Use of the brain parenchymal fraction to measure whole brain atrophy in relapsing-remitting MS

R.A. Rudick, MD; E. Fisher, PhD; J.-C. Lee, MS; J. Simon, MD, PhD; L. Jacobs, MD; and the Multiple Sclerosis Collaborative Research Group*

Article abstract—*Background:* Episodic inflammation in the CNS during the early stages of MS results in progressive disability years later, presumably due to myelin and axonal injury. MRI demonstrates ongoing disease activity during the early disease stage, even in some patients who are stable clinically. The optimal MRI measure for the destructive pathologic process is uncertain, however. *Methods:* In this post-hoc study, MRI scans were analyzed from patients with relapsing MS participating in a placebo-controlled trial of interferon β-1a. The brain parenchymal fraction, defined as the ratio of brain parenchymal volume to the total volume within the brain surface contour, was used to measure whole brain atrophy. The relationship between disease features and brain atrophy and effect of interferon β-1a were determined. *Results:* MS patients had significant brain atrophy that worsened during each of 2 years of observation. In many patients, brain atrophy worsened without clinical disease activity. Baseline clinical and MRI abnormalities were not strongly related to the rate of brain atrophy during the subsequent 2 years. Treatment with interferon β-1a resulted in a reduction in brain atrophy progression during the second year of the clinical trial. *Conclusions:* Patients with relapsing-remitting MS have measurable amounts of whole brain atrophy that worsens yearly, in most cases without clinical manifestations. The brain parenchymal fraction is a marker for destructive pathologic processes ongoing in relapsing MS patients, and appears useful in demonstrating treatment effects in controlled clinical trials. **Key words:** MS—MRI—Brain atrophy—Interferon beta.

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Individual MS patients face an unpredictable future during the relapsing-remitting stage of the disease, because severity is highly variable and accurate predictors of long-term outcome are lacking. Recurrent inflammation in optic nerves, brain, and spinal cord damages myelin and axons, leading to intermittent neurologic symptoms initially, and progressive disability later in the disease. Over 50% of patients with relapsing-remitting MS (RRMS) enter the secondary progressive disease stage, which is associated with more continuous physical, neuropsychologic, and socioeconomic decline. Clinical features during the early relapsing-remitting stage are not very accurate in predicting when an individual patient will enter the secondary progressive disease stage.

The poor predictive value of clinical features during RRMS may relate to ongoing subclinical disease activity, evident on MRI. Serial MRI scans demonstrate that new lesions occur 5 to 10 times as often as clinical relapses.[1-3] The predictive value of MRI-based disease markers has been studied for T2 hyperintense lesions. It was shown that the volume of T2 hyperintense lesions seen on cranial MRI scans at the time of first symptoms predicted subsequent clinical disease progression.[4] This supports the use of MRI as a surrogate marker in MS, but the optimal MRI measure is unknown.

Recent studies of patients in the relapsing stage of MS suggest an ongoing destructive pathologic process. MR spectroscopy demonstrated reduced brain levels of the neuronal marker N-acetylaspartate, suggesting neuronal involvement early in the disease.[5] Histopathologic studies demonstrated large numbers of transected axons at the sites of inflammatory lesions in brains from patients dying from MS, irrespective of the disease duration in the individual patients.[6] Conceivably, progressive loss of brain and spinal cord tissue in MS patients begins at disease onset. This possibility was supported by a recent report of increasing brain ventricle size and decreasing corpus callosum area and brain width during 1- and 2-year intervals in RRMS patients.[7] These findings indicate the need for a sensitive surrogate marker of the underlying destructive process

*See the Appendix on page 1703 for a listing of members of the Multiple Sclerosis Collaborative Research Group.

From the Departments of Neurology (Mellen Center) (Dr. Rudick), Biomedical Engineering (Dr. Fisher), and Biostatistics and Epidemiology (J.-C. Lee), Cleveland Clinic Foundation, Cleveland, OH; the Department of Radiology–MRI (Dr. Simon), University of Colorado Health Sciences Center, Denver, CO; and the Department of Neurology (Dr. Jacobs), Buffalo General Hospital, Buffalo, NY.

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Address correspondence and reprint requests to Dr. Rudick, Area U100, Mellen Center, Cleveland Clinic Foundation, Cleveland, OH 44195.

