Original Investigation

Fingolimod for the Treatment of Intracerebral Hemorrhage
A 2-Arm Proof-of-Concept Study

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IMPORTANCE Pronounced inflammatory reactions occurring shortly after intracerebral hemorrhage (ICH) contribute to the formation and progression of perihematomal edema (PHE) and secondary brain injury. We hypothesized that modulation of brain inflammation reduces edema, thus improving clinical outcomes in patients with ICH.

OBJECTIVE To investigate whether oral administration of fingolimod, a Food and Drug Administration–approved sphingosine 1–phosphate receptor modulator for multiple sclerosis, is safe and effective in alleviating PHE and neurologic deficits in patients with ICH.

DESIGN, SETTING, AND PARTICIPANTS In this 2-arm, evaluator-blinded study, we included 23 patients with primary supratentorial ICH with hematomal volume of 5 to 30 mL. Clinical and neuroimaging feature–matched patients were treated with standard care with or without oral fingolimod. The study was conducted in Tianjin Medical University General Hospital, Tianjin, China.

INTERVENTIONS All patients received standard management alone (control participants) or combined with fingolimod (FTY720, Gilenya), 0.5 mg, orally for 3 consecutive days. Treatment was initiated within 1 hour after the baseline computed tomographic scan and no later than 72 hours after the onset of symptoms.

MAIN OUTCOMES AND MEASURES Neurologic status and hematomal and PHE volumes (Ev) and relative PHE, defined as Ev divided by hematomal volume, were monitored by clinical assessment and magnetic resonance imaging, respectively, for 3 months.

RESULTS Patients treated with fingolimod exhibited a reduction of neurologic impairment compared with control individuals, regained a Glasgow Coma Scale score of 15 by day 7 (100% vs 50%, $P = .01$), and had a National Institutes of Health Stroke Scale score reduction of 7.5 vs 0.5 ($P < .001$). Neurologic functions improved in these patients in the first week coincident with a reduction of circulating lymphocyte counts. At 3 months, a greater proportion of patients receiving fingolimod achieved full recovery of neurologic functions (modified Barthel Index score range, 95-100; 63% vs 0%; $P = .001$; modified Rankin Scale score range, 0-1; 63% vs 0%; $P = .001$), and fewer reported ICH-related lung infections. Perihematomal edema volume and rPHE were significantly smaller in fingolimod-treated patients than in control individuals (Ev at day 7, 47 mL vs 108 mL, $P = .04$; Ev at day 14, 55 mL vs 124 mL, $P = .07$; rPHE at day 7, 2.5 vs 6.4, $P < .001$; rPHE at day 14, 2.6 vs 7.7, $P = .003$, respectively). We recorded no differences between groups in the occurrence of adverse events.

CONCLUSIONS AND RELEVANCE In patients with small- to moderate-sized deep primary supratentorial ICH, administration of oral fingolimod within 72 hours of disease onset was safe, reduced PHE, attenuated neurologic deficits, and promoted recovery. The efficacy of fingolimod in preventing secondary brain injury in patients with ICH warrants further investigation in late-phase trials.

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Editorial

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Intracerebral hemorrhage (ICH) accounts for about 10% to 15% of all strokes and is associated with high rates of mortality and morbidity.[1,2] Although surgical decompression is widely accepted as potentially lifesaving for many such patients, no proven medical treatment exists.[1,2] Hematomas induce injury by mechanical disruption of the neurons and glia, followed by mechanical deformation causing oligemia, neurotransmitter release, mitochondrial dysfunction, and membrane depolarization.[3-5] Activated microglia release products that induce breakdown of the blood-brain barrier,[1,6] which leads to a massive influx of inflammatory cells from the periphery. Resident glia cells and migrant lymphocytes produce cytokines and chemokines, coupled with cell death products, further activating intrinsic and migrant lymphocytes and guiding the subsequent homing of more lymphocytes from the periphery.[7-12] These inflammatory cascades contribute to the formation of edema that surrounds hematomas, exacerbates the mass effect, amplifies the cell death process via secondary ischemia, and produces inflammatory insults.[2] Perihematomal edema (PHE) increases in volume by about 75% in the first 24 hours after an ICH, peaks about 5 to 6 days later, and lasts up to 14 days.[13-15] An early voluminous edema, relative to hematomal volume, dramatically catalyzes the initial damage triggered by bleeding and critically endangers the overall outcomes of these patients.[16] Previous attempts to reduce edema by infusion of mannitol, glycerol, or dexamethasone have failed to benefit or control regional cerebral blood flow, neurologic functional outcomes, and mortality.[1,2] Although hypertonic saline solutions have been introduced as a promising alternative to reduce the total amount of cerebral edema,[17] no therapies have been directed toward altering the inflammatory and edemic processes of this disease.

