Neuropsychological Effects of Interferon β-1a in Relapsing Multiple Sclerosis

Jill S. Fischer, PhD,* Roger L. Priore, ScD,† Lawrence D. Jacobs, MD,‡ Diane L. Cookfair, PhD,‡ Richard A. Rudick, MD,* Robert M. Herndon, MD,§ John R. Richert, MD,‖ Andres M. Salazar, MD,¶ Donald E. Goodkin, MD,# Carl V. Granger, MD,** Jack H. Simon, MD,†† Jordan H. Grafman, PhD,‡‡ Muriel D. Lezak, PhD,§§ Kathleen M. O'Reilly Hovey, MS,† Katherine Kawczak Perkins, BA,* Danielle Barilla-Clark, MA,* Mark Schacter, PhD,‡ David W. Shucard, PhD,‡ Anna L. Davidson, MPH,† Karl E. Wende, PhD,† Dennis N. Bourdette, MD,§§ Mariska F. Kooijmans-Coutinho, MD, PhD,‖‖ and the Multiple Sclerosis Collaborative Research Group

Cognitive dysfunction is common in multiple sclerosis (MS), yet few studies have examined effects of treatment on neuropsychological (NP) performance. To evaluate the effects of interferon β-1a (IFNβ-1a, 30 μg administered intramuscularly once weekly [Avonex]) on cognitive function, a Comprehensive NP Battery was administered at baseline and week 104 to relapsing MS patients in the phase III study, 166 of whom completed both assessments. A Brief NP Battery was also administered at 6-month intervals. The primary NP outcome measure was 2-year change on the Comprehensive NP Battery, grouped into domains of information processing and learning/memory (set A), visuospatial abilities and problem solving (set B), and verbal abilities and attention span (set C). NP effects were most pronounced in cognitive domains vulnerable to MS: IFNβ-1a had a significant beneficial effect on the set A composite, with a favorable trend evident on set B. Secondary outcome analyses revealed significant between-group differences in slopes for Brief NP Battery performance and time to sustained deterioration in a Paced Auditory Serial Addition Test processing rate, favoring the IFNβ-1a group. These results support and extend previous observations of significant beneficial effects of IFNβ-1a for relapsing MS.

Fischer JS, Priore RL, Jacobs LD, Cookfair DL, Rudick RA, Herndon RM, Richert JR, Salazar AM, Goodkin DE, Granger CV, Simon JH, Grafman JH, Lezak MD, O'Reilly Hovey KM, Kawczak Perkins K, Barilla-Clark D, Schacter M, Shucard DW, Davidson AL, Wende KE, Bourdette DN, Kooijmans-Coutinho MF, Multiple Sclerosis Collaborative Research Group. Neuropsychological effects of interferon β-1a in relapsing multiple sclerosis. Ann Neurol 2000;48:885–892

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system in which demyelination is a prominent feature.[1] Recent studies have shown microscopic tissue abnormalities,[2] tissue destruction,[3] and axonal pathology[4] in the brains of MS patients even early in the disease course. Cognitive impairment is common in MS: nearly half of all MS patients exhibit measurable neuropsychological (NP) deficits relative to demographically matched healthy controls.[5,6] Impaired learning and memory and slowed information processing speed are most common, with deficits in visuospatial abilities and executive functions also occurring moderately often.[6] Just as the clinical presentation and course of MS vary across patients,[7] cognitive dysfunction is heterogeneous.[8]

Clinicians typically overestimate the relation between cognitive dysfunction and physical disability.[9] In fact, NP test performance correlates only modestly with disease duration, course, and level of physical disability (Expanded Disability Status Scale [EDSS]).[6,10,11] Cognitive function is moderately to strongly related to T2-weighted lesion burden on conventional magnetic resonance imaging (MRI),[12–14] magnetization transfer ratio,[15–17] and brain atrophy,[16] however. Recent large-scale clinical trials of disease-modifying medications for relapsing MS have yielded positive outcomes on tradi-

From the *Mellen Center for Multiple Sclerosis Treatment and Research, Cleveland Clinic, Cleveland, OH; †State University of New York, ‡Buffalo General Hospital, and **Center for Functional Assessment Research, Buffalo, NY; §University of Mississippi, Jackson, MS; ‖Georgetown Medical Center and ¶Walter Reed Army Medical Center, Washington, DC; ‡‡National Institute of Neurologic Disorders and Stroke, Bethesda, MD; #University of California, San Francisco, CA; ††University of Colorado, Denver, CO; §§Oregon Health Sciences University, Portland, OR; and ‖‖Department of Medical Research, Biogen, Cambridge, MA.

