
**OBJECTIVE:** This prospective, open-label study evaluated the efficacy, safety, and tolerability of glatiramer acetate (GA) in treatment-naive relapsing-remitting multiple sclerosis patients and in patients who had previously received interferon-beta (IFN-beta)-1b therapy.

**METHODS:** Two treatment cohorts were defined based on prestudy IFN-beta-1b use. At entry, prior IFN-beta-1b patients (*n* = 247) were older, had longer disease duration, and had higher mean Expanded Disability Status Scale (EDSS) scores, relapse rates, and ambulation indexes than treatment-naive patients (*n* = 558). Safety was assessed every 3 months and EDSS every 6 months for up to 3.5 years.

**RESULTS:** Overall, 247 treatment-naive and 107 prior IFN-beta-1b patients discontinued before study end. Median GA treatment durations were 36 and 24 months in treatment-naive and prior IFN-beta-1b patients, respectively. At last observation, annual relapse rates had declined by 75% in both cohorts (0.42 ± 0.84 and 0.34 ± 0.71 in treatment-naive and prior IFN-beta-1b groups, respectively; *P* = .1482). Mean changes in EDSS were less than 0.5 in both cohorts, regardless of entry EDSS, at 12 and 18 months and at last observation.

**CONCLUSIONS:** Prior IFN-beta-1b treatment does not negatively influence the efficacy, safety, or tolerability of subsequent GA therapy. Switching to GA can benefit patients who discontinue IFN-beta therapy.

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**OBJECTIVE:** To evaluate the relation between T2 lesions and disease severity in relapsing-remitting multiple sclerosis (MS).

**METHODS:** This article describes a 13-year longitudinal study in 30 patients.

**RESULTS:** Patients were 36.3 ± 6.0 years old, had MS for 6.1 ± 5.8 years, Expanded Disability Status Scale (EDSS) score was 2.2 ± 0.8, and brain parenchymal fraction (BPF) was 0.825 ± 0.015 at study entry. At last visit, EDSS score was 4.4 ± 1.95, Multiple Sclerosis Functional Composite was -0.34 ± 1.7, and BPF was 0.774 ± 0.037. Baseline T2 lesion volume correlated with the BPF of the last visit (*r* = -0.66; *P* < .0001), magnetization transfer ratio (MTR) in normal-appearing brain tissue (*r* = -0.52; *P* = .004), and lesion MTR (*r* = -0.76; *P* < .0001). Change in T2 lesion volume in the first 2 years correlated with BPF of the last visit (*r* = -0.40; *P* = .03), normal-appearing brain tissue MTR (*r* = -0.44; *P* = .015), lesion MTR (*r* = -0.46; *P* = .018), Multiple Sclerosis Functional Composite scores (*r* = -0.50; *P* = .005), and Paced Auditory Serial Addition Task scores (*r* = -0.52; *P* = .003). Age was a significant covariate for clinical but not magnetic resonance imaging outcomes.

**INTERPRETATION:** T2 lesions in relapsing-remitting MS correlate strongly with brain tissue loss and brain tissue integrity 13 years later, and with clinical disease severity, although age significantly impacts the clinical correlation. The results provide direct evidence for the disability threshold hypothesis in MS and support monitoring T2 lesions in relapsing-remitting MS.

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Cytokines and chemokines contribute to the pathogenesis of acute disseminated encephalomyelitis (ADEM). Using a multiplex immunochemiluminescence enzyme-linked immunosorbent assay, we measured 8 Th(1)/Th(2)
Autoinjectors were used for all injections. Week dose escalation period and a 12-week maintenance period were recorded at every injection. Dose escalation was slowed to every other day (EOD) with structured dose escalation and adverse event (AE) management in 22 patients (20 interferon beta-1b–naive [ND] and 2 interferon beta-1b–treated [SD]) and 7 healthy controls (HCs). Relative to HCs, ADEM patients had significantly high mean CSF concentrations of chemokines with attractant/activating properties toward neutrophils (CXCL1 and CXCL7), monocytes/T cells (CCL3 and CCL5), Th1 cells (CXCL10), and Th2 cells (CCL1, CCL22, and CCL17). Mean CSF concentrations of CXCL7, CCL1, CCL22, and CCL17 were higher in ADEM than in MS, whereas those of CCL11 were lower in MS than in ADEM and HCs. CSF pleocytosis correlated with CSF concentrations of CXCL1, CXCL10, CCL1, CCL17, and CCL22. Most of the functionally homologous chemokines correlated with each other. CSF Th1/Th2 cytokines were not detectable in most samples. Their mean concentrations did not differ in the 3 groups, and the same held for serum cytokines and chemokines. Our data suggest that the upregulation of chemokines active on neutrophils and Th2 cells differentiates ADEM from MS inflammation, and that both Th1 and Th2 chemokines might be produced in ADEM. Chemokines upregulated in ADEM could become CSF biomarkers after posteriori evaluation in unselected case series.


The approved interferon beta-1b (Betaseron/Betaferon) dose is 250 µg (8 MIU) administered subcutaneously (sc) every other day (eod). Clinical-trial data suggest a dose response effect for interferon beta in multiple sclerosis (MS) treatment and a maximum dose has yet to be established. The interferon Dose Escalation Assessment of Safety (IDEAS) study evaluated the safety and tolerability of interferon beta-1b 500 µg (16 MIU) sc eod with structured dose escalation and adverse event (AE) management in 22 patients [20 interferon beta-1b–treated [SD] and 2 interferon beta-1b–naive [ND]] with relapsing-remitting MS, secondary progressive MS, or progressive relapsing MS. IDEAS comprised an 8-week dose escalation period and a 12-week maintenance period, with modification as clinically warranted. Autoinjectors were used for all injections ≥0.4 mL. Clinical laboratory values were monitored monthly. Baseline and exit assessments included the MS Functional Composite score, Expanded Disability Status Scale, and neutralizing antibody myxovirus protein A assay. AEs were recorded at every injection. Dose escalation ranged from 2 to 12 weeks. Some 91% of patients (20/22) achieved the 500-µg dose and, of these patients, 90% (18/20) completed the maintenance phase. There were no differences in response between ND and SD patients. Most common AEs were decreased general well-being, insomnia, and injection site reactions (mostly mild). The 500-µg dose of interferon beta-1b was well tolerated in the short term with escalation and premedication in these patients, most of whom had previously been receiving 250 µg interferon beta-1b.


**OBJECTIVE:** Dysregulation of the blood-brain barrier (BBB) and transendothelial migration of immune cells are among the earliest central nervous system changes particular in lesion formation in both multiple sclerosis (MS) and its early clinical form, the clinically isolated syndrome. Evidence for the anti-inflammatory effects of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors within the central nervous system arose from studies demonstrating that statins improve clinical signs in the animal model of MS and reduce the number of gadolinium-enhancing lesions in MS.

**METHODS:** We sought to describe the impact of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor treatment on the physiology and immunology of human BBB-derived endothelial cells (ECs).

**RESULTS:** We demonstrate that lovastatin and simvastatin induce a 50% to 60% reduction in the diffusion rates of bovine serum albumin and ([14C])-sucrose across human BBB-ECs in vitro through abrogation of isoprenylation processes, but independent of the expression of the tight junction molecules occludin, VE-cadherin, JAM-1, zonula occluden-1, and zonula occluden-2. Simvastatin and lovastatin were equipotent in reducing BBB permeability and restrict leukocyte migration: relevance to multiple sclerosis.