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Fingolimod treatment in multiple sclerosis leads to increased macular volume

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ABSTRACT

Objective: To determine whether fingolimod, an oral sphingosine-1-phosphate receptor modulator approved for treatment of multiple sclerosis (MS), generally leads to increased retinal tissue volume.

Methods: In this longitudinal observational study, we compared changes in macular volume on spectral-domain optical coherence tomography (OCT) between consecutive patients with MS who initiated fingolimod and a matched reference cohort of patients with MS never exposed to the drug. The primary reference cohort was matched based on time interval between OCT examinations. A secondary reference cohort was matched based on age and disease duration. Change in macular volume within each group was analyzed using the paired t test. Change in macular volume between groups was examined using multiple linear regression.

Results: Macular volume increased by a mean of 0.025 mm^3 (95% confidence interval [CI] $+0.017$ to $+0.033$, $p < 0.001$) in the 30 patients with MS who initiated fingolimod over a mean follow-up time of 5 months (SD 3). Macular volume did not significantly change over a mean follow-up time of 6 months (SD 4) in a comparison group of 30 patients with MS never treated with fingolimod (mean change of -0.003 mm^3 , 95% CI -0.009 to $+0.004$, $p = 0.47$). Overall, 74% of eyes in the fingolimod-treated group exhibited an increase in macular volume vs 37% of eyes in the comparison group.

Conclusion: Initiation of fingolimod in MS is associated with a modest, relatively rapid increase in macular volume. *Neurology*® 2013;80:139-144

GLOSSARY

CI = confidence interval; **EDSS** = Expanded Disability Status Scale; **ETDRS** = Early Treatment Diabetic Retinopathy Study; **MS** = multiple sclerosis; **OCT** = optical coherence tomography; **RNFL** = retinal nerve fiber layer; **SD-OCT** = spectral-domain optical coherence tomography; **S1P** = sphingosine-1-phosphate.

Patients with multiple sclerosis (MS) treated with fingolimod (FTY-720), an oral sphingosine-1-phosphate (S1P) receptor modulator, exhibit less brain volume loss than patients treated with placebo or once-weekly interferon- β -1a.^{1,2} Whether this relative preservation of brain volume afforded by fingolimod reflects a form of “neuroprotection” or an increase in tissue volume by other mechanisms is unknown.

Fingolimod has been associated with the development of cystoid macular edema in a small subset of patients,¹⁻⁴ but little is known about how the drug generally affects retinal tissue volume in patients with MS.

Optical coherence tomography (OCT) is a noninvasive technique for measuring retinal thickness. Macular volume and retinal nerve fiber layer (RNFL) thickness are both typically reduced in MS⁵⁻⁷ and tend to decline over the course of disease.⁸ OCT is increasingly being utilized as a marker of axonal loss in MS treatment trials.

We hypothesized that since fingolimod can lead to frank cystoid macular edema and is also associated with a reduction in brain volume loss, this therapy leads to a rapid increase in retinal

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Supplemental data at
www.neurology.org

Supplemental Data



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tissue volume. In this longitudinal analysis of patients in our clinic who initiated treatment with fingolimod and received pretreatment and on-treatment spectral-domain OCT (SD-OCT), we examined whether initiation of fingolimod is associated with increased macular volume.

METHODS Study participants. Standard practice at our MS center is to perform a baseline OCT before initiating fingolimod and a surveillance OCT at or about 4 months on therapy. Consecutive patients with MS who initiated fingolimod and had received pretreatment and follow-up OCT evaluations in our laboratory as part of their routine clinical care were included for analysis. A comparison group of patients with MS never treated with fingolimod and who had received at least 2 SD-OCT evaluations in our laboratory were matched 1:1 to the fingolimod-treated cases based on time between OCT evaluations. As a sensitivity analysis, a second comparison group of patients with MS never exposed to fingolimod was matched 2:1 to the fingolimod-treated cases based on age and disease duration. All participants met 2005 International Panel MS diagnostic criteria.⁹ Participants were excluded from analysis if they had had any acute optic nerve pathology within 6 months before either OCT evaluation or if they had any history of cystoid macular edema at baseline, diabetes, glaucoma, uveitis, or other major retinal disease. Three eyes were excluded from analysis for suboptimal quality in the fingolimod-treated group (57 eyes), no eyes were excluded in the time interval–matched comparison group (60 eyes), and 1 eye was excluded for suboptimal quality in the age and disease duration–matched comparison group (119 eyes). The Expanded Disability Status Scale (EDSS) score, a measure of functional disability in MS,¹⁰ was assigned by the treating MS specialist and confirmed by medical record review. Disease duration was defined clinically as the time interval between the date of the first symptom attributable to MS and the date of the OCT evaluation. A clinical history of optic neuritis was defined as a subacute episode of visual blurring or loss associated with eye pain with or without recovery of vision and assessed by subject interview and record review.

