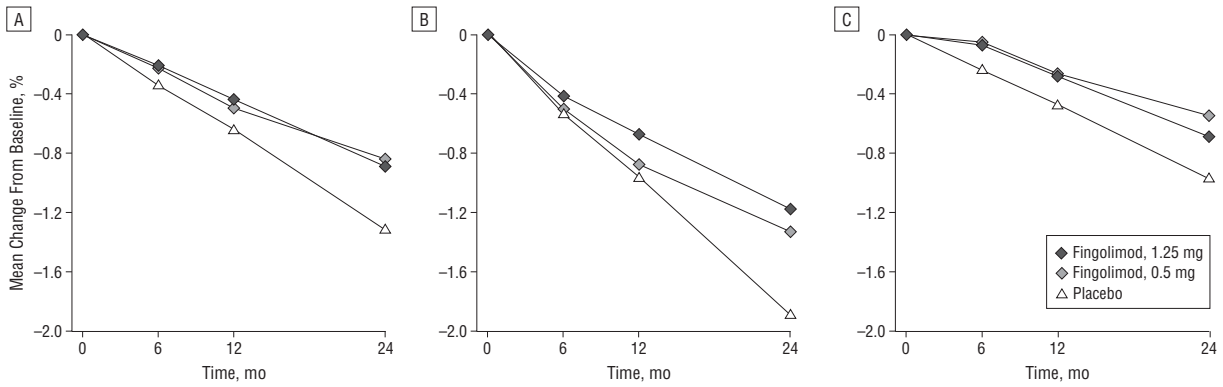
Burden of disease evolution, as assessed by change in T2 lesion volume, was lower in patients treated with either dose of fingolimod over 24 months than with placebo ($P < .001$ for all comparisons) (Table 3). Absolute T2 lesion volume decreased slightly from baseline to months 12 or 24 in both fingolimod groups and increased in the placebo group.

T1 HYPOINTENSE LESION VOLUME

Total T1 hypointense lesion volume remained stable during months 0 to 24 in patients receiving fingolimod, while a slight increase was observed in the placebo group. The difference in change from baseline to month 24 favored both doses of fingolimod over placebo ($P < .05$ for all comparisons) (Table 3).

BRAIN VOLUME CHANGE

As reported previously,[24] both fingolimod doses reduced mean PBVC during months 0 to 24 compared with placebo in the overall study population ($P < .001$). This reduction in PBVC was significant by month 6 and was



PBVC, mean (SD) [n]

	Months 0-6			Months 0-12			Months 12-24			Months 0-24		
	Placebo	Fingolimod, 0.5 mg	Fingolimod, 1.25 mg	Placebo	Fingolimod, 0.5 mg	Fingolimod, 1.25 mg	Placebo	Fingolimod, 0.5 mg	Fingolimod, 1.25 mg	Placebo	Fingolimod, 0.5 mg	Fingolimod, 1.25 mg
All patients	−0.34 (0.73) [n=383]	−0.22 (0.81) [n=395]	−0.21 (0.86) [n=384]	−0.65 (1.05) [n=358]	−0.50 (1.05) [n=383]	−0.44 (1.08) [n=371]	−0.67 (1.07) [n=329]	−0.37 (0.81) [n=356]	−0.42 (0.83) [n=327]	−1.31 (1.50) [n=331]	−0.84 (1.31) [n=357]	−0.89 (1.39) [n=334]
Relative reduction vs placebo, %		34.9	39.2		22.7	32.3		44.7	36.8		35.5	32.2
P value vs placebo		.006	.003		.03	.001		<.001	.002		<.001	<.001
Patients with Gd-enhancing lesions	−0.54 (0.73) [n=138]	−0.51 (0.94) [n=148]	−0.42 (0.94) [n=159]	−0.97 (1.16) [n=126]	−0.89 (1.31) [n=145]	−0.67 (1.24) [n=151]	−0.92 (1.22) [n=117]	−0.51 (0.91) [n=134]	−0.49 (0.79) [n=129]	−1.90 (1.72) [n=118]	−1.33 (1.62) [n=135]	−1.18 (1.52) [n=133]
Relative reduction vs placebo, %		6.4	23.1		8.3	30.9		44.3	46.6		29.9	38.0
P value vs placebo		.09	.05		.16	.002		<.001	.002		.01	<.001
Patients without Gd-enhancing lesions	−0.23 (0.72) [n=243]	−0.05 (0.67) [n=247]	−0.06 (0.78) [n=221]	−0.47 (0.95) [n=230]	−0.26 (0.77) [n=238]	−0.28 (0.93) [n=216]	−0.53 (0.96) [n=210]	−0.28 (0.73) [n=222]	−0.37 (0.86) [n=194]	−0.98 (1.26) [n=211]	−0.55 (0.97) [n=222]	−0.69 (1.27) [n=196]
Relative reduction vs placebo, %		77.4	75.2		44.1	40.3		46.3	29.6		44.1	29.2
P value vs placebo		.01	.003		.06	.006		.002	.11		.002	.02

