Rituximab add-on therapy for breakthrough relapsing multiple sclerosis

A 52-week phase II trial

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ABSTRACT

Objective: B cells and the humoral immune system have been implicated in the pathogenesis of multiple sclerosis (MS). This study sought to evaluate the efficacy, safety, and tolerability of add-on therapy with rituximab, a monoclonal antibody that depletes circulating B cells, in subjects with relapsing MS with breakthrough disease defined by clinical and MRI activity (Class III evidence).

Methods: Thirty subjects with a relapse within the past 18 months despite use of an injectable disease-modifying agent, and with at least 1 gadolinium-enhancing (GdE) lesion on any of 3 pretreatment MRIs, received rituximab administered at 375 mg/m² weekly $\times$ 4 doses. Three monthly posttreatment brain MRI scans were obtained beginning 12 weeks after the first infusion. Multiple Sclerosis Functional Composite (MSFC) and Expanded Disability Status Scale (EDSS) were obtained at baseline and throughout the posttreatment follow-up.

Results: GdE lesions were reduced after treatment with rituximab, with 74% of posttreatment MRI scans being free of GdE activity compared with 26% free of GdE activity at baseline ($p < 0.0001$). Median GdE lesions were reduced from 1.0 to 0, and mean number was reduced from 2.81 per month to 0.33 after treatment (88% reduction). MSFC improved as well ($p = 0.02$). EDSS remained stable.

Conclusion: Rituximab add-on therapy was effective based upon blinded radiologic endpoints in this phase II study. In combination with standard injectable therapies, rituximab was well-tolerated with no serious adverse events. B-cell-modulating therapy remains a potential option for treatment of patients with relapsing MS with an inadequate response to standard injectable therapies.

Classification of evidence: This study provides Class III evidence that add-on rituximab reduces gadolinium-enhancing brain lesions in multiple sclerosis. *Neurology*® 2010;74:1860-1867

GLOSSARY

DMT = disease-modifying therapy; **EDSS** = Expanded Disability Status Scale; **FOV** = field of view; **GdE** = gadolinium-enhancing; **HACA** = human antichimeric antibodies; **IgG** = immunoglobulin G; **MS** = multiple sclerosis; **MSFC** = Multiple Sclerosis Functional Composite; **NAbs** = neutralizing antibodies; **PASAT** = Paced Auditory Serial Addition Test; **RRMS** = relapsing-remitting multiple sclerosis; **TE** = echo time; **TI** = inversion time; **TR** = repetition time.

Multiple sclerosis (MS) is an autoimmune disease of the CNS, traditionally regarded as T-cell mediated.¹ Interest in the role of B cells and humoral immunity is supported by presence of antibodies and complement within active MS lesions, ectopic lymphoid follicles and B-cell-related chemokines in the CNS, and intrathecally produced immunoglobulins.²

Rituximab, a chimeric murine/human immunoglobulin G (IgG)₁ κ monoclonal antibody that targets CD20, is exclusively expressed on pre-B and mature B cells. Rituximab lyses circulating B cells while sparing stem cells and mature plasma cells.³ It was approved by the

Supplemental data at
www.neurology.org

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Figure 1 Rituximab study protocol

Food and Drug Administration in 1997 for B-cell lymphoma, and in 2006 for rheumatoid arthritis.^{4,5} Phase I and II studies have demonstrated reductions in MRI and clinical activity when used as monotherapy in patients with relapsing-remitting MS (RRMS) with relatively early disease.^{6,7}

This phase II investigator-initiated trial was designed to study rituximab as add-on therapy in subjects with relapsing MS with inadequate response to standard injectable disease-modifying therapies (DMTs). Pre-planned primary objectives were to examine the effect of rituximab on gadolinium-enhancing (GdE) lesions and to gather information on safety and tolerability. Secondary objectives were to determine the effects of rituximab on the Multiple Sclerosis Functional Composite (MSFC) and Expanded Disability Status Scale (EDSS).