Standard protocol approvals, registrations, and patient consents. The UCSF Committee on Human Research approved the study protocol, and all participants provided written informed consent.

SD-OCT and visual evaluations. High-density raster scans of the macula were obtained using the Heidelberg Spectralis SD-OCT system. To measure macular volume, a protocol incorporating 19 high-resolution horizontal line scans (1,024 A scans per B scan) centered at the fovea was used. Macular volumes were calculated from the region within a circle 3.45 mm in diameter centered on the fovea. To measure RNFL thickness, a high-resolution peripapillary line scan centered 3.4 mm from the papilla's center was used. A trained technician performed OCT examinations on the same machine using a standardized protocol. Laboratory standards require that optimal quality measures be met, including a minimum automatic real-time number of 16 and a quality number of 20. Visual acuity was measured using computerized Early Treatment Diabetic Retinopathy Study (ETDRS) letters (Pro-Video system) in the same room under standardized luminance conditions. A clinically significant change in visual acuity was defined as a 2-line change on the ETDRS chart.

Statistical analyses. Change in macular volume and RNFL thickness within each of the groups was evaluated using the paired *t* test. In order to adjust for potential confounders, we also performed a between-groups comparison using multiple linear regression, adjusting for sex, and also examined models adjusting for age, disease duration, baseline EDSS, and history of optic neuritis. To account for possible within-patient intereye correlations when 2 eyes from the same patient were included in the model, the standard error was adjusted using the robust clustered sandwich estimator. For table 1, the Wilcoxon rank sum test was used to compare the EDSS and disease duration between groups, and the χ^2 test was used to compare sex. A 2-sided *p* value of less than 0.05 was considered significant. Stata 11 was used for statistical analyses. GraphPad Prism 5.0 was used to create statistical figures.

RESULTS We identified 30 consecutive patients with MS who had initiated fingolimod and received pretreatment and on-treatment SD-OCT in our laboratory. Compared to the reference group of 30 patients with MS never exposed to fingolimod matched by time between OCT scans, the sex, baseline macular volume, baseline RNFL thickness, and visual acuities were similar between groups (table 1). The fingolimod-treated group was slightly older, had longer disease duration, and had slightly higher disability scores (EDSS) than the reference group. The proportion of patients with relapsing and progressive phenotypes of MS was also similar between groups. As a sensitivity analysis, a second reference group of patients with MS never treated with fingolimod was matched 2:1 by age and disease duration to fingolimod-treated cases. There were no major differences between the fingolimod-treated group and this secondary reference group in terms of sex, baseline macular volume, RNFL thickness, and visual acuity, but the time interval between OCT scans was longer in the nonfingolimod group (table e-1 on the *Neurology*[®] Web site at www.neurology.org). The major reasons for initiating fingolimod were breakthrough relapsing–remitting disease in 7 patients, progressive disease in 9 patients, and personal preference in 14 patients.

Table 1 Baseline demographics

	Patients with MS never treated with fingolimod matched by time between SD-OCT scans to the fingolimod-treated group (n = 30)	Patients with MS who initiated fingolimod between baseline and follow-up SD-OCT (n = 30)	<i>p</i> Value
Age, y, mean (SD)	41.0 (12.1)	47.6 (9.7)	0.02 ^a
Female, n (%)	13 (43.3)	17 (56.7)	0.18 ^b
Disease duration, y, median (IQR)	3.45 (1.2–8.4)	7.8 (4.7–15.2)	0.002 ^c
Disease subtype, n (%)			
Relapsing	27 (90)	24 (80)	0.28 ^b
Progressive	3 (10)	6 (20)	
EDSS median (IQR)	2 (1–2.5)	3.5 (2.5–6)	<0.001 ^c

Abbreviations: EDSS = Expanded Disability Status Scale; IQR = interquartile range; MS = multiple sclerosis; SD-OCT = spectral-domain optical coherence tomography.

^aStudent *t* test.

^b χ^2 test.

^cWilcoxon rank sum test.