Figure 2. Mean percentage of brain volume change (PBVC) from baseline in the overall study population (A) and in patients with (B) or without (C) gadolinium (Gd)-enhancing lesions at baseline.

sustained during months 0 to 12 and 12 to 24 ($P < .05$ for both doses at all 3 intervals) (**Figure 2**A). The relative reduction in brain volume loss for fingolimod, relative to placebo, ranged from 23% to 45% at the various intervals.

To evaluate the influence of the anti-inflammatory effect of fingolimod on brain volume change, the results were stratified according to whether patients had Gd-enhancing lesions at baseline. The first finding of note is that brain volume declined approximately twice as quickly in patients with Gd-enhancing lesions at baseline as in those without Gd-enhancing lesions in both the placebo and fingolimod groups. Second, irrespective of baseline Gd-enhancing lesion activity, both fingolimod doses significantly reduced brain volume loss over 2 years compared with placebo (Figure 2B and C). Finally, the temporal evolution of brain volume loss differed between patients with Gd-enhancing lesions at baseline and those without (Figure 2B and C). For individuals with active inflammation at baseline (Gd-enhancing lesions present), brain volume in the placebo group decreased steadily throughout the study and at a faster rate than in those without Gd-enhancing lesion activity. In patients receiving fingolimod, brain volume loss occurred at a similar rate to placebo during the first 6 months, slowed slightly during the second 6 months, and then was considerably slower than placebo during the second year. For patients without Gd-enhancing lesions at baseline, brain volume again decreased steadily in those receiving placebo. In contrast, with fingolimod therapy, there was an immediate reduction in the rate of brain volume loss compared with placebo, which was greatest during the first 6 months and relatively steady thereafter but progressed more slowly than placebo. No significant differences in the magnitude of the effect between the 2 fingolimod doses were noted ($P > .10$ for subgroup interactions). At no point did the rate of brain volume loss in fingolimod-treated patients exceed that in the placebo group, irrespective of baseline MRI activity.

Other subgroup analyses (**Table 4**) assessing PBVC during months 0 to 24 indicated that both fingolimod doses were superior to placebo irrespective of T2 lesion volume at baseline ($\leq$3300 mm^3 or $>$3300 mm^3) and that fingolimod, 0.5 mg, was superior to placebo regardless of whether patients had received disease-modifying therapy for MS; the difference approached significance

Table 4. Magnetic Resonance Imaging Outcomes for Percentage of Change in Brain Volume During Months 0 to 24 by Patient Subgroup (Intent-to-Treat Population)[a]