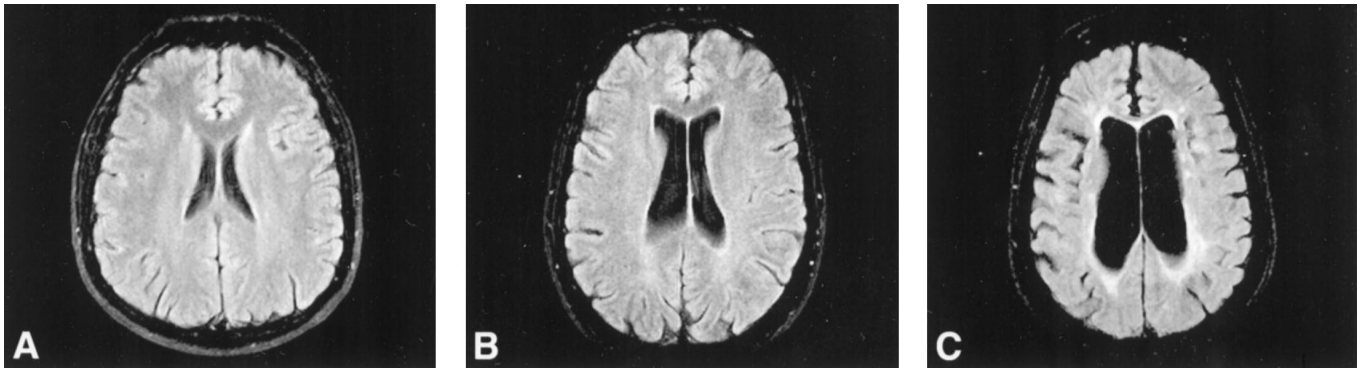

Figure 1. Axial cranial MRI in three individuals shows increasing ventricular size with decreasing brain parenchymal fractions (BPF). (A) A 31-year-old healthy man, BPF 0.87. (B) A 36-year-old woman with relapsing remitting MS, 2 years' disease duration, BPF 0.85 (Z-score = −2.6). (C) A 43-year-old woman with secondary progressive MS, 19 years' disease duration, BPF 0.71 (Z-score = −20.8).

that could be used during the early stages of MS to follow groups of patients and to ascertain therapeutic effects.

Interferon beta (IFNβ) has been shown to reduce the frequency and severity of relapses in MS patients, to reduce the progression of neurologic disability, to reduce the frequency of gadolinium enhancing lesions, and to reduce progressive accumulation of T2 hyperintense lesions.[8-11] The effect of IFNβ on the destructive pathologic process is unknown, however. We applied a new reproducible method to quantify whole brain atrophy in relapsing MS patients who participated in the IFNβ-1a (Avonex; Biogen, Inc., Cambridge, MA) clinical trial.

Methods. *Clinical trial.* We used a double-blind, placebo-controlled, randomized design.[12] A total of 301 patients were enrolled at four US sites. Patients had relapsing MS with mild disability (baseline Expanded Disability Status Scale scores (EDSS)[13] from 1.0 through 3.5), and at least two documented clinical relapses in the 3 years prior to study entry. Study patients were evaluated clinically every 6 months and at the time of new neurologic symptoms, and yearly with MRI. Patients also had CSF analysis at entry into the study and at year 2. Treatment consisted of weekly intramuscular IFNβ-1a, 30 mcg (6.0 million international units), or placebo for up to 104 weeks. IFNβ-1a is a natural sequence, glycosylated, recombinant interferon (Avonex). Patients also received standard medical care including treatment of relapses with IV methylprednisolone.

As planned in advance of the study, patients had variable lengths of follow-up, because the primary outcome measure—time to the onset of disability progression—was based on a survival analysis. The primary outcome was defined as an arm to arm comparison of the time to the onset of at least one point worsening from baseline EDSS, lasting at least 6 months. A total of 172 patients were followed on the study for at least 2 years. The remaining 129 patients were followed for less than 2 years, and were not considered for this study.

Cranial MR scans were obtained yearly using a standardized high-field imaging protocol.[10] Five-millimeter interleaved (nongapped) dual-echo spin-echo series were acquired with intermediate and stronger T2 weighting (repetition time [TR] 2000, echo time [TE] 30,90 msec) through the brain, with a 192 × 256 matrix, a 24-cm field of view, and one excitation. This was followed by a pre- and postcontrast-enhanced T1-weighted axial spin echo series with TR/TE 600/20, with otherwise similar parameters. Volume of T2 lesions, the number and volume of enhancing lesions following injection of gadolinium DTPA, and the volume of T1 hypointensities (black holes) were calculated. The numbers of new and enlarging T2 lesions were determined by comparing MR scans at year 2 with the baseline scans.[14]

Controls. Data from healthy controls were not acquired as part of the original IFNβ-1a study. Therefore, normative data acquired during a separate pilot study were used. MRI were acquired from 16 healthy controls with age and gender distribution similar to the MS patients. The imaging protocol included a T2-weighted fluid attenuated inversion recovery (FLAIR) sequence with 5-mm–thick contiguous slices, 256 × 256 matrix size, and 24-cm field of view.