Received Apr 27, 2000, and in revised form Jul 13. Accepted for publication Jul 14, 2000.

Address correspondence to Dr Fischer, 170 Fuller Lane, Winnetka, IL 60093.

tional disease parameters (eg, relapse frequency and severity,[18–21] time to sustained EDSS progression[20–22]) and MRI measures (eg, lesion activity,[20,23–26] brain atrophy[27,28]). Although NP outcome assessment has been limited in most trials,[29,30] the interferon (IFN) β-1a (Avonex) trial for relapsing MS included a comprehensive assessment of NP outcomes.[31] In this article, we report (1) the effects of 2 years of IFNβ-1a treatment on a wide range of cognitive functions (principal NP outcome analysis) and (2) analysis of NP change on a subset of measures during treatment (secondary outcome analyses).

Subjects and Methods

Study Participants

Patients aged 18 to 55 years (inclusive) who had relapsing MS, symptoms for at least 1 year, at least two documented exacerbations in the preceding 3 years, and EDSS[32] scores of 1.0 to 3.5 (inclusive) were eligible for enrollment in the phase III study. All were clinically stable at baseline (ie, had no exacerbations within 2 months of study entry). The primary outcome measure was time to sustained EDSS progression; thus, patients were treated and followed for varying lengths of time. The study design has been described in detail previously.[31]

Treatment

Patients were treated with either IFNβ-1a (30 μg intramuscularly [Avonex]) or placebo intramuscularly once weekly for 104 weeks (2 years). Details of IFNβ-1a treatment are available in previous publications.[20,31]

Instruments and Procedures

After providing informed consent and undergoing a neurological examination to confirm eligibility and establish baseline EDSS scores, patients were administered the Comprehensive NP Battery and other secondary outcome measures. The Comprehensive NP Battery was a broad-spectrum battery comprising measures from the core battery recommended by the National Multiple Sclerosis Society Cognitive Function Study Group[33] as well as additional measures covering cognitive domains of theoretical interest. This extensive battery permitted evaluation of the effects of IFNβ-1a on a diverse array of cognitive functions, including those not typically captured by traditional clinical NP measures. The Comprehensive NP Battery was administered in a standardized order in two 3-hour testing sessions on consecutive days at week 0 and again at week 104. A subset of the Comprehensive NP Battery consisting of measures of cognitive domains most vulnerable to MS (ie, information processing, learning/recent memory) and global NP screening measures was designated as the Brief NP Battery. The Brief NP Battery was administered in a single 90-minute testing session at 26-week intervals during treatment.

A complete listing of NP measures in the comprehensive and brief batteries has been published[31]; variables used in the primary and secondary NP outcome analyses are listed in Table 1. When available, alternate forms of NP measures were administered to attenuate practice effects associated with repeated test administrations (see Table 1). NP technicians were trained using standardized procedures. Administration and scoring of all NP measures were centrally verified at the Cleveland site (Multiple Sclerosis Collaborative Research Group [MSCRG] Neuropsychology Coordinating Center) before data entry.

Statistical Analysis

Procedures for evaluating NP outcomes in the IFNβ-1a trial were prospectively defined as outlined in Figure 1. Selection of variables for the principal NP outcome analysis (analysis of 2-year change) was guided by a factor analysis (maximum-likelihood factor analysis, with orthogonal rotation)[44] of baseline data from the Comprehensive NP Battery for the entire sample without reference to treatment status. The purpose of the factor analysis was to identify the most parsimonious set of variables to characterize performance on the Comprehensive NP Battery. Ten independent factors (cognitive domains) that met our criteria for strength (eigenvalues > 1.0) and composition (>1 variable with strong loadings) were identified. (An eigenvalue of 1.0 is a conventional criterion for identifying strong and reasonably stable factors.)