	Fingolimod, 1.25 mg (n = 429)	Fingolimod, 0.5 mg (n = 425)	Placebo (n = 418)
T2 lesion volume ≤3300 mm^3			
No. of patients[b] ([c])	201 (156)	212 (185)	206 (169)
Mean (SD)	−0.40 (1.15)	−0.47 (0.92)	−0.75 (0.96)
Median (range)	−0.41 (−5.2 to 3.0)	−0.44 (−3.5 to 2.2)	−0.65 (−4.0 to 2.4)
P value vs placebo[d]	.001	.02	. . .
Percentage of relative reduction vs placebo in mean PBVC	46.7	37.3	. . .
T2 lesion volume >3300 mm^3			
No. of patients[b] ([c])	224 (174)	212 (172)	210 (160)
Mean (SD)	−1.33 (1.45)	−1.24 (1.54)	−1.90 (1.74)
Median (range)	−1.02 (−6.3 to 1.9)	−1.05 (−13.5 to 2.0)	−1.52 (−7.6 to 1.5)
P value vs placebo[d]	.003	<.001	. . .
Percentage of relative reduction vs placebo in mean PBVC	29.9	34.5	. . .
Treatment naive			
No. of patients[b] ([c])	259 (203)	244 (212)	249 (202)
Mean (SD)	−0.84 (1.32)	−0.90 (1.37)	−1.19 (1.32)
Median (range)	−0.66 (−5.6 to 2.0)	−0.70 (−13.5 to 2.2)	−1.01 (−6.5 to 2.4)
P value vs placebo[d]	.002	.02	. . .
Percentage of relative reduction vs placebo in mean PBVC	29.1	24.4	. . .
Previously treated			
No. of patients[b] ([c])	170 (131)	181 (145)	169 (129)
Mean (SD)	−0.95 (1.49)	−0.76 (1.22)	−1.49 (1.74)
Median (range)	−0.73 (−6.3 to 3.0)	−0.61 (−6.3 to 1.6)	−0.97 (−7.6 to 1.5)
P value vs placebo[d]	.05	.002	. . .
Percentage of relative reduction vs placebo in mean PBVC	36.1	48.8	. . .
EDSS score 0-3.5			
No. of patients[b] ([c])	351 (279)	363 (308)	346 (280)
Mean (SD)	−0.79 (1.38)	−0.79 (1.28)	−1.18 (1.40)
Median (range)	−0.57 (−6.3 to 3.0)	−0.64 (−13.5 to 2.2)	−0.89 (−7.6 to 2.4)
P value vs placebo[d]	<.001	<.001	. . .
Percentage of relative reduction vs placebo in mean PBVC	33.0	32.7	. . .
EDSS score >3.5			
No. of patients[b] ([c])	78 (55)	62 (49)	72 (51)
Mean (SD)	−1.37 (1.31)	−1.16 (1.49)	−2.00 (1.84)
Median (range)	−0.94 (−4.2 to 1.3)	−1.05 (−6.3 to 1.5)	−1.51 (−7.0 to 1.3)
P value vs placebo[d]	.52	.10	. . .
Percentage of relative reduction vs placebo in mean PBVC	31.8	42.2	. . .

Abbreviations: EDSS, Expanded Disability Status Scale; ellipses, not applicable; PBVC, percentage of brain volume change.

[a] There were no differences in the magnitude of the treatment effect of fingolimod between any of the subgroups of patients (eg, EDSS score 0-3.5 vs EDSS score >3.5) as indicated by a lack of significance ($P>.10$) in interaction for treatment × subgroup.

[b] Number of patients within subgroup in intent-to-treat population.

[c] Number of patients within subgroup with nonmissing values from month 0 to month 24 (intent-to-treat population).

[d] Rank analysis of covariance adjusted by treatment, baseline normalized brain volume, and geographic region (2-sided significance level of .05 within each group).

for fingolimod, 1.25 mg, in previously treated patients. Brain volume loss was also significantly reduced by both fingolimod doses in individuals with EDSS scores of 0 to 3.5; although a similar numerical difference was observed in those with scores more than 3.5 ($P = .50$ for subgroup interaction between patients with lower and higher EDSS scores), the difference did not reach significance compared with placebo in this smaller subgroup. Patients with higher EDSS scores and larger T2 volumes at baseline had greater degrees of brain volume loss than their complementary group (both placebo and fingolimod groups). There was relatively little difference in the extent of brain volume loss between groups when segregated by previous therapy status.

Overall, the magnitude of PBVC, relative to placebo, ranged from 24% to 49% for the various subgroups, with the greatest relative changes seen in the previously treated fingolimod, 0.5 mg, group and the smallest relative effect in the treatment-naive fingolimod, 0.5 mg, group. However, effect size was reversed in these same subgroups for the fingolimod, 1.25 mg, group.