Image analysis methods. Whole brain atrophy was measured using an automated image analysis method that incorporated a three-dimensonal segmentation algorithm designed for brain surface detection and brain volume calculation.[15] Based on the segmentation, a normalized measure of atrophy, the brain parenchymal fraction (BPF), was calculated as the ratio of brain parenchymal tissue volume to the total volume contained within the brain surface contour (figure 1).

The brain segmentation algorithm was evaluated to determine the accuracy and reproducibility of the brain volume measurements (manuscript in preparation). Application of the algorithm to phantom images of known volumes resulted in a mean absolute error $< 1.1\%$. We also compared automatically generated brain contours to manually traced contours. The mean interclass correlation coefficient between the contours was 0.833 and the mean similarity index between automatically segmented brain and manually segmented brain was 0.95, indicating excellent agreement. To determine the reproducibility of the method, six MS patients and six healthy volunteers had three separate MRI scans within 1 week. BPF was calculated for each image set. Reproducibility was determined

Table 1 *Characteristics of the patients included in this study*

Patient characteristics at baseline	MS		Controls, n = 16
	Interferon β-1a, n = 68	Placebo, n = 72	
Age, y	36.5 (7.2)	36.4 (7.1)	32.3 (7.1)
Percent women	76.5	75	69
Prestudy disease duration, y	6.6 (5.8)	6.2 (5.5)	NA
Prestudy annual relapse rate	1.1 (0.46)	1.1 (0.51)	NA
EDSS score	2.32 (0.79)	2.38 (0.91)	NA
T2 lesion volume, mL	14.2 (16.1)	16.3 (14.7)	NA
(%) With ≥1 enhancing lesions	32/66 (48.5)	38/72 (52.8)	NA
Enhancing lesions, n	3.3 (9.2)	2.3 (4.6)	NA
Volume of T1 black holes, mL	1.38 (1.69)	1.70 (2.24)	NA

Values are mean (±SD) or percent.
NA = not applicable; EDSS = Expanded Disability Status Scale.

by calculating a coefficient of variation (CV) (100% × standard deviation/mean) between the repeated measurements. The mean CV for BPF in this group was 0.19%.

The original image analysis algorithm was modified to analyze dual echo T2-weighted images from the IFNβ-1a study, as FLAIR images were not available in the IFNβ-1a study. A combined image was generated from the dual echo T2 series by subtracting the late echo image from the early echo image in order to achieve similar tissue contrast as in FLAIR images. To determine whether this yielded results that differed from FLAIR images, we imaged six healthy controls repeatedly with both FLAIR images and with dual-echo T2 images. BPF calculated from the two protocols did not differ significantly (FLAIR mean BPF = 0.867 ± 0.008; dual echo mean BPF = 0.864 ± 0.006; p = 0.22). Reproducibility obtained with the dual echo T2 image series was also similar to that achieved with the FLAIR images (mean CV = 0.17%).

MRI data from patients in the IFNβ-1a trial were transferred in digital format from the University of Colorado Health Science Center to the Cleveland Clinic Foundation. Both University of Colorado investigators and Cleveland Clinic investigators were masked to treatment arm until after the image analysis had been completed. Each image set was checked and incomplete image sets or images with inconsistent gaps between the slices were omitted from further processing. The dual-echo spin-echo image series were used to measure atrophy. Before calculation of BPF, images were preprocessed to eliminate effects of nonuniform intensity. Image sets from each patient's year 1 and year 2 visits were then normalized to the grayscale range of the patient's baseline image set using a linear transformation. BPF was calculated in each of the volumetric image sets and contours from the segmentation were displayed to visually verify the results. No editing or manipulation of the segmentation results was performed.