METHODS Standard protocol approvals and patient consents. Approval was granted by the Washington University Human Research Protection Office. All subjects provided informed consent.

Patients. Thirty subjects completed this single-center trial between April 2002 and February 2009. Enrollment criteria were clinically definite RRMS,⁸ age 18–65 years, baseline EDSS ≤ 6.5 , treatment with an injectable DMT for at least 6 months, clinical relapse in the prior 18 months while taking the DMT, and at least 1 GdE lesion on any of 3 monthly pretreatment brain MRI scans. Screening began at least 8 weeks after relapse onset or completion of glucocorticoids.

Subjects were excluded for 1) other medical illness; 2) aspartate aminotransferase, alanine aminotransferase, or creatinine twice normal upper limit; 3) prior use of a major immunosuppressive agent (cyclophosphamide, mitoxantrone, cladribine, na-

talizumab, or any monoclonal therapeutic); or 4) methotrexate or azathioprine treatment within 6 months.

Study design and outcome measures. This MRI-blinded, single-center study of add-on rituximab included 52 weeks post-treatment follow-up. The primary endpoint was reduction in the sum of GdE lesions on serial T1-weighted MRI brain scans at 12, 16, and 20 weeks after treatment, in comparison to 3 monthly MRI scans before treatment (Class III evidence). Brain MRIs were obtained at –8, –4, and 0 weeks to determine eligibility and baseline MRI disease activity (figure 1). This design has been used for phase II studies to determine the short-term effect of study drug upon the MRI surrogate endpoint of disease activity.⁹ Because MRI scans were randomized, GdE lesions which persisted for over 4 weeks were counted more than once. MRI scans were randomized and read blinded by a single reader (R.T.N.) with a coefficient of variation of 0 for GdE number, 0.081 for GdE volume, 0.079 for T2 number, and 0.12 for T2 volume.

Study procedures and endpoints. MSFC was performed per standard protocol at each visit. MSFC practice sets were performed at weeks –8, –7, and –6, followed by study baseline sets at –4, 0, and 1 week.¹⁰ There was no significant difference in the mean and median MSFC performed between the –4 and 0 week timepoints. EDSS was performed by a single examiner (A.H.C.) at weeks –4, 0, 1, 4, 8, 16, 24, 32, and 52. Lumbar punctures were performed at baseline and 24 weeks after treatment.

Subjects continued to take their DMT throughout the study. Rituximab dosing (at weeks 1, 2, 3, and 4) was based upon dosing for B-cell lymphoma (375 mg/m² IV weekly $\times$ 4). Acetaminophen and diphenhydramine were given as pretreatment. Corticosteroids were not used for pretreatment or infusion reactions. New neurologic symptoms were assessed within 14 days.

MRI protocol. Brain MRI scans were obtained at 1.5 T (Sonata, Siemens, Germany) with 5-mm contiguous slices using field of view (FOV) 230 cm and 256 $\times$ 256 matrix. T1-weighted scans were performed with repetition time (TR)/echo time (TE) 539/17 msec, fluid-attenuated inversion recovery with TR/inversion time (TI)/TE 9,200/2,310/108 msec, and T2-weighted scans with TR/TE 3,600/95 msec. The initial study design used triple-dosed gadopentetate dimeglumine (Magnevist[®], Bayer Healthcare, Germany). In 2007, the risk for nephro-

Figure 2 Study protocol

BMT = bone marrow transplant; Gd = gadolinium.

genic systemic fibrosis was reported with high-dose gadolinium.¹¹ The protocol was changed to use single-dose gadobenate dimeglumine (Multihance[®], Bracco Diagnostics, Italy), which is superior to single-dose gadopentetate for lesion conspicuity. Individual subjects completed all 6 scans using the same agent and dose, with 24 subjects receiving triple-dose gadopentetate and 6 receiving single-dose gadobenate.¹²

MRIs were analyzed in sets of 6, randomized by date, with image analysis software (Amira 4.0, Visage Imaging, CA). Regions of interest were drawn manually, with calculation of lesion counts and volumes performed by the software program.