Macular volume increased by a mean of 0.025 mm³ (95% confidence interval [CI] +0.017 to +0.033, $p < 0.001$) in the 30 patients with MS who initiated fingolimod over a mean follow-up time of 5 months (SD 3) (table 2). In the primary reference group of patients with MS never treated with fingolimod, macular volume did not significantly change over a mean follow-up time of 6 months (SD 4) (mean change -0.003 mm³, 95% CI -0.009 to $+0.004$, $p = 0.47$). In the second reference group of patients with MS never treated with fingolimod that was matched by age and disease duration, macular volume decreased slightly over a mean follow-up time of 12 months (SD 6 months) (-0.006 mm³, 95% CI -0.010 to -0.001 , $p = 0.02$) (table e-2).

In a multivariable linear regression analysis adjusting for sex, the mean difference in change in macular volume was 0.026 mm³ higher (95% CI +0.011 to +0.041, $p = 0.001$) in the fingolimod-treated group compared to patients with MS not treated with fingolimod matched by time between OCT scans (figure and table 3). Adjustment for age, disease duration, baseline EDSS, and history of optic neuritis in the regression model did not meaningfully change the results. The results were also similar in a sensitivity analysis examining the fingolimod-treated group to the comparison group that was matched by age and disease duration (figure e-1 and table e-2). A sensitivity analysis looking separately at patients who initiated fingolimod for breakthrough disease vs patient preference revealed similar results (mean macular volume change for fingolimod patients in the elective group was +0.04 mm³ and mean for the breakthrough disease group was +0.01 mm³). One patient in the fingolimod-treated group developed the retinal OCT phenotype of microcystic macular edema of the inner nuclear layer¹¹ in a single eye on follow-up OCT evaluation; a sensitivity analysis excluding this patient led to similar results (mean macular volume change within groups = +0.024 mm³, 95% CI +0.015 to +0.032, $p < 0.0001$). A sensitivity analysis stratifying by eyes with or without optic neuritis in the fingolimod-treated group and assessing for differences in

macular volume change showed that eyes without prior optic neuritis ($n = 52$) exhibited a similar mean macular volume increase as the entire group (+0.028 mm³), whereas macular volume did not change significantly (mean -0.004 mm³) in the 5 eyes with prior optic neuritis. However, given the very small sample size of optic neuritis eyes, caution should be exercised in the interpretation of this finding.

RNFL thickness did not change significantly in the fingolimod-treated group (mean RNFL change -0.03 μm , 95% CI -0.58 to $+0.52$) and declined slightly in the primary comparison group (tables 2 and 3). There was no significant difference in RNFL loss between groups using multiple linear regression adjusting for sex. Adjustment for age, disease duration, baseline EDSS, and optic neuritis history did not meaningfully change the results. The results were similar in the sensitivity analysis matching by age and disease duration (tables 2 and e-2). A similar sensitivity analysis as above revealed that the mean RNFL thickness in eyes with no history of optic neuritis ($n = 52$) increased slightly ($+0.10$ μm), while mean RNFL thickness in eyes with a history of optic neuritis ($n = 5$) decreased by -1.4 μm . However, given the very small sample size of optic neuritis eyes, caution should again be exercised.

In the fingolimod-treated group, 22 of the 30 patients exhibited an increase in macular volume in one or both eyes. Of the 22 patients with an increase in macular volume, 18 increased bilaterally, and 4 increased unilaterally. Visual acuity did not change significantly from baseline to follow-up evaluation in the fingolimod-treated group. Of the 42 eyes with an increase in macular volume, only 1 had a significant worsening of acuity of more than 2 lines. Furthermore, there was no major change in visual acuity in any of the 10 patients with the largest increase in macular volume.

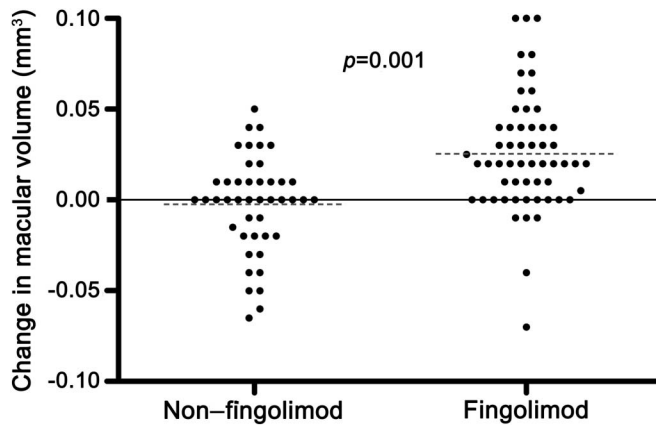
DISCUSSION This study reveals that initiation of fingolimod in patients with MS is associated with a modest increase in macular volume within months of starting therapy. Indeed, 74% of eyes in the fingolimod-treated group exhibited an increase in macular volume