Fingolimod (FTY720, Gilenya), the first oral therapy in this category, was approved by the Food and Drug Administration in 2010 for a relapsing form of multiple sclerosis (MS). This drug reduces the occurrence of MS relapses as well as limits the loss of brain volume.[18] Fingolimod is a sphingosine 1-phosphate receptor (S1PR) modulator that inhibits the egress of lymphocytes from lymph nodes and prevents their recirculation,[19,20] thereby reducing the trafficking of pathogenic cells into the central nervous system (CNS).[16] Fingolimod also readily penetrates the CNS and can act directly on neural and glial cells.[16] Modulation of S1PR by fingolimod in both the immune system and CNS may offer a combination of anti-inflammatory and neuroprotective effects in patients with cerebral hemorrhage. Indeed, in experimental ICH in rats, fingolimod reduced cerebral lymphocyte infiltration and alleviated the short- and long-term sequelae.[21-23] This might be applicable to patients with ICH because it has been demonstrated that fingolimod ameliorated motor and cognitive deficits.[24,25] On the basis of fingolimod's pertinent mechanism of action in MS and in preclinical experiments, we hypothesized that modulation of brain inflammatory and immune reactions at selected points could reduce PHE and improve clinical outcomes of patients with ICH. In this study, we investigated the safety and impact of fingolimod on PHE and clinical recovery in patients with ICH.

Methods

Participants

During the open enrollment, a total of 220 patients with ICH were screened. Twenty-three patients met the criteria, matched clinical characteristics and hematomal location and volume, and were directly recruited into this open-label trial at Tianjin Medical University General Hospital, Tianjin, China. The study was designed as a 2-arm, evaluator-blinded, case-control clinical trial. The trial protocol and supporting documentation were approved by the Tianjin Medical University General Hospital institutional review board. Written informed consent was obtained from each patient or a legally acceptable surrogate.

Several inclusion and exclusion criteria were used. Men and nonpregnant women aged 18 years and older with a primary supratentorial ICH of 5 to 30 mL with symptom onset less than 72 hours prior to admission and a Glasgow Coma Scale (GCS) score of 6 or greater were included. To limit variability due to different hematoma locations, this study enrolled patients with basal ganglia hemorrhage only. Exclusion criteria included patients with a GCS score of 3 to 5, planned surgical evacuation of a large hematoma (>30 mL), various degrees of dysphagia, and nausea/vomiting, any of which renders oral administration of fingolimod difficult. Also excluded were patients with hematoma expansion; secondary ICH; preexisting disability (modified Rankin Scale [mRS] score >1); any history of bradycardia or atrioventricular block; concomitant use of antineoplastic, immunosuppressive, or immune-modulating therapies; or macular edema. Patients were matched with National Institutes of Health Stroke Scale (NIHSS) scores, hematomal volumes, and locations of hematomas, and they were randomly assigned to the fingolimod-treatment or control groups.

Study Intervention

Twenty-three patients with ICH with well-matched clinical characteristics (**Table 1**) and hematomal location and volume, as defined by CT (**Figure 1**), were placed into 2 groups, the first of which received standard management for ICH and the second given standard management plus fingolimod (FTY720, Gilenya), 0.5 mg, orally once daily for 3 consecutive days. Fingolimod was given within 1 hour after the baseline CT scan and no later than 72 hours after the onset of symptoms (Figure 1). Management of ICH adhered to current American Heart Association guidelines with antihypertensives to keep mean arterial pressure 130 mmHg or less and administration of nimodipine to prevent cerebral vasospasm and control blood pressure.

Clinical Assessments

Each patient underwent clinical assessment by 2 neurologists blinded to treatment at administration of the first fingolimod dose and on days 7, 14, 30, and 90 thereafter (Figure 1). The extent of neurologic deficit was assessed with the GCS as global impact during hospitalization and score according to the NIHSS assessed as focal. Rehabilitation outcomes at 90 days

Table 1. Baseline Characteristics of Patients With ICH

Characteristic	Mean (SD)		*P* Value
	Control (n = 12)	Fingolimod (n = 11)	
Time to treatment, h	12.2 (13.1)	19.5 (19.5)	.50
Age, y	58.2 (9.1)	60.7 (12.3)	.57
Female, No. (%)	1 (9)	7 (64)	<.001
Medical history, No.			
Previous ICH	0	0	
Ischemic stroke	0	3	
Hypertension	12	11	
Diabetes mellitus	1	3	
Medication, No. (%)			
Warfarin anticoagulation	0 (0)	0 (0)	>.99
Antithrombotic treatment	0 (0)	2 (18)	.21
History of alcohol abuse, No. (%)	6 (50)	3 (27)	.40
Clinical features			
Blood pressure, mm Hg			
Systolic	160 (21)	156 (28)	.90
Diastolic	94 (12)	86 (16)	.53
On admission			
GCS score	12.8 (2.5)	11.5 (2.4)	.30
NIHSS score	13.0 (5.3)	15.6 (6.0)	.26
APACHE II score	4.89 (3.2)	7.64 (2.6)	.04
Hematomal volume, mL	15.4 (8.3)	16.7 (6.7)	.68
Location of hematoma, No.[a]			
Lobar	0	0	>.99
Deep	12	11	
Intraventricular extension, No.	1	1	>.99

Abbreviations: APACHE II, Acute Physiology, Age, and Chronic Health Evaluation II; GCS, Glasgow Coma Scale; ICH, intracerebral hemorrhage; NIHSS, National Institutes of Health Stroke Scale.