Neutralizing antibodies to β -interferon (NABs) were determined using a viral cytopathic effect assay (Athena Diagnostics, Inc., Worcester, MA). Human antichimeric antibodies (HACA) against rituximab were assayed at baseline and weeks 20 and 28 by Genentech Laboratories using a proprietary ELISA (sensitivity 5 ng/mL). CSF IgG, IgG index, IgG synthesis rate, and blood immune competence panels were performed by the Barnes-Jewish Hospital laboratory. A change in technique for detecting CSF oligoclonal bands occurred during this study. The first 19 CSF pairs were analyzed by isoelectric focusing; the remaining 7 samples by agarose gel electrophoresis.

Statistical analysis. Prestudy power calculations estimated that 30 subjects would provide 80% power to detect a 50% decrease in enhancing lesions, from a mean 4.3 to 2.1 lesions, at the 95% confidence level. The primary outcome was assessed by the nonparametric, paired, signed-rank test. Due to individual variability in the number of lesions, with some individuals having a large number of GdE lesions, each individual set of 3 pre-

treatment and posttreatment MRIs were categorized as having 0, 1, 2, or >2 enhancing lesions.

Role of the funding source. The study protocol was designed by the senior author (A.H.C.). All data were collected, housed, and analyzed on site. Study sponsors had no role in study design, data collection, analysis, interpretation, or in writing the manuscript.

RESULTS Sixty-nine patients were screened and 35 qualified with at least 1 GdE lesion on a baseline scan. Three withdrew consent prior to receiving rituximab. Thirty subjects completed all 4 rituximab infusions with 52 weeks follow-up (figure 2). Two subjects were withdrawn during the first infusion due to infusion reactions.

Subject demographics (table 1) were notable for median age of 43.5 years, disease duration of 7.5 years, DMT treatment duration of 2.5 years, EDSS of 4.0, and mean MS severity score within the worst 30th percentile.

Rituximab reduced gadolinium-enhancing lesions. GdE lesion numbers on brain MRIs decreased after treatment in comparison to pretreatment MRIs (signed-rank test, $p < 0.0001$, table 2). Seventy-four percent of the 3 posttreatment MRI scans were free of enhancing lesions, whereas only 26% of the 3 baseline scans lacked enhancing lesions. No MRI scans done after treatment had >2 enhancing lesions, whereas 32% of individual MRI scans prior to treatment had >2 enhancing lesions (table 2).

The median number of enhancing lesions declined from 1 per month to 0 after treatment. The mean number of enhancing lesions per month prior to treatment was 2.81 compared to 0.33 after treatment, an 88% reduction (figure 3). Mean volume of enhancing lesions per month before treatment was 0.778 cm³, and was 0.036 cm³ after treatment, a 78% decrease.

No differential MRI response was identified after stratification for baseline demographics or disease severity. Demographics included age (90% reduction in GdE in subjects <44 years vs 87% for ≥ 44 years), EDSS (94% reduction in GdE for EDSS ≤ 4.0 vs 72% for >4.0), disease duration (94% GdE decrease for duration ≤ 7 years vs 79% for >7 years), and baseline treatment (86% GdE decrease for IFN vs 94% for GA). Rituximab treatment had no discernible effect upon secondary MRI metrics, including black hole number (10.0 pretreatment vs 10.2 posttreatment), black hole volume (3.0 cm³ pretreatment vs 3.1 cm³ posttreatment), T2 lesion number (27.6 pretreatment vs 26.7 posttreatment), or T2 lesion volume (25.9 cm³ pretreatment vs 24.6 cm³ posttreatment).