Reasoning that sensitivity to treatment effects would be linked to the probability of impairment in a given cognitive domain, we grouped these 10 factors into three sets based on the prevalence of deficits in a large community-based sample of MS patients.[6] Learning/recent memory and information processing (cognitive domains most often impaired in MS) were assigned to set A; visuospatial abilities and executive functions (domains impaired moderately often) were assigned to set B; and verbal abilities and attention span (domains infrequently impaired) were assigned to set C (see Table 1). For each factor, we identified a relatively "pure" exemplar, a variable with a strong loading (>0.500) on that factor and no more than modest loadings (<0.300) on others. (A factor loading indicates the degree to which a variable is associated with that factor.) The factor analysis, grouping of factors into sets, and selection of variables were performed before undertaking the principal and secondary NP outcome analyses.

Our outcome analysis strategy was hierarchical. The principal NP outcome analysis consisted of three MANOVAs, one for each variable set. (Sample sizes for these analyses varied because of missing data, most of which was attributable to administration errors on two tasks [Tower of London and 20 Qs] and to a computer programming error on a third task [California Computerized Assessment Package]. We decided prospectively to retain these variables because they assess unique aspects of cognitive function.) Treatment group (IFNβ-1a vs placebo) was the independent variable, and 2-year change score (week 104 score − week 0 score) served as the dependent variable. Scores were adjusted for demographic factors that can affect NP performance (ie, age, education, gender) before calculating change scores. A significant treatment effect was followed up with a MANCOVA (using week 0 score as a covariate) to evaluate the impact of baseline performance on treatment effects and with univariate ANOVAs to assess the contribution of individual variables to the overall treatment effect.

Secondary NP outcome analyses consisted of ANOVA and categorical analysis of change on selected Brief NP Bat-

Table 1. Neuropsychological Measures in the Principal and Secondary Neuropsychological Outcome Analyses

	Factor (cognitive domain)	Representative Variable	Reference
Principal Neuropsychological Outcome Analysis (Comprehensive Neuropsychological Battery)			
Set A composite Information processing/memory	Information processing	CALCAP Sequential reaction time	Miller and co-workers[34]
	Visual learning/recall	RFFT error ratio[a]	Ruff[35]
	Verbal learning/recall	CVLT trials 1–5 total[b]	Delis and co-workers[36]
Set B composite Visuospatial abilities/executive function	Visuospatial abilities	WMS-R Visual Memory Span-Forward	Wechsler[37]
	Problem solving	WCST perseverative responses	Heaton[38]
	Visual scanning	Visual search number of trials[b]	Lewis and Rennick[39]
	Planning/sequencing	TOL % planning time	Shallice[40]
	Deductive reasoning	20 Qs % good hypothesis Qs[b]	Laine and Butters[41]
Set C composite Verbal abilities/attention span	General verbal abilities	WAIS-R information	Wechsler[42]
	Attention span	WMS-R Digit Span-Forward	Wechsler[37]
Secondary Neuropsychological Outcome Analyses (Brief Neuropsychological Battery)			
Brief NP Battery composite	Visual learning/recall	RFFT error ratio[a]	Ruff[35]
	Verbal learning/recall	CVLT trials 1–5 total[b]	Delis and co-workers[36]
	Information processing + visuospatial abilities	RFFT total unique designs	Ruff[35]
Single multidimensional variable	Information processing + (general verbal abilities) + (visual scanning) + (visuospatial abilities)	PASAT processing rate[b]	Gronwall[43], Rao and co-workers

[a]Arcsine transformation was applied to this variable.
[b]Alternate forms were used (two for CVLT, 20 Qs, and PASAT; four for Visual Search).

CALCAP = California Computerized Assessment Package; RFFT = Ruff Figural Fluency Test; CVLT = California Verbal Learning Test; WMS-R = Wechsler Memory Scale–Revised; WCST = Wisconsin Card Sorting Test; TOL = Tower of London; WAIS-R = Wechsler Adult Intelligence Scale–Revised; PASAT = Paced Auditory Serial Addition Test.

tery measures (see Table 1): (1) a three-variable composite of domains impaired frequently (ie, learning/memory, information processing) or moderately often (visuospatial abilities) in MS and (2) the Paced Auditory Serial Addition Test (PASAT) processing rate (ie, number of correct items per second averaged across the 2- and 3-second interstimulus interval presentations). The analytic strategy for the ANOVA followed that outlined for the principal NP outcome analysis, except that the dependent variable in the secondary outcome analysis was the slope of a patient's demographically adjusted scores (plotted across weeks 0, 26, 52, 78, and 104).