[a] Location of deep hematoma includes basal ganglia or thalamus; cerebellum or brain stem is excluded.

were assessed with the mRS and the ability to perform activities of daily living was measured with the modified Barthel Index (mBI).

Neuroimaging

Head CT scans without contrast media were performed on all patients at admission. Magnetic resonance imaging was done on a 3-T GE and Siemens Signa scanner at days (SE) 7 (1), 14 (2), and 90 (2) (Figure 1). Hematomal volume (Hv) and PHE volume (Ev) were measured on gradient-recalled echo and fluid-attenuated inversion recovery. Relative PHE was defined as Ev divided by Hv. Measurements were independently and blindly conducted by 2 neuroradiologists. Hematomal volume was manually outlined on the CT scan; gradient-recalled echo and Ev were manually outlined on the fluid-attenuated inversion recovery slices and calculated for each slice from the measured area and corresponding slice thickness using MIPAV software.

Lymphocyte Subpopulation

Lymphocyte subset analyses were performed on whole-blood samples from all participants at the baseline (before the first fingolimod dose) and at 72 hours after the first dose (Figure 1). Isolated mononuclear cells were immunostained with antibodies to CD4-fluorescein isothiocyanate, CD8-peridinin-chlorophyll protein complex, and CD19-phycoerythrin (BD Biosciences). Data were acquired using a FACSCalibur (Becton Dickinson) and analyzed with Flow Jo software (Tree Star).

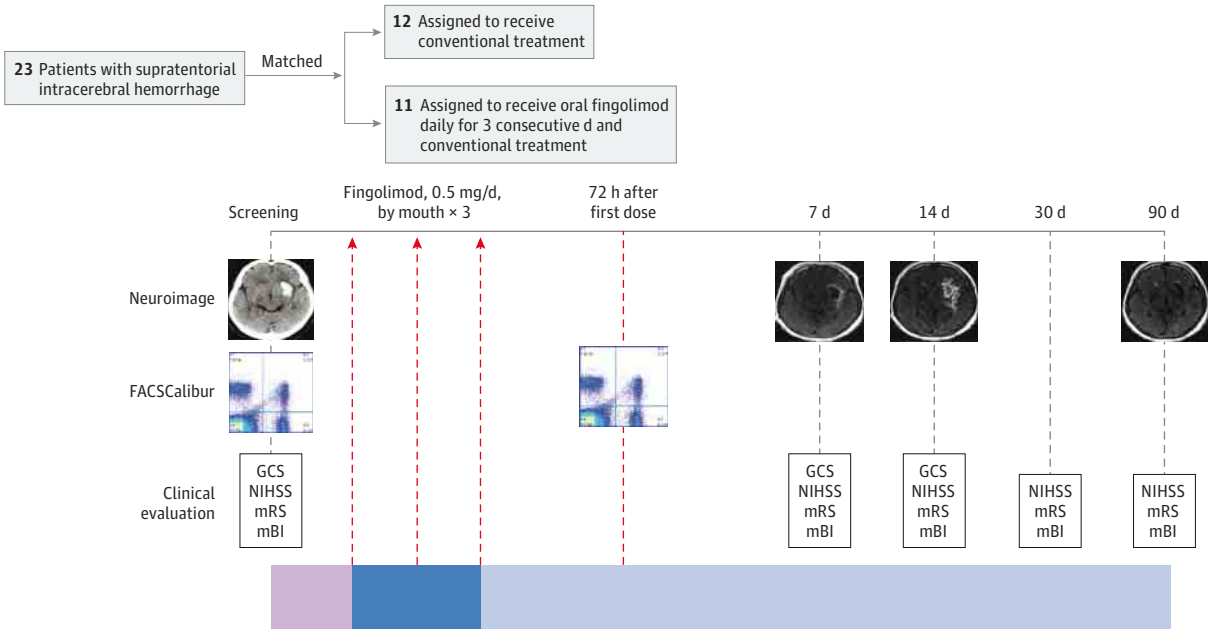
Safety Monitoring

We recorded the details of all adverse events until the time of hospital discharge and all serious adverse events until study day 90. A nonserious adverse event was defined as any undesirable medical experience occurring to a patient whether or not considered related to the test treatment, not including abnormal laboratory values without clinical consequences. A serious adverse event was defined as an event suggesting a significant hazard or adverse effect related to the test treatment. The main safety outcome measures were the frequency of infection and cardiac arrhythmia. Electrocardiography was monitored in all participants for 24 hours after the first dose of fingolimod.

