

The Effect of Fingolimod on Conversion of Acute Gadolinium-Enhancing Lesions to Chronic T1 Hypointensities in Multiple Sclerosis

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ABSTRACT

BACKGROUND: Brain lesions converting to chronic T1 hypointensities ("chronic black holes" [CBH]), indicate severe tissue destruction (axonal loss and irreversible demyelination) in multiple sclerosis (MS). Two mechanisms by which fingolimod could limit MS lesion evolution include sequestration of lymphocytes in the periphery or direct neuroprotective effects. We investigated the effect of fingolimod on the evolution of acute gadolinium-enhancing (Gd+) brain lesions to CBH in patients with MS.

METHODS: This was a retrospective nonrandomized comparison of patients with Gd+ brain lesions at the time of starting oral fingolimod [.5 mg/day, $n = 26$, age (mean \pm SD) 39.2 ± 10.6 years, Expanded Disability Status Scale (EDSS) score - median (range): 1.75 (0, 6.5)] to those on no therapy [$n = 30$, age 41.7 ± 9.3 years; EDSS 1.0 (0, 6)]. Each lesion was classified by whether it converted to a CBH in the year following treatment.

RESULTS: In the fingolimod group, 99 Gd+ baseline lesions (mean \pm SD, range: 3.8 ± 5.1 ; 1, 21 per patient) were identified of which 25 (25%) evolved to CBH (1.0 ± 2.0 ; 0, 10 per patient). The untreated group had 62 baseline Gd+ lesions (2.1 ± 2.3 ; 1, 13), 26 (42%) of which evolved to CBH ($.9 \pm 1.4$; 0, 7) ($P = .063$). Thirteen patients (50%) receiving fingolimod and 17 untreated patients (57%) developed CBH ($P = .79$).

CONCLUSION: This pilot study shows a trend of fingolimod on reducing the conversion rate from acute to chronic destructive MS lesions. Such an effect awaits verification in larger randomized prospective studies.

Keywords: Black holes, fingolimod, gadolinium-enhancing lesions, MRI, Multiple sclerosis.

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Introduction

Multiple sclerosis (MS) is an inflammatory autoimmune disease of the central nervous system with neurodegenerative consequences. Gadolinium-enhancing (Gd+) lesions on post-contrast T1-weighted MRI scans indicate localized disruption of the blood brain barrier and are a sensitive marker of active demyelination.¹ On average, enhancement lasts for 3 weeks during which time the lesion often appears hypointense on noncontrast T1-weighted images when compared to surrounding white matter.¹ When enhancement ends, lesions evolve into either T1 isointense or persistently hypointense areas. The latter are commonly referred to as "chronic black holes" (CBHs) and represent irreversible demyelination and axonal loss.^{1,2} Longitudinal MRI has shown that CBHs correlate better with disability than T2-weighted hyperintense lesions, indicating a more clinically relevant surrogate of disease progression.²

During the past 2 decades, more than 10 disease-modifying therapies (DMTs) have been approved for MS.³ The first orally administered of these therapies, fingolimod, limits clinical and MRI aspects of disease by reducing relapse rate, progression of physical disability, formation of new T2 hyperintense and Gd+ lesions, and brain atrophy.⁴⁻⁶ Other approved DMTs also limit the rate of evolution of new Gd+ lesions to CBH.⁷⁻⁹ The purpose of this pilot study was to explore the effect of fingolimod on such lesion conversion.

Methods

This was a nonrandomized 2-arm retrospective study of 56 patients with MS (Table 1) who had Gd+ brain lesions while either newly started on fingolimod (.5 mg/day) or receiving no DMTs. There was a mean of 7 months (range 0, 81 months) between previous DMT use and fingolimod initiation. Baseline MRI was

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Table 1. Patient Clinical, Demographic, and MRI Data