Statistical analysis. Student's t-tests were used to compare baseline and percent changes in BPF between placebo and IFNβ-1a treatment groups, and between MS patients and healthy controls. Effect of treatment was evaluated using analysis of covariance adjusting for baseline covariates. Percent changes in BPF were studied according to the number of relapses and changes in Kurtzke EDSS using analysis of variance. Spearman rank correlations were used to measure associations between baseline BPF and other baseline factors. Multiple regression analysis was used to evaluate the relationship between percent change in BPF and baseline or on-study characteristics, using a forward stepwise procedure. A p value of 0.15 was required for a variable to be included in the model and a p value of 0.05 was required to retain the variable in the final model.

Results. *Patients included in this study.* In the original clinical trial, 172 patients (placebo, 87; IFNβ-1a, 85) completed the year 2 study visit. Of these patients, 140 (81.4%) (placebo, 72; IFNβ-1a, 68) had MR scans at all three time points and were included in this study. Clinical and MR characteristics of the study participants were representative of the entire study population and cases were well matched in the IFNβ-1a and placebo groups (table 1).

BPF at baseline. BPF was lower in MS patients compared with the healthy control group ($p < 0.0001$) (table 2). The BPF in MS patients was more than five standard deviations below the mean of the healthy control group. Of 140 patients, 135 (96%) had baseline BPF at least two standard deviations below the mean of the healthy controls. BPF in placebo and IFNβ-1a patients was not different ($p = 0.81$). There were no significant correlations between baseline BPF and prestudy relapse rate, number or volume of gadolinium enhancing lesions, CSF free kappa chains, or CSF leukocyte counts. Baseline BPF was

Table 2 *Brain parenchymal fraction (BPF) at the baseline visit*

Group	BPF, mean (±SD)	Z Score*	Significance†
Interferon β-1a, n = 68	0.831 (0.015)	−5.10	0.0001
Placebo, n = 72	0.830 (0.019)	−5.18	0.0001
Healthy controls, n = 16	0.871 (0.008)	0	—

* Z Score = Number of standard deviation units from the mean of the healthy controls.
† Differences compared with healthy controls. The interferon β-1a group and the placebo group did not differ ($p = 0.81$).

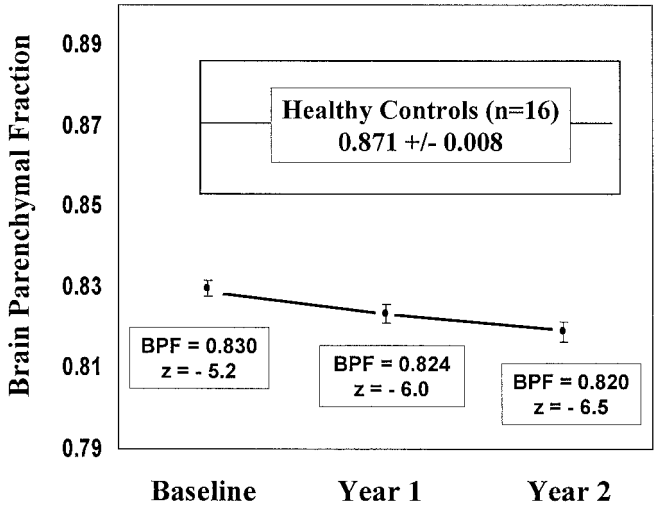

Figure 2. Mean (standard error) brain parenchymal fraction (BPF) at baseline, year 1, and year 2 in placebo patients (n = 72). The mean (±2 SD) of the healthy control group is shown as a reference. The BPF at baseline in the MS patients is lower than in the healthy controls ($p < 0.0001$*). BPF at year 1 in the MS patients is significantly (*$p < 0.0001$*) lower than at baseline; BPF at year 2 is significantly (*$p < 0.0001$*) lower than at year 1.*

correlated with age (Spearman $r = -0.17$, $p = 0.04$), disease duration (Spearman $r = -0.286$, $p < 0.001$), EDSS (Spearman $r = -0.29$, $p < 0.001$), baseline volume of T2 lesions (Spearman $r = -0.49$, $p < 0.001$), and baseline volume of T1 black holes (Spearman $r = -0.49$, $p < 0.001$).

Atrophy progression in placebo patients. Placebo patients had a progressive decrease in BPF during each year of observation (figure 2). Between the baseline and year 1, BPF decreased from 0.83 ± 0.019 to 0.824 ± 0.021 (percent change −0.699 ± 0.92) ($p < 0.0001$). BPF decreased again during the second year to 0.820 ± 0.022 (percent change −0.52 ± 0.80) ($p < 0.0001$). Percent change in BPF in 2 years was −1.22 ± 1.30 ($p < 0.0001$). The BPF decreased by more than 0.5% in 68% of the placebo patients, by more than 1% in 52.7% of the placebo patients, and by more than 2% in 19.4% of placebo patients (figure 3).