Table 1 Baseline characteristics of participants who completed the study

Characteristics	Values
No.	30
Age, y, median (range)	43.5 (20–53)
Gender, F/M	22/8
Disease duration, y, median (range)	7.5 (2.0–32.0)
DMT duration, y, median (range)	2.5 (0.5–13)
Relapses prior 18 mo, total; median (range)	57; 2 (1–4)
Annualized baseline relapse rate	1.27
EDSS, mean; median (range)	4.7; 4.0 (2–6.5)
PASAT, median (range)	43 (9.5–60.0)
25FTW, s, median (range)	8.55 (4.4–56.7)
9HPT, s, median (range)	
Dominant	27.0 (16.8–125.0)
Nondominant	25.8 (15.8–77.5)
MRI T2, n	
Median (range)	22.0 (3–83)
Mean $\pm$ SE	27.58 $\pm$ 1.94
MRI T2 volume, cm ³	
Median (range)	21.88 (4.90–72.55)
Mean $\pm$ SE	25.87 $\pm$ 17.24
MRI gadolinium, n	
Median (range)	1 (0–20)
Mean $\pm$ SE	2.81 $\pm$ 0.41
MRI gadolinium volume, cm ³	
Median (range)	0.22 (0–10.18)
Mean $\pm$ SE	0.78 $\pm$ 0.19
MRI T1H, n	
Median (range)	7 (0–49)
Mean $\pm$ SE	9.99 $\pm$ 0.95
MRI T1H volume, cm ³	
Median (range)	1.59 (0–26.33)
Mean $\pm$ SE	3.02 $\pm$ 0.50
MS treatment, n	
Interferon β 1a IM	7
Interferon β 1b SC	13
Glatiramer acetate	6
Interferon β 1a SC	4
Pre-Tx CD19, % B cells in blood	16.3 $\pm$ 6.4
Pre-Tx CD3, % T cells in blood	75.9 $\pm$ 6.8
CSF IgG index, median (range)	0.69 (0.44–7.20)
CSF oligoclonal bands, median (range)	
IEF	4 (0–9)
AGE	6 (0–11)
CSF IgG synth rate (mg/24 h), median (range)	3.7 (0.0–68.3)

Abbreviations: 9HPT = 9-Hole Peg Test; 25FTW = 25-Foot Timed Walk; AGE = agarose gel electrophoresis; DMT = disease-modifying therapy; EDSS = Expanded Disability Status Scale; IEF = isoelectric focusing; IgG = immunoglobulin G; MS = multiple sclerosis; PASAT = Paced Auditory Serial Addition Test.

Predefining a positive individual response as $\geq 50\%$ reduction in GdE after treatment, 25 of the 30 subjects were responders. Of the 5 nonresponders, 3 had an increase in GdE lesions following treatment: from 3 pretreatment to 4 posttreatment GdE lesions, from 1 to 3 GdE lesions, and from 1 to 2 GdE lesions. The remaining 2 nonresponders had lesser degrees of GdE lesion reduction of 33% (3 GdE lesions to 2) and 25% (4 to 3).

This study was not designed or powered to examine relapse rate reduction. However, 57 relapses occurred in the 18 months prior to the study in the 30 enrolled subjects, yielding an annualized baseline relapse rate of 1.27. Seven confirmed relapses in 7 subjects occurred during the 52-week study, yielding an annualized relapse rate of 0.23 following treatment. On-study relapses were treated with IV glucocorticoids in 3, oral glucocorticoids in 2, and IV immunoglobulin infusions (5 infusions of 400 mg/kg/day) in 1 case. One sensory exacerbation was not treated. Two treated relapses each occurred 8 weeks before the first posttreatment MRI. The other 4 occurred after the sixth MRI scan.