Statistical Analysis

Continuous variables are reported as means (SE), and categorical variables appear as percentages. The Kolmogorov-Smirnoff test was used to assess the normality of the continuous variables, and baseline characteristics were compared by either *t* test for continuous variables or the χ^2 test (or Fisher exact test when the expected value was <5) for categorical data. With the χ^2 test, we compared the frequency of GCS score of

Figure 1. Effects of Fingolimod in Patients With Intracerebral Hemorrhage



Twenty-three patients with supertentorial intracerebral hemorrhage were assigned into 2 arms with matched clinical characteristics and hematomal location and volume, as defined by computed tomography. Patients were assigned to receive standard management or standard management plus fingolimod (FTY720, Gilenya) at doses of 0.5 mg orally once daily for 3 consecutive days. Circulating lymphocyte subset counts were monitored by flow cytometry. Clinical assessments (Glasgow Coma Scale [GCS], National Institutes of Health Stroke Scale [NIHSS], modified Rankin Scale [mRS], and modified Barthel Index [mBI]) were conducted in blind fashion at the indicated points. All patients had noncontrast head computed tomography at admission and subsequent magnetic resonance imaging, also in blinded fashion. Hematomal volume, perihematomal edema volume, and relative perihematomal edema, defined as perihematomal edema volume/hematomal volume, were measured on gradient-recalled echo and fluid-attenuated inversion recovery at the indicated points and calculated.

15, mRS scores of 0 and 1, and mBI scores of 95 to 100. The *t* test was used to compare the means of GCS, NIHSS, mBI, and mRS scores; Hv; Ev; and relative PHE. Statistical significance was defined as $P < .05$. SPSS for Windows version 17.0 software (SPSS Inc) was used for the analyses.

Results

Baseline Characteristics of Patients With ICH

A total of 23 patients with ICH were recruited into our study between March 1, 2013, and December 15, 2013. There were no fatalities, no loss of follow-up, and no dropouts. The mean (SE) time from onset to fingolimod treatment was 19.5 (19.5) hours. Of the 11 fingolimod-treated patients, 7 received the first drug dose at 3 to 12 hours after admission, 3 at 12 to 30 hours, and 1 at 71 hours. The average mean (SE) time to admission of the control group was 12.2 (13.1) hours (Table 1). The 11 patients in the fingolimod-treated group had a mean (SD) age of 60.7 (12.3) years and male to female ratio of 7:4. The control group of 12 patients had a mean (SD) age of 58.2 (9.1) years and male to female ratio of 1:11. Demographic, clinical, and radiologic characteristics are shown in Table 1. The GCS score, NIHSS score, hematomal volumes on admission, and locations of hematomas in the fingolimod treatment group and control individuals were similar (Table 1).