Predictors of brain atrophy. Multiple regression models were used to evaluate the relationship between baseline characteristics in the placebo group and percent change in BPF between baseline and year 2. The following factors were found to not relate to change in BPF: age, gender, duration of disease, prestudy relapse rate, baseline EDSS, baseline number of gadolinium enhancing lesions, baseline volume of T1 black holes, or baseline BPF. Baseline T2 volume was inversely correlated with percentage change in BPF ($p = 0.015$), but accounted for only 8.2% of the variance in progressive brain atrophy. BPF at the baseline visit or change in BPF during 2 years did not differ in male and female placebo patients.

On study correlates of atrophy. Multiple regression analysis was used to evaluate the relationship between clinical and MR measures of disease activity in the placebo patients and change in BPF during the 2-year follow-up. The following factors were found to not relate to progressive atrophy during 2 years: change in EDSS between baseline and 2 years, the number of clinical relapses during 2 years, the frequency of corticosteroid use in 2 years, the number of new or enlarging T2 lesions during 2 years, the total number of gadolinium enhancing lesions in 2 years, and the change in the volume of T1 black holes between baseline and 2 years. Change in T2 volume between baseline and year 2 was inversely correlated with percent change in BPF ($p = 0.05$).

The relationship between clinical measures and atrophy progression was determined in the 140 patients in the study. A subgroup of patients with high levels of clinical disease activity had higher rates of brain atrophy over 2 years. Fifty-six patients with three or more relapses during 2 years had greater percent change in BPF compared with 84 patients with less than two relapses (−1.46 ± 1.60 versus −0.83 ± 0.91; $p = 0.01$). Twenty-two patients with at least two points worsening on the EDSS had high percent change in BPF compared with 117 patients with less than two points worsening (−2.06 ± 1.72 versus −0.94 ± 1.07; $p < 0.001$). Among the 84 patients (60%) with less than two clinical relapses or 118 patients (85%) with less than two points worsening on the EDSS, there was no correlation between the clinical measures and change in BPF.

Effect of treatment with IFNβ-1a. Percent change in BPF was similar ($p = 0.71$) during the first year in the IFNβ-1a group (−0.76 ± 1.11) and the placebo group (−0.699 ± 0.92) (figure 4). In the second year, change was less ($p = 0.03$) in the IFNβ-1a group (−0.233 ± 0.74) compared with the placebo group (−0.521 ± 0.80). This

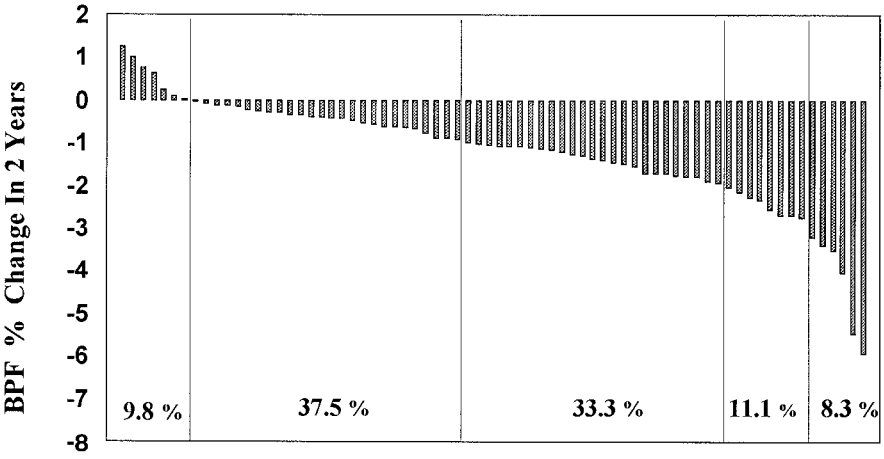

Figure 3. Percent change in brain parenchymal fraction (BPF) between baseline and year 2 for each placebo patient. A total of 9.8% of the patients increased and 90.2% decreased. A total of 37.5% of the patients decreased between 0 and 1%; 33.3% of the patients decreased between 1% and 2%; 11.1% of the patients decreased between 2% and 3%; and 8.3% of the patients decreased by more than 3%.