MSFC improved over baseline after 32 weeks. Comparing mean MSFC at weeks -4 , 0 , and 1 (pretreatment) to mean MSFC at weeks 24 , 28 , and 32 (posttreatment), times when all subjects remained B-cell depleted in blood, the MSFC improved by $+0.093$ z score ($p = 0.02$; 95% confidence interval 0.018 – 0.17). Improvement was largely due to changes in Paced Auditory Serial Addition Test (PASAT) scores; median PASAT score improved from baseline and remained higher throughout the study ($p = 0.009$ for comparing PASAT between weeks 0 and 32 , $p < 0.05$ between weeks 0 and 52); 25-Foot Timed Walk and 9-Hole Peg Test did not change significantly over the course of the study.

EDSS remained stable 32 weeks after treatment. After rituximab, the EDSS improved in 7 subjects, remained the same in 21 subjects, and worsened in 2. A sustained change in EDSS was based upon comparing the baseline to week 32, with confirmation at week 52, utilizing a 1.0-point change from EDSS < 5.5 or a 0.5-point change from EDSS ≥ 5.5 .

CSF B and T cells did not predict or correlate with MRI response. No relation was found between CSF B-cell and T-cell counts and MRI outcome. No relationship between baseline number of enhancing lesions and number of B cells or T cells in the CSF at baseline was seen. Likewise, there was no correlation between MRI posttreatment and CSF B-cell or T-cell numbers posttreatment. The individual reduction in enhancing lesions was not predicted by the reduction of CSF B cells or T cells after treatment.

Table 2 MRI scans categorized by number of enhancing lesions^a

Scan time relative to rituximab	Total no (%) of gadolinium-enhancing lesions per scan				Total
	0	1	2	>2	
Pre-rituximab	23 (26)	26 (29)	12 (13)	29 (32)	90
Post-rituximab	67 (74)	16 (18)	7 (8)	0 (0)	90
Total	90	42	19	29	180

^a For each of 30 individuals, 3 baseline scans and 3 posttreatment scans were obtained.

CSF oligoclonal bands, IgG index, and IgG synthesis rate did not predict or correlate with MRI response. They also did not correlate with baseline Gd contrast lesion number.

Rituximab did not impact neutralizing antibodies to β -interferon. NAb (titer >1:20) were detected in 10 subjects on interferon for a median 4 years. Of 6 subjects with positive titers at baseline, 2 subjects reverted to normal, 2 declined, and 2 remained unchanged after rituximab. Four subjects developed NAb after treatment (table e-1 on the *Neurology*[®] Web site at www.neurology.org).

HACA to rituximab were tested prior to and at weeks 20 and 28 after treatment. Four subjects (13%) tested positive for HACA after study drug. One subject became HACA-positive at both post-treatment timepoints. Three subjects were HACA-positive only at week 28, with unconfirmed persistence. All 4 demonstrated complete B-cell

depletion after treatment and none were MRI nonresponders.

Adverse events. Infusion reactions led to discontinuation in 2 subjects. One had shortness of breath that remitted upon stopping the infusion, requiring no further intervention. The second subject developed increased muscle spasms associated with fever during the infusion, and was treated with oral prednisone. Eleven additional subjects of the 30 who completed the study had minor infusion reactions that did not preclude additional infusions, consisting of fever, chills, flushing, itching of body or throat, and/or diarrhea.

Additional adverse events with unknown relation to study medication included 4 uncomplicated urinary tract infections in 4 subjects, and 1 episode each of transient mild thigh pain, presumed viral upper respiratory tract infection, uncomplicated bronchitis treated with antibiotics, hand tendonitis, and recurrence of prior dizziness.

DISCUSSION This phase II study showed a significant radiologic benefit of rituximab on relapsing MS, including subjects with moderate to severe disability. Rituximab add-on therapy in subjects with breakthrough disease activity on DMT was associated with an 88% reduction in GdE lesion counts compared to baseline. Reduced numbers of GdE lesions were noted regardless of

Figure 3 Reduction in mean number of enhancing lesions after rituximab

CI = confidence interval.

age, disease duration, or EDSS. Rituximab add-on therapy was associated with reduction in annualized relapse rate from 1.27 to 0.23 and improvement on PASAT. Infusion reactions were typically mild, but resulted in 2 study discontinuations.