Table 2 Macular volume change between baseline and follow-up SD-OCT scans

	Macular volume change within each group, mean in mm ³		p Value (paired t test)	RNFL thickness change within each group, mean in μm		p Value (paired t test)
	Mean	95% CI		Mean	95% CI	
Patients with MS who initiated fingolimod	+0.025	+0.017 to +0.034	<0.001	-0.03	-0.58 to +0.52	0.91
Patients with MS never treated with fingolimod (matched by time interval between OCT scans)	-0.003	-0.009 to +0.004	0.47	-0.82	-1.43 to -0.22	0.009
Patients with MS never treated with fingolimod (matched by age and disease duration)	-0.006	-0.010 to -0.001	0.02	-1.19	-1.64 to -0.74	<0.001

Abbreviations: CI = confidence interval; MS = multiple sclerosis; OCT = optical coherence tomography; RNFL = retinal nerve fiber layer.

Figure Fingolimod treatment in multiple sclerosis is associated with an increase in macular volume



Macular volume increased by a mean of 0.03 mm³ (95% confidence interval 0.01–0.04, $p = 0.001$ adjusting for sex) in 30 patients with multiple sclerosis (MS) who initiated fingolimod between baseline and follow-up spectral-domain optical coherence tomography (OCT) evaluations (mean 4.9 months [SD 3.1] between OCTs) compared to 30 patients with MS never exposed to fingolimod (mean 6.3 months [SD 3.6] between OCTs). Adjustment for age, disease duration, and optic neuritis did not substantially change the results. Each data point is from an individual eye. The dotted line denotes the mean. Possible within-patient intereye correlations were accounted for in the multiple linear regression models using the clustered sandwich estimator.

compared to 37% of eyes in a comparison group of patients with MS never treated with fingolimod. Moreover, only 9% of eyes in fingolimod-treated patients showed a decline in macular volume compared to 42% of eyes in the non-fingolimod group.

Although disease durations were longer and ages were slightly older in the fingolimod-treated group in our primary analysis, we do not believe these factors explain this observed increase in macular volume, as a sensitivity analysis examining a second reference group of patients

with MS matched by these variables demonstrated the same results. Similarly, although the time between OCT scans in the secondary reference group matched by age and disease duration was longer (12 months vs 5 months), this difference in follow-up times is unlikely to confound these results, as macular volumes were not just reduced to a lesser degree but were clearly increased in the fingolimod-treated group. Overall, the results were similar regardless of which comparison group was used for analysis.

Fingolimod was associated with the development of cystoid macular edema in less than 1% of patients in published phase III clinical trials.^{1,2} Cystoid macular edema associated with fingolimod is thought to resolve with cessation of therapy in most cases. Given the relatively rapid timeframe in which macular volume increased in our study and the known associations of fingolimod with cystoid macular edema, we suspect that this observed increase in macular volume most likely reflects a form of tissue swelling as opposed to “neuroprotection,” but more research is needed to determine the kinetics and underlying mechanism. Whether this small increase in macular volume represents a subclinical form of cystoid macular edema or an entirely different physiologic process accounting for tissue volume change remains to be determined. Frequent visual monitoring would be prudent in patients with MS who demonstrate increases in macular volume, but more research is needed to determine if this degree of macular volume increase is a risk factor for the development of clinically significant cystoid or diffuse macular edema. Additional research may also establish whether this degree of macular volume increase is associated with mild metamorphopsia.