Dynamics of Lymphocyte Subset Counts After Fingolimod Treatment

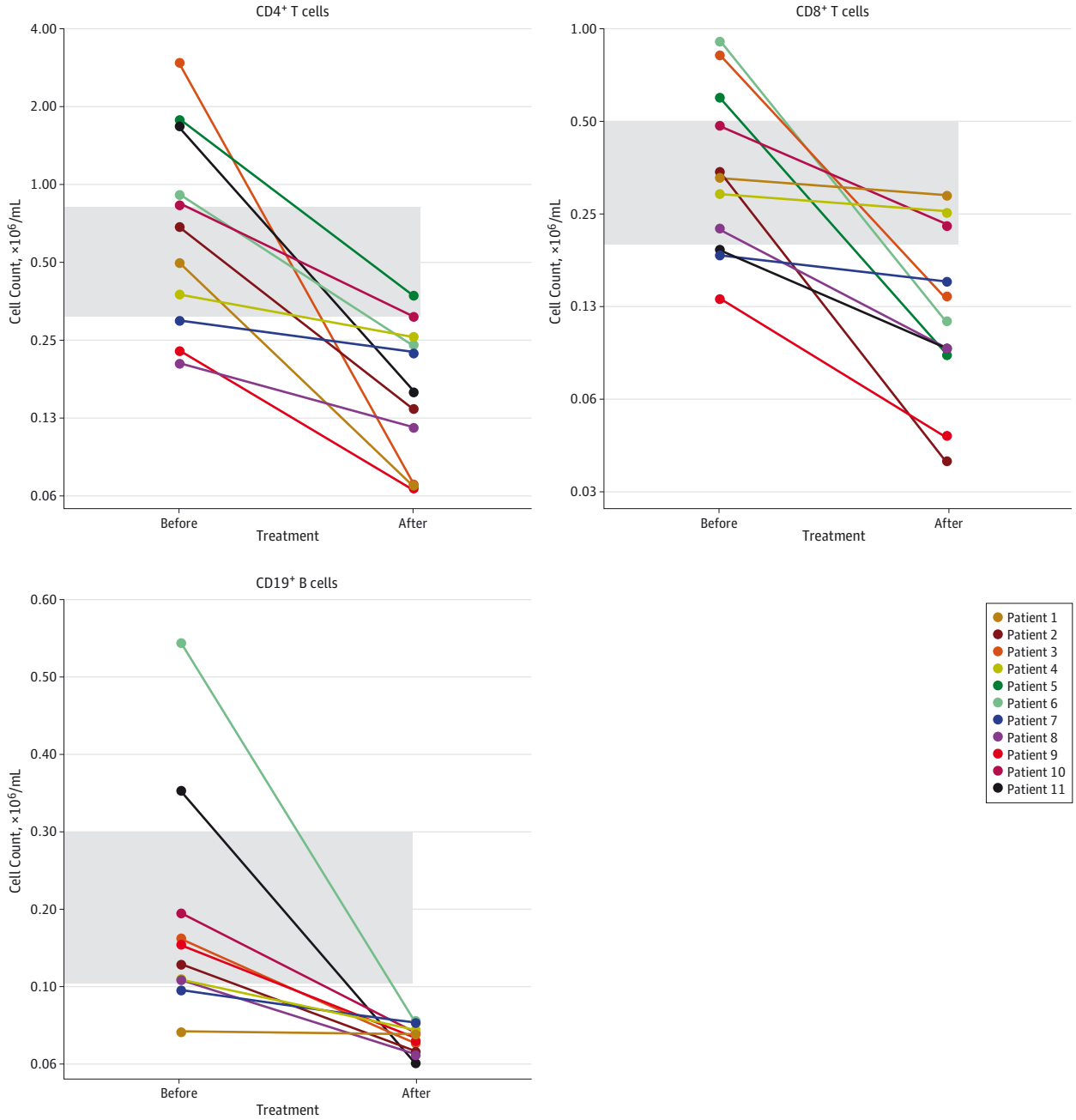
When all patients with ICH who received fingolimod for 3 consecutive days were monitored 72 hours after the first dose, the number of $CD4^+$ T cells, $CD8^+$ T cells, and $CD19^+$ B cells decreased significantly relative to baseline cell counts and in comparison with control individuals (**Figure 2**). Specifically, there were 75% ($P = .004$), 63% ($P = .04$), and 83% ($P < .001$) decreases from baseline in $CD4^+$ T cells, $CD8^+$ T cells, and $CD19^+$ B cells, respectively. These counts were similar for the other lymphocyte subsets including $CD11b^+$, $CD11c^+$, $CD56^+$, $CD56^+$, and $CD3^+$. In the 3-month follow-up, the total lymphocyte counts were comparable with baseline levels for all fingolimod-treated recipients with ICH.

Clinical Outcomes in Fingolimod-Treated Patients With ICH

As illustrated in **Table 2**, the overall GCS scores at baseline were comparable in both groups (ie, a GCS score of 15 was recorded in 42% of control patients at baseline, 50% at 7 days, and 58% at 14 days). In contrast, of the patients treated with fingolimod, 18% had a GCS score of 15 at baseline but 100% by 7 days later. Thus, the global impact of ICH, as reflected by GCS assessment, was attenuated by fingolimod at 7 days and 14 days of treatment ($P = .01$ and $P = .04$, respectively).

The baseline NIHSS scores were comparable in the fingolimod-treated and control patients (15.6 vs 13.0, $P = .26$). How-

Figure 2. Lymphocyte Subset Alteration in 12 Control Participants and 11 Patients With Intracerebral Hemorrhage Treated With Fingolimod



Blood was drawn from patients at the baseline (mean [SE], 19.5 [6.1] hours) and 72 hours after the first dose (mean [SE], 88.3 [6.1] hours). Mononuclear cells were extracted and stained with antibodies to cells. Percentages of $CD4^+$ T cells, $CD8^+$ T cells, and $CD19^+$ B cells were determined by flow cytometry, and absolute numbers were calculated and expressed as $\times 10^6$ per milliliter of blood for each patient with intracerebral hemorrhage. The range of counts for $CD4^+$, $CD8^+$, and $CD19^+$ cells in control individuals on day 4 (mean [SE], 96 [3.4] hours) are depicted as gray background. $CD4^+$ T cells, $CD8^+$ T cells, and $CD19^+$ B cell counts of every patient (depicted with individual lines) decreased significantly relative to baseline and were significantly lower than the numbers of the control group on day 4.

ever, the fingolimod-treated group had markedly lower NIHSS scores than control individuals at 7, 14, and 30 days ($P = .03$, both $P < .001$). The NIHSS scores in control patients decreased by 0.5 for the first week and 1.7 for the second week. In sharp contrast, such reductions were 7.5 for the first week and 2.3 for the second week in fingolimod-treated patients (7.5 vs 0.5, $P < .001$; 2.3 vs 1.7, $P = .42$; Table 2). Fingolimod treatment diminished focal neurologic impairment resulting from ICH, and such reductions were most pronounced within the first 7 posttherapy days.