This study enrolled subjects with active brain MRIs, using a design similar to other published studies examining short-term antiinflammatory treatment effects from pretreatment to posttreatment.^{13,14} Although GdE lesion numbers might be expected to diminish over time due to natural regression, the decline herein exceeded what has been reported for similar patients with relapsing MS. Natural history studies suggest GdE lesion reduction to be 30%–50% over 9 months, but the reduction in mean enhancing lesions by 88% surpassed that expectation.¹⁵ Another natural history study indicated that 30%–40% of subjects followed with monthly MRIs for 6 months might demonstrate a 50% reduction in GdE lesion numbers over the last 3 MRIs, but in the present study 80% of subjects declined by 50% or more.¹⁶ Also, no spontaneous regression in GdE lesions was seen in another trial that, like the present trial, required 1 enhancing brain MRI lesion for entry and incorporated monthly MRIs over 9 months.¹⁷ Moreover, in the present study, no regression in mean GdE lesion number was seen during the 3 pretreatment MRI scans, whereas a clear reduction was observed beginning with the first posttreatment MRI scan at 12 weeks that was sustained throughout all 3 posttreatment scans (figure 3).

The population enrolled in this study was different from 2 other early-phase trials of rituximab in relapsing MS. Compared to a placebo-controlled phase II trial of rituximab that reported a reduction of GdE lesions (91%),⁷ this study enrolled a more disabled and older population based upon median baseline EDSS of 4.0 (vs 2.5 in the placebo-controlled study), average baseline age of 43.5 years (vs 39.6 years), and with a longer disease duration of 7.5 years (vs 6.2 years in the placebo-controlled study). In another open-label study of 26 subjects with active RRMS given rituximab, GdE counts declined by 95% over 48 weeks.⁶ Subjects in that study were also younger (mean age 40.4 years) and less disabled (mean EDSS of 2.3 ± 0.9). In the present study, 20% of subjects used a cane at baseline (EDSS = 6.0), and another 20% required bilateral assistance (EDSS = 6.5), levels of disability that are excluded by many RRMS trial designs.^{6,7} Another important difference in the present trial is that rituximab was given in combination with standard DMT, not as monotherapy. Use of rituximab as an add-on therapy led to apparent additional benefit based on the blinded MRI results.

Accumulating evidence implicates a pathogenic role for B cells in MS. Elevated intrathecal immunoglobulin production occurs in >90% of patients with MS, with higher levels correlating with worse prognosis.^{18–20} B cells, plasma cells, and immunoglobulin are present in active MS lesions, and have been identified in normal-appearing white matter of MS autopsies.^{21–23} However, in the present study little evidence was found to support that a beneficial effect from B-cell depletion was due to reduction in antibodies, as CSF IgG levels did not change greatly at 24 weeks posttreatment. Notably, the major sources of immunoglobulins are plasma cells, which do not express CD20 and can live for months to years.²⁴ Because plasma cells are replenished by memory B cells, a prolonged B-cell depletion should eventually impact immunoglobulin levels.²⁵

B cells are highly effective antigen-presenting cells, expressing major histocompatibility complex II constitutively and costimulatory B7 molecules upon activation. B-cell surface receptors provide for efficient uptake of their target antigen, even at low concentration.^{26,27} B cells bearing receptors that recognize myelin components may be pathogenic in MS through focused uptake, processing, and presentation of myelin antigens to T cells. In this study, B cells were depleted in both blood and CSF, and thus any effect on T-cell activation may have occurred in the periphery, the CNS, or both.²⁸ B cells also influence the immune response via production of cytokines and chemokines.²⁸

A pressing need for biomarkers to select and monitor therapeutic agents for MS exists. In this study, 5 subjects had an MRI response $\leq 50\%$, and an additional 2 had a sustained EDSS worsening. Unexpectedly, neither CSF B-cell nor T-cell levels at baseline, nor changes in these cells after treatment, were correlated with treatment effect. Likewise, baseline IgG concentration, IgG index, and oligoclonal band number did not correlate with MRI response. The present study did identify a decline following treatment of 2 chemokines in CSF, CXCL13 and CCL19, that might be related to beneficial effects (data not shown).