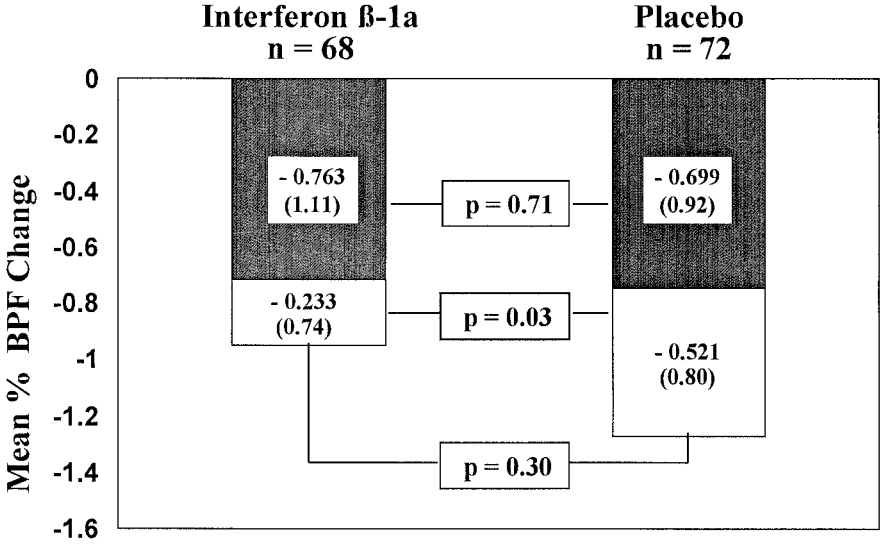

Figure 4. Change in brain parenchymal fraction (BPF) according to treatment arm in the interferon β-1a clinical trial. The rate of brain atrophy in year 1 (solid bars) was not affected by treatment arm, but there was significantly less brain atrophy in interferon β-1a patients during the second year (open bars).

represented a 55% reduction in the rate of brain atrophy during the second year in the IFNβ-1a group compared with the placebo group. Over 2 years of follow-up, percent change in BPF was 18% less in the IFNβ-1a group compared with the placebo group (-0.996 ± 1.22 versus -1.22 ± 1.30), but this was not statistically significant ($p = 0.30$). Treatment group difference in the second year remained after adjusting for baseline age, disease duration, prestudy relapse rate, EDSS, number of gadolinium enhancing lesions, and T2 volume (group differences year 1, $p = 0.49$; year 2, $p = 0.03$; and baseline to year 2, $p = 0.35$).

We evaluated whether the use of corticosteroid might account in part for the treatment arm effect observed in the second year of the clinical trial. Patients who received corticosteroids within 20 or 40 days of an MRI scan were removed, and the analysis repeated. Eight patients who had steroid treatment within 20 days of an MRI scan and 16 patients who had steroid treatment within 40 days of an MRI scan were removed. In both cases, repeat analysis of the remaining patients showed a statistically significant treatment effect in favor of IFNβ-1a in the second year of the study. Thus, corticosteroid use did not account for the observed differences between the IFNβ-1a and placebo groups in the second year of the study.

Discussion. Most prior studies of CNS atrophy in MS patients have used measures of atrophy applied to regions of interest, and have included patients with more advanced disease.[16-19] The only prior atrophy study in relapsing MS patients used linear measures of ventricular size and brain width, and corpus callosum area, to document focal atrophy.[7] That study found increased ventricular size and decreased brain width and corpus callosum area at 1 year and at 2 years in the same placebo patients analyzed here. We applied a new quantitative measure of global brain atrophy, the BPF, to this patient cohort.

BPF was defined as the ratio of brain parenchymal volume to total brain volume. We believe there are two inherent advantages in this approach to quantifying whole brain atrophy. First, normalizing brain parenchymal volume to brain size reduced variability that is caused by individual variation in brain size. For example, the CV between healthy individuals was approximately 6% for the brain parenchymal volume, but was 0.9% for the BPF. Reduced variability between individuals would be expected to improve power to detect significant changes in longitudinal studies.[20] Second, the BPF has high test–retest reproducibility. We believe this is because errors introduced during repeat image acquisition are present in both the numerator and denominator and therefore cancel out. The combination of excellent precision, low normal individual variability, and high accuracy should make the BPF well suited for detecting small amounts of change in longitudinal studies, and for detecting treatment effects.