	Fingolimod (n = 26)	Untreated (n = 30)	P Value
Age (years) (mean ± SD)	39.2 ± 10.6	41.7 ± 9.3	0.36 ⁺
Females, n (%)	23 (88%)	28 (93%)	0.65 [*]
Disease category, n (%)			
Relapsing-remitting	24 (92%)	29 (97%)	0.21 [*]
Secondary progressive	2 (8%)	–	
Clinically isolated syndrome	–	1 (3%)	
Disease duration [†] (years) (mean ± SD)	8.0 ± 6.1	8.1 ± 6.1	0.91 ⁺
Clinical data			
-Baseline			
EDSS score (median, range)	1.75 (0, 6.5)	1 (0, 6)	0.10 [#]
T25FW (median, range)	4.7 (3.3, 99)	5.0 (3.5, 7.0)	0.89 [#]
-1-Year follow-up			
EDSS score (median, range)	1.5 (0, 6)	1 (0, 4)	0.045 [#]
T25FW (median, range)	4.9 (3.7, 18.7)	4.5 (3.0, 9.0)	0.35 [#]
Number of on-study relapses	8	6	0.38 [*]
Gd+ lesions # (% per patient)	99 (100%)	62 (100%)	
Per patient mean ± SD (range)	3.8 ± 5.1 (1, 21)	2.1 ± 2.3 (1, 13)	0.077 [#]
CBH resulting from Gd+ lesions # (%)	25 (25%)	26 (42%)	0.063 [^]
Per patient mean ± SD (range)	1.0 ± 2.0 (0, 10)	0.9 ± 1.4 (0, 7)	
Patients developing CBH from acute Gd+ lesions, n (%)	13 (50%)	17 (57%)	0.79 [*]

SD = standard deviation; EDSS = expanded disability status scale; T25FW = timed 25 foot walk, seconds; Gd+ = gadolinium-enhancing; CBH = chronic black hole.

[†]Since first symptoms.

⁺Two-sample t-test.

^{*}Fisher's exact test.

[#]Wilcoxon rank sum test.

[^]Generalized estimating equations model.

performed (mean ± SD) 1.8 ± 2.2 months within fingolimod initiation (range 3 months prior to 4 months after). Fifty-seven percent of the patients in the untreated group had received DMTs in the past. These patients discontinued therapy, on average, 33.7 (range 2, 107) months prior to baseline MRI. The remaining patients in the untreated group had no prior exposure to DMTs. Follow-up MRI was performed 12.6 ± 2.0 (range 9, 19) months later. All patients had MS by the International Panel criteria.¹⁰ A neurologist scored the Expanded Disability Status Scale (EDSS)¹¹ and timed 25-foot walk (T25FW).¹² None had corticosteroids within 30 days prior to MRI. The Partners Institutional Review Board approved this study.

Patients underwent MRI on 1.5T GE scanners which included dual-echo conventional spin-echo T2-weighted, and pre- and postcontrast T1-weighted images using axial 3 mm gapless slices. Two experienced observers, who were blind to clinical details, identified (by consensus) baseline Gd+ lesions which coincided with T2 hyperintensities and determined if they converted to CBHs.

Age and disease duration were compared using 2-sample t-tests. Gender, disease category, presence of an attack, and at least 1 CBH were compared using Fisher's exact tests. Wilcoxon rank sum tests compared ordinal or skewed variables (EDSS, T25FW, and number of baseline Gd+ lesions). A generalized estimating equations model with an exchangeable working correlation structure and robust standard errors compared the groups on the probability of conversion of a Gd+ lesion to a CBH, accounting for the correlation of within-subject lesions. A *P* value < .05 was considered significant, and > .05 but < .10 was considered a trend.

Results

Results are summarized in Table 1 and Figure 1. The demographic and clinical characteristics were similar except that

the fingolimod group had higher follow-up EDSS scores (*P* = .045) and a trend toward higher baseline Gd+ lesions (*P* = .077) which may have caused a selection bias. In the fingolimod group, of 99 baseline Gd+ lesions, 25 (25%) evolved to CBH. In the untreated group, of 62 baseline Gd+ lesions, 26 (42%) evolved to CBH. Lesions trended to being more likely to convert to CBH in the untreated versus fingolimod group (OR = .48; 95% CI: .22, 1.04; *P* = .063). Thirteen patients (50%) receiving fingolimod and 17 untreated patients (57%) developed at least 1 CBH from acute lesions (*P* = .79).

Discussion

Previously completed randomized placebo-controlled clinical trials demonstrated fingolimod's ability to limit the progression of cerebral lesion load and atrophy as defined by MRI.⁴⁻⁶ Our pilot study aimed to explore an additional aspect of a therapeutic effect of this agent, namely the effect on the evolution of acute lesions. While this study was limited by a retrospective design, possible selection bias, and small sample size, these preliminary results suggest that fingolimod favorably limits the conversion of acute lesions to chronic destructive lesions.