Table 3 Interocular differences

	Eyes of patients with MS never treated with fingolimod matched by time between SD-OCTs (n = 60)	Eyes of patients with MS who initiated fingolimod between baseline and follow-up SD-OCTs (n = 57 ^a)	p Value
Baseline visual acuity, logMAR, median (IQR)	-0.12 (-0.12 to 0)	0 (-0.12 to 0)	0.01 ^b
			0.61 ^c
Baseline macular volume, mm ³ , mean (SD)	3.03 (0.17)	3.02 (0.22)	0.64 ^c
Baseline RNFL thickness, μm, mean	91.0	87.4	0.50 ^c
Time between baseline and follow-up OCT scan, mo, mean (SD)	6 (4)	5 (3)	0.12 ^d
Macular volume change, mm ³ , mean between groups (SD)	0.00 (0.03)	+0.03 (0.03)	0.001 ^c
RNFL thickness change, μm, mean between groups (SD)	-0.82 (2.35)	-0.03 (2.07)	0.11 ^c
Proportion of eyes with increased macular volume, n (%)	22 (37)	42 (74)	<0.001 ^e
Proportion of eyes with decreased macular volume, n (%)	25 (42)	5 (9)	<0.001 ^e

Abbreviations: IQR = interquartile range; MS = multiple sclerosis; OCT = optical coherence tomography; RNFL = retinal nerve fiber layer; SD-OCT = spectral-domain optical coherence tomography.

^aThree eyes were excluded due to poor signal-to-noise ratio.

^bWilcoxon rank sum test.

^cMultiple linear regression, adjusting for sex and using the clustered sandwich estimator for possible within-patient intereye correlations.

^dMultiple linear regression, adjusting the standard error for within-patient intereye correlations.

^eχ² test.

As disease severity has been associated with the retinal OCT phenotype of microcystic macular edema of the inner nuclear layer,¹¹ it is possible that greater disease activity in the fingolimod-treated group could have contributed to the observed increase in macular volume. We believe this explanation to be less likely as patients with acute optic nerve pathologies within 6 months of either OCT evaluation were excluded from analysis, only a subset of patients in the fingolimod-treated group selected this agent secondary to breakthrough disease activity, and a sensitivity analysis revealed that this group was not driving the result. As the technology improves, it would be instructive to examine retinal segmentation in this patient population to determine which retinal layers account for this observed increase in macular volume with fingolimod.

While there was a small (<1 μm) statistically significant decline of RNFL thickness in the non-fingolimod-treated comparison group and no significant difference in RNFL change in the fingolimod-treated group using a within-group analysis, there was no significant difference in the change in RNFL thickness between groups using multivariable analysis. It is possible that fingolimod may also affect RNFL thickness through similar mechanisms, but more research is needed to study this further.

Fingolimod targets the S1P receptor system, one effect of which is to prevent egress of lymphocytes from lymph nodes into the bloodstream.¹² The S1P system, however, is also involved in many other biological processes, including maintenance of endothelial barrier function in a wide variety of tissues¹³ as well as vascular permeability.^{14,15} S1P receptor antagonism also affects neuronal¹² and astrocytic functioning,¹⁶ the latter being a cell type involved in the maintenance of tight junction and blood-brain barrier integrity.¹⁷

Neuronal and axonal loss is thought to be a major contributor to long-term disability in MS, and MRI measures of brain volume are commonly used as a marker of brain tissue loss in MS treatment trials. The observation that fingolimod is associated with a relatively rapid increase in macular volume raises the question of whether S1P receptor modulating therapy also leads to a relatively rapid increase in brain volume, analogous to what is seen in the macula. In 2 large phase III trials in MS, fingolimod at both the 0.5 mg and 1.25 mg daily doses was associated with reduced brain volume loss at 6, 12, and 24 months compared to placebo² and at 12 months compared to once weekly IM interferon- β -1a.¹ Nearly all disease-modifying therapies in MS lead to near-term reductions in brain volume that are thought to be unrelated to actual brain tissue loss, a phenomenon referred to as "pseudoatrophy."¹⁸ Further research is needed to determine whether the macular volume increase seen with fingolimod is fleeting or sustained, but if it is sustained, the results from our study suggest that we must also be cautious about the possibility of

"reverse pseudoatrophy"—an increase in CNS tissue volume apart from a restoration of neuronal or axonal loss.

Macular volume increases with fingolimod should be taken into account when interpreting retinal OCT measures in patients with MS. In addition, further psychophysical and structural assessments of vision in patients taking fingolimod may help us better understand this phenomenon.

AUTHOR CONTRIBUTIONS

Rachel Nolan: design/conceptualization of the study, analysis/interpretation of the data, revising the manuscript. Jeffrey Gelfand: design/conceptualization of the study, analysis/interpretation of the data, drafting/revising the manuscript. Ari Green: design/conceptualization of the study, analysis/interpretation of the data, drafting/revising the manuscript.

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DISCLOSURE

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