At the beginning of the study, the patients had average disease duration of 6.5 years and average EDSS scores of 2.4. Despite being early in the disease and having only mild clinical disability, mean BPF in these patients was more than five standard deviations below the mean of healthy age- and gender-matched controls, and atrophy increased significantly in placebo patients at each year of follow-up. Strong correlates of brain atrophy were lacking at entry into the study. The only baseline factor that predicted brain atrophy during follow-up was the volume of T2 lesions. This factor, however, was a weak predictor, accounting for less than 10% of the variance in progressive brain atrophy. This indicates that the major factors determining brain atrophy in MS as measured by the BPF were not identified by this study. Similarly, the only disease factor during the study that correlated with progressive brain atrophy was the change in T2 lesion volume. This was also only weakly correlated.

BPF is promising as an objective, reliable, and meaningful global surrogate for the destructive pathologic process in MS patients. Such a surrogate

measure is needed in view of accumulating evidence that the disease is active during periods of clinical remission in RRMS. In particular, the finding of axonal transection at sites of active inflammation in MS brain,[6] irrespective of the duration of disease, suggests that irreversible axonal injury may accumulate in patients who are relatively asymptomatic. Once a threshold is surpassed, however, compensatory mechanisms fail and progressive neurologic disability may ensue.[21] An important role of a surrogate measure in MS is demonstrating the pathologic process early in the disease, prior to extensive, irreversible tissue injury. To the extent that BPF accurately reflects the net effect of the pathologic processes, it may prove useful in monitoring MS patients early in the disease course.

In this study, brain atrophy progressed more rapidly in patients with extremely high levels of clinical disease activity, but these patients represented only a small proportion of the patients. However, in most patients, the number of relapses or changes in EDSS score were not related to the rate of brain atrophy progression. This underscores concerns that traditional clinical disease measures are not sensitive to the destructive pathologic processes in RRMS. In particular, many patients with no relapses who had stable EDSS scores had increasing amounts of brain atrophy. To the extent that the BPF reflects ongoing brain tissue loss, clinical relapses and EDSS were not informative with respect to the underlying destructive pathologic process. This finding may explain why clinical features have not been more useful as prognostic markers in patients with relapsing MS. It remains to be determined whether brain atrophy during the relapsing-remitting stage of MS will predict long-term disability progression better than clinical features in the majority of patients. Prospective studies are needed to test this hypothesis.

Importantly, IFNβ-1a had no effect on brain atrophy during the first year of the study, but was associated with reduced atrophy in the second year of treatment. There are two alternative explanations for this observation. The first possibility is that IFNβ-1a had a delayed therapeutic effect. However, IFNβ-1a has been shown to reduce disability progression and the number of gadolinium enhancing lesions during the first treatment year.[10,14] A second possibility is related to the time course of atrophy in the CNS. Wallerian degeneration in mammalian CNS reportedly proceeds over the course of months or years following an injury.[22] We hypothesize that IFNβ-1a had therapeutic effects in the first year of treatment that were evident on the atrophy measure only in the second treatment year. Ongoing disease activity before study entry may have resulted in brain atrophy during the first year of the study irrespective of the treatment arm assignment, while reduced disease activity in IFNβ-1a recipients may have reduced brain atrophy during the second year of observation. The kinetics and duration of the therapeutic effect of IFNβ-1a on brain atrophy beyond the second year remain to be determined, however, as follow-up in this study was limited to 2 years.

The BPF is an attractive surrogate measure of the global pathologic process in relapsing MS patients. This measure is informative in demonstrating change over time, shows a relationship with severe clinical disease progression, and is capable of demonstrating therapeutic effects. Additional prospective studies are needed to determine the biologic factors associated with atrophy progression, the clinical significance of BPF change during the relapsing-remitting disease stage, and the impact and time course of therapeutic intervention.