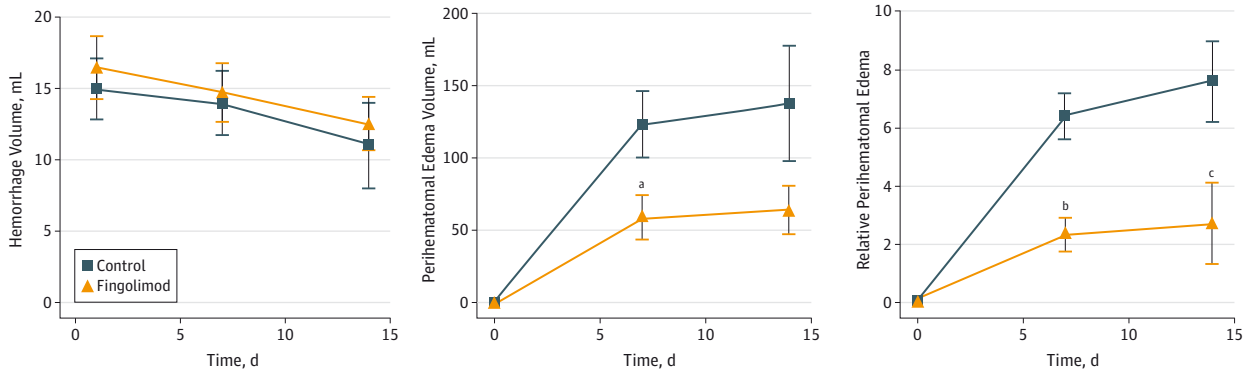
Simultaneously, mRS scores of 0 and 1 and mBI scores of 95 to 100 values at 3 months were 0% in the control group

Table 2. Clinical Assessment of Patients With Intracerebral Hemorrhage

Scale	Mean (SE)		*P* Value
	Control (n = 12)	Fingolimod (n = 11)	
GCS			
On admission	12.8 (0.7)	11.7 (0.6)	.30
GCS 15, No. (%)			
Admission	5 (42)	2 (18)	.37
Day			
7	6 (50)	11 (100)	.01
14	7 (58)	11 (100)	.04
NIHSS			
On admission	13.0 (1.6)	15.6 (1.8)	.26
Day			
7	12.5 (1.5)	8.1 (1.2)	.03
14	10.8 (1.4)	5.8 (0.8)	<.001
30	9.3 (1.5)	3.4 (0.8)	<.001
90	5.0 (0.6)	2.0 (0.7)	.07
NIHSS decrease from admission to d 7	0.5 (0.4)	7.5 (1.0)	<.001
NIHSS decrease from d 7 to d 14	1.7 (0.4)	2.3 (0.6)	.42
mRS			
On admission	4.3 (0.1)	4.4 (0.2)	.90
Day			
7	4.5 (0.2)	3.7 (0.2)	<.001
14	4.1 (0.1)	3.6 (0.2)	.05
30	3.6 (0.2)	2.5 (0.4)	.03
90	2.7 (0.3)	1.5 (0.4)	.17
mRS 0-1 on d 90, No. (%)	0 (0)	7 (63)	.001
mBI			
On admission	17.9 (5.4)	11.4 (3.3)	.31
Day			
7	20.0 (5.4)	35.9 (5.8)	.06
14	27.5 (4.5)	42.3 (6.0)	.06
30	36.2 (6.0)	72.3 (6.6)	.01
90	83.3 (1.7)	86.8 (5.4)	.75
mBI 95-100 on d 90, No. (%)	0 (0)	7 (63)	.001

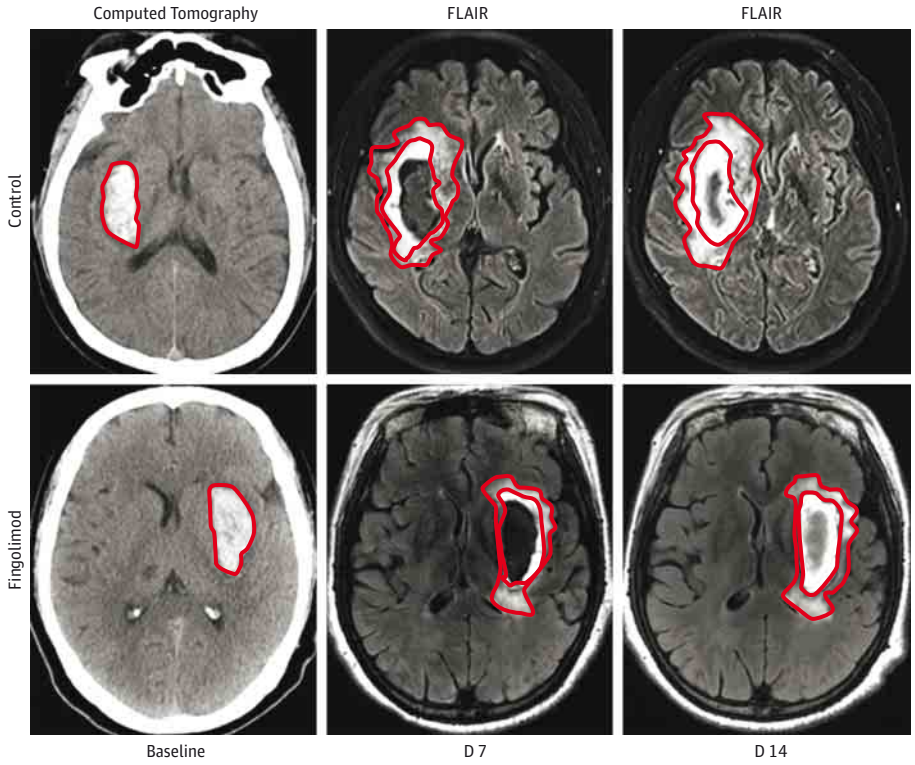
Abbreviations: GCS, Glasgow Coma Scale; mBI, modified Barthel Index; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale.