COMMENT

These analyses from the 2-year FREEDOMS study confirm that the efficacy of fingolimod therapy is robust across all MRI end points. The anti-inflammatory effects of fingolimod therapy, as depicted by Gd-enhancing lesions and new/newly enlarged T2 lesions, were evident as early as 6 months after treatment initiation and were sustained over 2 years. Approximately half the patients receiving fingolimod therapy were free from any new inflammatory lesions throughout this 2-year study,

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compared with only 21% of patients receiving placebo. The rapid anti-inflammatory effect of fingolimod is corroborated by a 6-month, placebo-controlled, phase 2 study of fingolimod.[29] In this phase 2 study, significant reductions in the number of Gd-enhancing lesions were detected after only 2 months and at each monthly MRI up to month 6 compared with placebo.

Importantly, the rate of brain volume loss over 2 years was significantly reduced by fingolimod therapy vs placebo in the overall study population. This effect was evident by month 6 and was sustained during the remainder of the 2-year study. These data are consistent with results of the companion 1-year Trial Assessing Injectable Interferon Versus FTY720 Oral in Relapsing-Remitting Multiple Sclerosis (TRANSFORMS) study comparing fingolimod with intramuscular interferon beta-1a.[30] In TRANSFORMS, fingolimod reduced brain volume loss relative to intramuscular interferon beta-1a during the controlled phase of the study, while patients switching from intramuscular interferon beta-1a to fingolimod in the 1-year extension experienced marked slowing of brain atrophy.[31]

In contrast to consistent benefits of fingolimod therapy on brain atrophy observed in FREEDOMS and TRANSFORMS, similar phase 3 studies of interferon beta or natalizumab have shown an early acceleration of brain volume loss (equal to or exceeding that of controls) during the first year of treatment and a slowing during the second year, but no significant difference over 2 years.[17,21,22] For instance, in the AFFIRM study of natalizumab,[24,30] brain volume loss over 2 years was similar in the natalizumab (–0.80%) and placebo (–0.82%) groups but during the first year was greater with natalizumab (–0.56%) than with placebo (–0.40%). The observed average rate of brain volume loss in patients in the placebo and intramuscular interferon beta-1a groups in FREEDOMS and TRANSFORMS ranged from 0.40% to 0.56% during the first year,[7,11,15,32] values that are consistent with the natalizumab studies but at the lower end of those reported previously for patients with relapsing-remitting MS (0.5%-1.35% per year).[18,33-36] This is consistent with a population of patients that has shorter disease duration (<10 years) and low disability (median EDSS score of 2.0) compared with earlier studies or natural history cohorts.[29]

In the present study, the subgroup analyses revealed more about the nature of the reductions in brain volume loss during fingolimod therapy. In patients with Gd-enhancing lesions at baseline, the greater rate of brain volume loss in year 1 than in year 2 in patients treated with fingolimod may be consistent with the presence of some degree of pseudoatrophy. In these individuals, the anti-inflammatory effect of fingolimod results in fewer lesions[15,17] and reduced edema and may lead to initial loss of brain volume compared with those without Gd-enhancing lesions at baseline. The fact that this does not lead to a greater rate of brain volume loss than in the placebo group, as seen with other MS therapies,[17] may either reflect a weaker anti-inflammatory effect[24,29-31] or other as yet unidentified mechanism independent of inflammation. However, the rapid and significant reductions in Gd-enhancing lesions indicate that fingolimod has potent anti-inflammatory effects similar to other therapies.[17] Differences in the effect of disease-modifying therapies on brain atrophy may be explained by differences in mechanism of action, including the extent of anti-inflammatory, neurodegenerative, and remyelinating effects in the central nervous system.[33,37-39]

The results of other subgroup analyses indicate that fingolimod therapy is consistent across subgroups. Irrespective of baseline T2 lesion volume or previous treatment status (the licensed 0.5-mg dose only), fingolimod therapy significantly reduced brain volume loss over 2 years. The absence of a significant effect in patients with EDSS scores more than 3.5 is probably due to the small sample size in this group because the magnitude of the reduction in brain volume loss was not substantially different from that in the much larger group of patients with EDSS scores of 3.5 or less. The higher rates of brain volume loss across treatment groups observed in patients with Gd-enhancing lesions or high T2 lesion volume (>3300 mm^3) at baseline vs those without Gd-enhancing lesions or low T2 lesion volume are consistent with previous studies in individuals with relapsing MS.[15,16,19,33,38,39]