Appendix

Members of the Multiple Sclerosis Collaborative Research Group include: **Buffalo, NY—***Department of Neurology, The Buffalo General Hospital:* Lawrence Jacobs, MD, Frederick E. Munschauer, III, MD, Carol M. Brownscheidle, PhD, Colleen E. Miller, RN, NP, DNS; *William C. Baird Multiple Sclerosis Research Center, Millard Fillmore Health System:* Patrick M. Pullicino, MD, PhD, Lynne M. Bona, Mayra E. Colon-Ruiz, BS, Nadine A. Donovan, RN, Sandra Bennett Illig, RN, MS, NP, Yvonne M. Kieffer, RN, BSN, Margaret A. Umhauer, RN, MS, NP; *Division of Developmental and Behavioral Neurosciences, The Buffalo General Hospital:* Mark Schachter, PhD, David W. Shucard, PhD, Valerie Weider, PhD, Ayda K. Kilic, MS, Erica L. Sargent, BS; *Physicians Imaging Center of Western New York:* Barbara A. Catalano, RT, Jeanne M. Cervi, RT, Colleen Czekay, RT, John L. Farrell, RT, Joseph S. Filippini, RT, Robert C. Matyas, RT, Kathleen E. Michienzi, RT; *Department of Microbiology, Roswell Park Cancer Institute:* Michio Ito, MD, Judith A. O'Malley, PhD; *Department of Social and Preventive Medicine, School of Medicine and Biomedical Sciences, State University of New York at Buffalo:* Carl V. Granger, MD, Maria A. Zielezny, PhD; *MSCRG Data Management and Statistical Center, Department of Neurology, The Buffalo General Hospital:* Diane L. Cookfair, PhD, Karl Wende, PhD, Roger L. Priore, ScD, Anna Martens-Davidson, MS, Jean M. Brun, BS, Lydia A. Green, RRA, BS, Kathleen M. O'Reilly, MS, James A. Shelton, MS. **Cleveland, OH—***Mellen Center for Multiple Sclerosis Treatment and Research, Cleveland Clinic Foundation:* Richard Rudick, MD, Jill S. Fischer, PhD, Donald E. Goodkin, MD, R. Phillip Kinkel, MD, Bianca Weinstock-Guttman, MD, Danielle Y. Barilla, MA, Sharon L. Boyle, BS, Katherine Kawczak Perkins, BA, Janet E. Perryman, Barbara G. Stiebeling, RN, MSN; *Department of Diagnostic Radiology, Cleveland Clinic Foundation:* Jan F. Konecsni, RT, Jeffrey S. Ross, MD. **Denver, CO—***Department of Radiology–MRI, University of Colorado Health Sciences Center:* Jack Simon, MD, PhD, Kim Choi, PhD, Michele Lajaunie, MD, David E. Miller, PhD, Ann L. Scherzinger, PhD, Cathy J. Gustafson, RT, Deborah Singel, RT, Darren Lindsey, RT, Ken McCabe, BS, Mary Joel Meyer, MS, Bobbie J. Quandt, Rebecca Leek, BS, Jeanelle Sheeder, BS. **Portland, OR—***Department of Neurology, Good Samaritan Hospital and Medical Center:* Robert M. Herndon, MD, Michele K. Mass, MD, Debra A. Griffith, RN; *Department of Neurology, Oregon Health Sciences University:* Dennis N. Bourdette, MD, Ruth H. Whitham, MD, Jeanne M. Harris, BS, Muriel D. Lezak, PhD, Ivan Mimica, PhD, Julie A. Saunders, RN, ANP; *Department of Radiology, Good Samaritan Hospital and Medical Center:* William E. Coit, MD, Carolyn R. Force, RTR, Frances J. Gilmore, RTR, Lisa B. Harris, RTR, McAndrew M. Jones, MD, Jeffery A. Kauffman, RTR, Karen E. Marberger, RTR, Jeff W. McBride, RTR, Lora L. Miller, RTR, Gail K. Wright, RTR. **Washington, DC—***Department of Neurology, Walter Reed Army Medical Center:* Andres M. Salazar, MD, David M. Bartoszak, MD, Jonathan Braiman, MD, Michael E. Coats, MD, David S. Dougherty, MD, Barbara J. Scherokman, MD, Judith A. Brooks, RN, MSN, Herbert R. Brown, Maria E. Graves, RN, Judith A. Schmidt, RN, DNSc; *Department of Neurology, Georgetown University Medical Center:* John R. Richert, MD, Stanley L. Cohan, MD, Jacqueline W. Mothena, BSN, RN; *Cognitive Neuroscience Unit, National Institute of Neurological Disorders and Stroke, NIH* (Bethesda, MD): Jordan H. Grafman, PhD, Mary K. Kenwor-

thy, BA, Margaret M. Morton, BS, MEd; *Department of Radiology, Walter Reed Army Medical Center:* Denise M. Brown, RT, Douglas C. Brown, MD; *Department of Radiology, Georgetown University Medical Center:* Lucien M. Levy, MD, PhD.

The following scientific consultants were involved in planning the MSCRG IFNβ-1a study: *University of Maryland Cancer Center* (Baltimore, MD)—Ernest C. Borden, MD; *Research Institute, Cleveland Clinic Foundation* (Cleveland, OH)—Richard M. Ransohoff, MD; *Department of Microbiology, New York University Medical Center* (New York, NY)—Jan T. Vilcek, MD.

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