There are 2 potential mechanisms by which fingolimod could exert a treatment effect on lesion evolution. First, by modulating the sphingosine-1-phosphate (S1P) receptor, fingolimod sequesters lymphocytes in secondary lymphoid organs, resulting in fewer circulating autoreactive T cells available to infiltrate the CNS.¹³ Thus, the acute lesions in our patients starting fingolimod therapy may have developed less inflammation infiltration in their early stages, leading to less severe long-term injury. Second, fingolimod is hypothesized to have direct treatment effects within the brain.¹³⁻¹⁵ For example, Fingolimod's lipophilic properties allow it to cross the blood brain

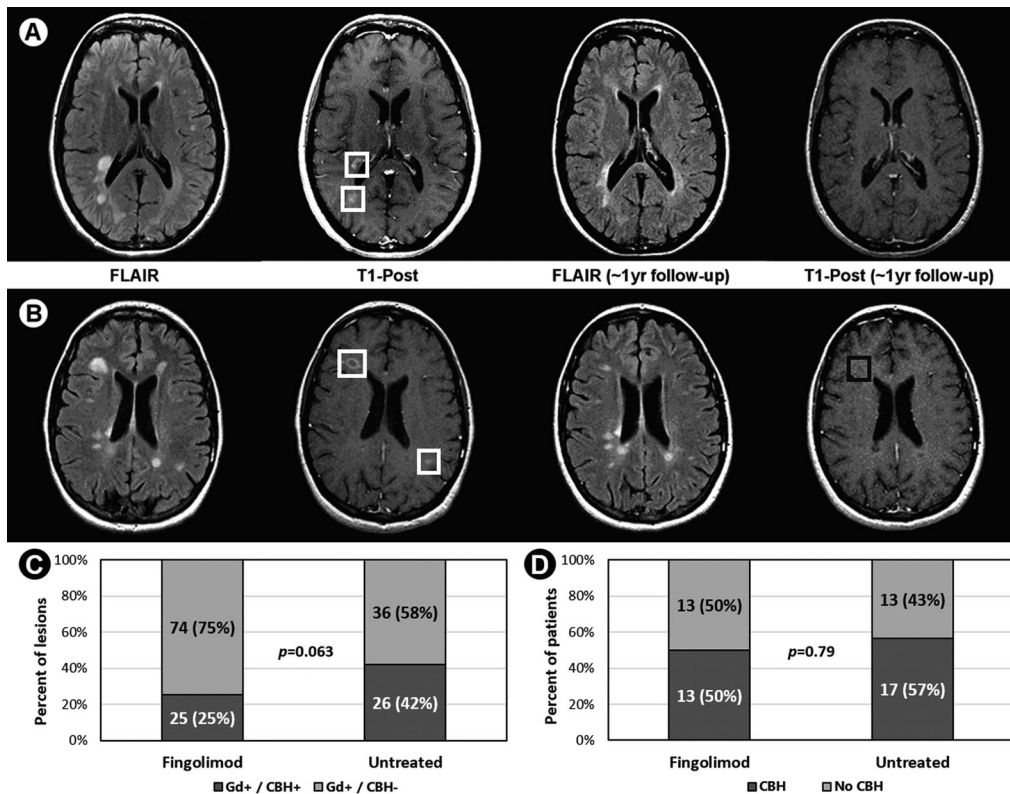


Fig 1. (A) Two baseline gadolinium-enhancing (Gd+) lesions (white boxes) not converting to chronic black holes (CBH). (B) Two baseline Gd+ lesions (white boxes); 1 converted to a CBH (black box). (C) and (D) Fingolimod versus untreated groups on (C) percent of baseline Gd+ lesions converting to CBH at follow-up, and (D) percent of patients developing CBH. Key for A/B: FLAIR: fluid-attenuated inversion-recovery; T1-Post: T1-weighted post-contrast gadolinium scan. Key for C: Gd+/CBH+: baseline Gd+ lesions converting to CBH; Gd+/CBH-: baseline Gd+ lesions not converting to CBH.

barrier where it may provide in situ neuroprotective effects by modulating the S1P receptor on neural cells.^{14,15}

Furthermore, all 3 pivotal phase III clinical treatment trials of fingolimod in patients with MS have shown an effect on limiting the rate of brain atrophy, appearing as early as 6 months after starting therapy.^{4-6,16} Taken together, these findings suggest that one of the mechanisms by which fingolimod limits tissue destruction is through a favorable effect on limiting the damage resulting from new lesions.

In conclusion, these preliminary results suggest that fingolimod attenuates the evolution of newly formed lesions to a less destructive pathology. However, the effect was partial and showed a trend but did not reach statistical significance in this small single-center study. Furthermore, the results appeared to be driven by large effects on a subset of patients rather than consistent effects throughout all subjects. More definitive results on such a treatment effect of fingolimod will likely be derived from post hoc analyses of large randomized placebo-controlled multicenter clinical trial data sets. Such analyses are currently ongoing.¹⁷

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