Brain atrophy is widely recognized as a useful marker for monitoring disease progression in MS.[15,18] The clinical relevance of therapeutically reduced brain volume loss is underscored by the observations that atrophy is evident during the earliest stages of MS,[7,18] proceeds relentlessly throughout the course of MS at higher rates than in healthy individuals,[15,19] and has a significant correlation with physical disability.[15,19] Furthermore, brain atrophy is considered to be a better MRI predictor of future disability than T2 lesion load or T1 hypointense lesion load.[7,15,19] Therefore, the significant reduction in brain atrophy over 2 years with fingolimod therapy complements the reported reductions in relapse rate and disability progression vs placebo.

Accepted for Publication: March 28, 2012.
Published Online: July 2, 2012. doi:10.1001/archneurol.2012.1051
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Author Contributions: All authors take full responsibility for the content of the article. Dr Radue had full access to all of the study data and takes full responsibility for the integrity of the data and the accuracy of the data

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Financial Disclosure: Dr Radue has received personal compensation from Bayer Schering, Biogen Idec, Novartis, and Merck Serono for consulting and speaking services and financial support for research activities from Actelion, Basilea Pharmaceutica Ltd, Biogen Idec, Merck Serono, and Novartis. Dr O'Connor has received personal compensation for consulting and serving on scientific advisory boards and research funding from Novartis Pharma AG. Dr Polman has received honoraria and/or consultation fees and/or research support from Actelion, Biogen Idec, Bayer Schering, GlaxoSmithKline, Merck Serono, Novartis, Roche, Teva, and UCB. Dr Hohlfeld has received personal compensation for serving on scientific advisory boards and/or speaking activities as principal or on advisory boards from Bayer Schering Pharma, Biogen Idec, Merck Serono, Novartis, sanofi-aventis, and Teva and research grant support from Bayer Schering Pharma, Biogen Idec, Novartis, sanofi-aventis, and Teva. Dr Calabresi has received personal compensation for consulting and serving on scientific advisory boards from Abbott, Biogen Idec, Genzyme, Novartis, Teva, and Vaccinex and has received research funding from Abbott, Bayer, Biogen Idec, EMD-Serono, Genentech, Teva, and Vertex. Dr Selmaj has received honoraria and/or consultation fees and/or research support from Biogen Idec, Genzyme, Merck Serono, Novartis, ONO Pharmaceuticals, and Roche. Drs Agoropoulou, Burtin, de Vera, and Zhang-Auberson are employees of Novartis Pharma AG. Drs Holdbrook and Francis are employees of Novartis Pharmaceuticals Corporation. Dr Kappos has received compensation, used as research funding, for consulting, serving on scientific advisory boards, acting as a clinical trial principal investigator and member or chair of planning and steering committees, and/or speaking activities as principal or on advisory boards from Actelion, Advancell, Allozyne, BaroFold, Bayer HealthCare, Bayer Schering Pharma, Bayhill, Biogen Idec, BioMarin, CSL Behring, Elan, Genmab, GeNeuro SA, GenMark, GlaxoSmithKline, Lilly, Merck Serono, MediciNova, Novartis, Novo Nordisk, Peptimmune, sanofi-aventis, Santhera, Roche, Teva, UCB, and Wyeth. Research and clinical operations (nursing and patient care services) at the MS Center in Basel have been supported by unrestricted grants from 1 or more of these companies and by grants from the Swiss MS Society, the Swiss National Research Foundation, the European Union, the Gianni Rubatto Foundation, Novartis, and the Roche Research Foundation.

Funding/Support: The study was funded by Novartis Pharma AG, Basel, Switzerland.

Online-Only Material: The eAppendix and eTable are available at http://www.archneurol.com.

Additional Contributions: We thank the patients and investigators who took part in this study. They thank Hashem Salloukh of Novartis Pharma AG and Tom Potter and Sarah Griffiths of Oxford PharmaGenesis Ltd for editorial assistance, collating comments from authors and other named contributors, and editing the manuscript for submission. Such editorial help was funded by Novartis Pharma AG.

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