This study has several limitations. Although the primary MRI endpoint was blinded, this study was open label with no control group. Neurologic assessments and relapse rate determinations were not blinded. Whether the benefit of rituximab was additive or synergistic with the injectable DMT is unclear.⁷ In other diseases, progressive multifocal leukoencephalopathy has been reported following rituximab treatment. Whether rituximab itself or in combination with DMT increases risk of PML or

other opportunistic infection in the MS population is unknown.

By targeting B cells, rituximab would provide a therapeutic option with a unique mechanism of action. Heterogeneity in MS lesion pathogenesis may require individually tailored therapeutics, especially in nonresponders to standard DMTs.²⁹ Although rituximab specifically depletes B cells, T-cell responses are indirectly affected.^{28,30} The T-cell and B-cell effector arms of the adaptive immune system are interdependent and, along with other cell types and soluble mediators, orchestrate immune responses in MS. This study supports B-cell modulation as a prime therapeutic target in relapsing MS.

AUTHOR CONTRIBUTIONS

Statistical analysis was conducted by Dr. K. Trinkaus.

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DISCLOSURE

Dr. Naismith has received travel expenses and/or honoraria for lectures and educational activities from Bayer Schering Pharma, Biogen Idec, Teva Pharmaceutical Industries Ltd., and Elan Corporation; serves on speakers' bureaus for Bayer Schering Pharma, Biogen Idec, Elan Corporation, and Teva Pharmaceutical Industries Ltd.; and receives research support from Acorda Therapeutics Inc., the NIH (K23NS052430-01A1 [PI] and K12RR02324902 [PI]), and the National MS Society. Dr. Piccio has received speaker honoraria from Teva Pharmaceutical Industries Ltd. and has received research support from the National Multiple Sclerosis Society USA and Federazione Italiana Sclerosi Multipla. Dr. Lyons, J. Lauber, and N.T. Tutlam report no disclosures. Dr. Parks serves on a speakers' bureau for Biogen Idec; has served as a consultant for and received speaker honoraria from Bayer Schering Pharma, Biogen Idec, Teva Pharmaceutical Industries Ltd., Merck Serono, and Pfizer Inc.; and receives research support from BioMS Medical, Novartis, and Pharmaceutical Industries Ltd. Dr. Trinkaus reports no disclosures. Dr. Song has received research support from the National MS Society USA and the NIH (NINDS R01 NS047592 [PI], R01 NS054194 [PI], and P01-NS 059560 [Co-I]). Dr. Cross serves on scientific advisory boards for Eli Lilly and Company, Genentech, Inc., and Biogen Idec; serves on the editorial boards of *Brain Pathology* and the *Journal of Neuroimmunology* and as an editor and contributor to *CONTINUUM*; receives royalties from the publication of *Handbook of Multiple Sclerosis, 4th Ed.* (Taylor & Francis Group, 2006); serves on speakers' bureaus for Bayer Schering Pharma and Biogen Idec; has received speaker honoraria from Amgen and Pfizer Inc.; and receives research support from Sanofi-Aventis, Acorda Therapeutics Inc., Genentech Inc., Biogen Idec, the NIH (NINDS P01 NS059560-01 [PI], NINDS U01 NS45719-01A1 [Co-I], R01 NS047592 [Co-I], NINDS R01 NS 051591 [PI]), ICTS Washington University, the National MS Society USA, Consortium of Multiple Sclerosis Centers, and the Barnes-Jewish Hospital Foundation; and holds stock in Affymetrix, Inc.

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