Figure 3. Evolution of Hemorrhage Volume and Perihematomal Edema in Control Participants and Fingolimod-Treated Patients With Intracerebral Hemorrhage



Significant decreases in relative perihematomal edema and perihematomal edema volume were noted in the fingolimod-treated group compared with the control group at 7 and 14 days after administration. Hemorrhage volume gradually decreased during the next 14 days in both groups and showed no significant difference on test days. Error bars represent SEs.
[a]*P* < .05.
[b]*P* < .001.
[c]*P* < .01.

Figure 4. Representative Computed Tomographic and Magnetic Resonance Images of Control Participants and Fingolimod-Treated Patients With Intracerebral Hemorrhage



The upper panels depict tissues from a control patient with a spontaneous right putaminal hemorrhage. In the lower panels are views from a fingolimod-treated patient with a left putaminal hemorrhage. With similar location and hematomal volume at the baseline, the latter patient who received fingolimod had significant resolution of edema without a midline shift, whereas in control patients, perihematomal edema persisted between days 7 and 14, accompanied by a midline shift. Margins of perihematomal edema for both patients appear as lines. FLAIR indicates fluid-attenuated inversion recovery.

compared with 63% in the fingolimod-treatment group (P = .001, Table 2). These results denote that fingolimod potentially preserved neural functions and promoted rehabilitation in patients with ICH. The overall benefits of fingolimod therapy might extend throughout both acute and recovery stages for these patients with ICH.

Volume of PHE

As shown in **Figures 3** and **4**, the control patients' edema volumes expanded rapidly in the first 7 days and continued up to 14 days. In contrast, in the fingolimod-treated group, expansion of edema volume was much slower in the first 7 days and remained essentially level during the ensuing 8 to 14 days. Significant decreases in relative PHE were noted in the fingolimod-treated group compared with the control group at 7 and 14 days (2.5 vs 6.4, P < .001; 2.6 vs 7.7, P = .003, respectively), and significant decreases in Ev were noted at 7 days (47 vs 108 mL, P = .04). The Ev at 14 days also showed the favorable effect of fingolimod treatment on outcome (55 vs 124 mL, P = .07); however, this effect was not statistically significant owing to a large floor effect. Overall, fingolimod reduced PHE in these patients. However, the ICH volume gradually decreased over the next 14 days in both groups, showing no significant difference between them.

Safety

None of the 11 patients who received fingolimod had heart symptoms; electrocardiography monitoring found no cardiac arrhythmia or aterioventricular blocks. A reduction of heart rate from 60 to 55 was recorded in 1 patient after 6 hours of the first oral fingolimod treatment and, spontaneously, return to baseline was observed 12 hours later. The patient had no cardiac symptoms. As to the following 2 doses, no significant reduction of heart rate occurred. Blood pressure before and after the treatment had no obvious fluctuation. Suspected lung infection occurred in 5 of 12 control patients (42%) in contrast to 2 of 11 fingolimod-treated patients (18%, P = .12). Cough, fever, leukocytosis, and infiltrates on chest x-rays were the criteria used for the diagnosis of lung infection. Symptoms were relatively mild in the fingolimod-treated patients and controlled by antibiotics in both groups.

Discussion

In this study, we have shown that patients with small- to moderate-sized basal ganglia ICH tolerate fingolimod well, with improvements in outcome as well as PHE. These findings encourage further investigation of fingolimod as a potential therapy for acute ICH. Although the evaluator-blinded trial design minimized bias, the small sample size restricted us from drawing a firm conclusion.

The administration of fingolimod produced a significant reduction of PHE at day 7, and that trend lasted through day 14 (Figure 3). Fingolimod appeared to reach its peak actions at 12 to 36 hours and elimination half-life averaged 8.8 days.