For the categorical analysis, patients were classified as to whether their performance at any study visit (adjusted for demographic variables and baseline) worsened by more than 0.5 SD relative to their week 0 performance or did not. Change in performance was evaluated by plotting slopes from week 0 through the time point of interest. Statistically significant practice effects (linear in form) were apparent on the Brief NP Battery variables and were taken into account in the classification of change. (The 0.5-SD criterion is an accepted statistical convention when there is no a priori standard for evaluating the magnitude of change; in this analysis, the SD was that for the slope through all five time points for all patients.) To minimize the impact of transient fluctuations, worsening had to be sustained at the subsequent study visit to meet criteria for "sustained deterioration." Kaplan-Meier methods[45] were used to compare the 2 groups on time to onset of sustained deterioration, with statistical significance determined by a log-rank test.

Results

Sample Baseline Characteristics

DEMOGRAPHIC AND DISEASE VARIABLES. Two hundred seventy-six patients (206 female, 70 male) were administered the Comprehensive NP Battery on entry into the trial. One hundred sixty-six patients (128 female, 38 male) also completed the Comprehensive NP Battery at week 104. Patients in the NP outcome analysis sample were representative of all patients entering the study. IFNβ-1a (Avonex) and placebo patients were well matched in terms of demographic and disease characteristics (Table 2).

COMPREHENSIVE NP BATTERY PERFORMANCE. IFNβ-1a and placebo patients were well matched on two of the three composite scores in the principal NP outcome analysis (sets A and C). On set A, the baseline mean (±SD) z score for the IFNβ-1a group was 0.45 (±1.88) compared with 0.19 (±1.69) for the placebo group. On set C, the IFNβ-1a group had a baseline mean z score of 0.18 (±1.55), and that of the placebo group was −0.13 (±1.58). (The z scores were calculated with reference to the entire sample of patients with week 0 data.) There were significant between-group differences in the baseline set B composite (p = 0.003): the mean z score of the IFNβ-1a group (−0.82 ± 2.56) was significantly lower than that of

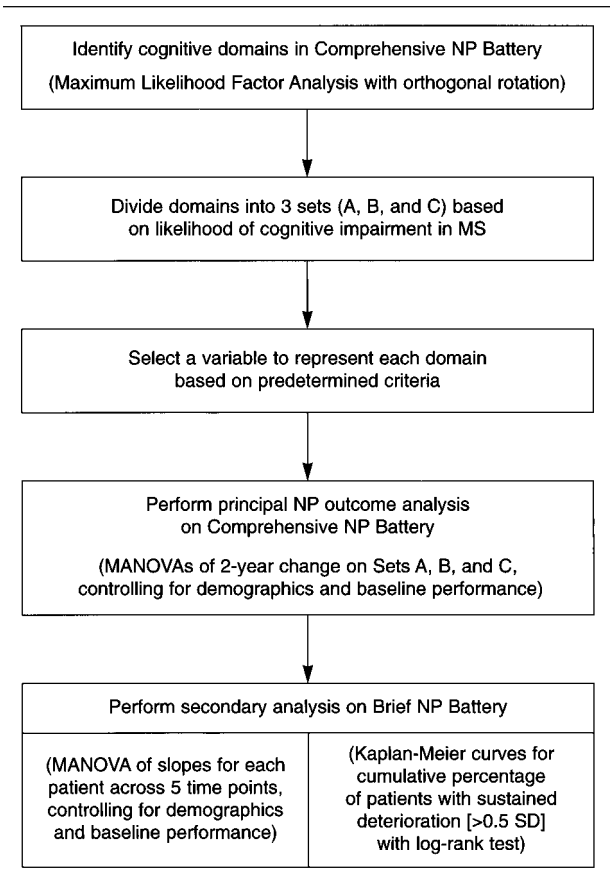

Fig 1. Overview of neuropsychological outcome analyses in the interferon β-1a trial.

the placebo group (0.64 ± 2.11) because of significant between-group differences on two individual variables in set B, Wechsler Memory Scale–Revised Visual Span Forward and 20 Qs % good hypothesis Qs ($p = 0.02$ for each).