Table 3. Complications and Adverse Events

Event	No. (%) Control (n = 12)	No. (%) Fingolimod (n = 11)	*P* Value
Complications			
Death	0 (0)	0 (0)	>.99
Myocardial infarction	0 (0)	0 (0)	>.99
Recurrent stroke	0 (0)	0 (0)	>.99
Cerebral hernia	0 (0)	0 (0)	>.99
Hemorrhage of digestive tract	3 (25)	0 (0)	.22
Fever (>38°C)	5 (42)	3 (27)	.67
Antibiotic	5 (42)	3 (27)	.67
Infection	5 (42)	3 (27)	.67
All events			
At least 1 adverse event	6 (50)	4 (36)	.68
Any adverse event leading to discontinuation	0 (0)	0 (0)	>.99
Any serious adverse event	0 (0)	0 (0)	>.99
Frequent or special-interest adverse events			
Infection			
Suspected lung	5 (42)	3 (27)	.67
Urinary tract	0 (0)	0 (0)	>.99
Herpes virus	0 (0)	0 (0)	>.99
Abnormal laboratory liver-function test result	0 (0)	0 (0)	>.99
Gastrointestinal disorder	1 (9)	0 (0)	>.99
Leukopenia	0 (0)	0 (0)	>.99
Lymphopenia	0 (0)	0 (0)	>.99
Bradycardia	0 (0)	1 (9)	>.99
Atrioventricular block	0 (0)	0 (0)	>.99
Macular edema	0 (0)	0 (0)	>.99

A 3-day consecutive drug administration protocol produced lymphopenia that lasted 7 to 9 days, coincident with the peak stage of edema. Thus, delivery of fingolimod within 72 hours, with its swift action, ameliorated the progression of PHE. The persistence of lymphopenia after drug cessation has been documented in the literature, although the relationship between dosage, persistence, and lymphopenia was not linear.[26-31] Whether the administration of fingolimod beyond 3 days can prolong the reduction in edema is still in need of investigation. Because any form of brain insult, including ischemic stroke, induces a state of immune deficiency,[32,33] the administration of fingolimod beyond 3 days may not offer additional benefit but could prolong an immune-deficient state and compromise the tissue repair mechanism carried out by inflammatory cells during the recovery phase of neural injury.[34,35]

Our primary motivation for using fingolimod as therapy for ICH is its immunologic effect of inhibiting pathogenic cells from migrating into the brain. Alleviation of both global and focal neurologic deficits occurred in the first week of disease (Table 2) and coincided well with the attenuation of PHE, as measured by magnetic resonance imaging at day 7 (Figure 3). These observations strongly suggest that fingolimod operated in patients with ICH by preventing inflammatory cells from homing to the brain. The preservation of CNS tissues by fingolimod was apparent in patients with relapsing MS.[18] Accordingly, fingolimod may exert direct CNS effects that confer neural protection. That is, S1PR is expressed by most CNS cells, and fingolimod modulates S1PR, thereby impacting astrocytes, oligodendrocyes, and neurons. Accumulating studies have revealed that S1P signaling is important during embryonic CNS development and growth, cytoskeletal reorganization, cytoprotection, neural stem cell proliferation, and migration to the site of neural injury.[19,36] Recent studies showed that fingolimod preserves blood-brain barrier integrity.[37,38] The striking difference in terms of complete recovery (0% vs 63% for mRS scores 0-1 and mBI scores 95-100) we observed between the 2 subgroups at 3 months after ictus may be a summation of immune modulation, neuroprotection, and inhibition of vascular leakage.

Fingolimod was well tolerated by all 11 patients with ICH described here. A slight reduction in heart rate was recorded in only 1 of the patients, and that rate resumed its baseline level without intervention. The brief duration of fingolimod therapy at the dose of 0.5 mg per day adopted in this study may have contributed to its safety.

Conclusions

Several medications with potentially anti-inflammatory properties, such as cyclo-oxygenese inhibitor celecoxib, pioglitazone, and rosuvastatin, have been investigated in pilot studies of ICH or early-phase clinical trials,[2] and results are

awaited. To our knowledge, this is the first controlled study of human ICH in which an anti-inflammatory medication, fingolimod, minimized neurologic deficits during the acute stage and promoted neurologic recovery long-term. The effectiveness of fingolimod in reducing PHE, thereby alleviating its mass effect, as well as its direct effect on the CNS, are the proposed mechanisms for this drug's clinical benefit. Importantly, fewer of our patients with ICH who received fingolimod exhibited complications than is commonly seen with other therapies (**Table 3**). Patients treated with fingolimod did better in regaining consciousness, mobility, and normality. Limitations of the current study, such as the open-label design, the small number of patients sampled, and the sex imbalance, precluded drawing any generalizability of our finding. However, our results promote further investigation on this promising strategy to control inflammation and immune responses at selected points in patients with ICH.

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Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Fu, Hao, Sun, Shi.
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