BRIEF NP BATTERY PERFORMANCE. The IFNβ-1a and placebo groups did not differ significantly in their baseline performance on the Brief NP Battery composite: the IFNβ-1a group had a mean (±SD) z score of 0.17 (±2.03) compared with 0.19 (±2.37) for the placebo group. The 2 groups were also well matched in their baseline PASAT processing rates: the mean (±SD) PASAT processing rate for the IFNβ-1a group was 0.58 (±0.13) items per second, and that of the placebo group was 0.55 (±0.16) items per second.

Principal NP Outcome Analysis: 2-Year Change on Comprehensive NP Battery

Figure 2 depicts the 2-year change in performance for the IFNβ-1a and placebo groups on the three Comprehensive NP Battery composite measures without (see Fig 2a) and then with (see Fig 2b) baseline performance as a covariate.

SET A COMPOSITE (INFORMATION PROCESSING/MEMORY). IFNβ-1a significantly improved performance on measures of information processing and memory relative to placebo ($F[1,135] = 4.50$, $p = 0.036$; see Fig 2a). The treatment effect was accentuated when baseline performance was included as a covariate ($F[1,134] = 6.59$, $p = 0.011$; see Fig 2b). Examination of the 2-year change on individual set A variables revealed that the between-group difference was most pronounced on a measure of verbal learning, the California Verbal Learning Test trials 1 through 5 total ($p = 0.025$ with baseline as a covariate).

SET B COMPOSITE (VISUOSPATIAL ABILITIES/EXECUTIVE FUNCTIONS). Although the effect of IFNβ-1a on measures of visuospatial abilities and executive functions (set B) was statistically significant when baseline performance was not controlled ($F[1,95] = 8.11$, $p = 0.005$; see Fig 2a), the treatment effect was attenuated when baseline differences were taken into account ($F[1,94] = 3.03$, $p = 0.085$; see Fig 2b). Group differences in 2-year change on individual set B variables were in the predicted direction on four of five variables, however, and attained statistical significance on a measure of planning ability, Tower of London % planning time ($p = 0.032$ with baseline adjustment).

SET C COMPOSITE (VERBAL ABILITIES/ATTENTION SPAN). No treatment effects were evident on set C variables (verbal abilities and attention span).

Secondary NP Outcome Analysis: Brief NP Battery Composite

Figure 3 presents Brief NP Battery composite scores for the IFNβ-1a and placebo groups at baseline and at 26-week intervals during the treatment phase. As anticipated, the performance of both groups improved relative to baseline as a result of practice effects. The mean slope for the IFNβ-1a group (plotted through all five time points) was significantly greater than that of the placebo group, however ($F[1,151] = 5.52$, $p = 0.020$ without baseline as a covariate; $F[1,150] = 5.54$, $p = 0.020$ with baseline performance controlled). Group differences in slopes were in the predicted direction for each variable in the Brief NP Battery composite, with the Ruff Figural Fluency Test error ratio attaining statistical significance ($p = 0.048$ with baseline as a covariate). Sustained deterioration in Brief NP Battery composite performance was observed in fewer IFNβ-1a patients (17.7%) than placebo patients (29.7%), with a trend for IFNβ-1a to lengthen time to onset of sustained deterioration (log-rank[1] = 2.80, $p = 0.094$).

Secondary NP Outcome Analysis: PASAT Processing Rate

PASAT processing rates of both groups improved during the treatment phase, reflecting practice effects. Al-

Table 2. Demographic and Disease Characteristics of Interferon β-1a and Placebo Patients Completing the Comprehensive Neuropsychological Battery at Weeks 0 and 104

	Interferon β-1a (n = 83)	Placebo (n = 83)	Range
Age (mean years ± SD)	36.1 ± 6.4	36.2 ± 6.8	16–53
Education (mean years ± SD)	14.2 ± 2.2	14.7 ± 2.7	9–26
Disease duration (mean years ± SD)[a]	6.7 ± 5.7	6.4 ± 5.1	0.7–26.5
EDSS (mean score ± SD)	2.3 ± 0.8	2.4 ± 0.9	1.0–3.5

[a]Since symptom onset.

EDSS = Expanded Disability Status Scale.

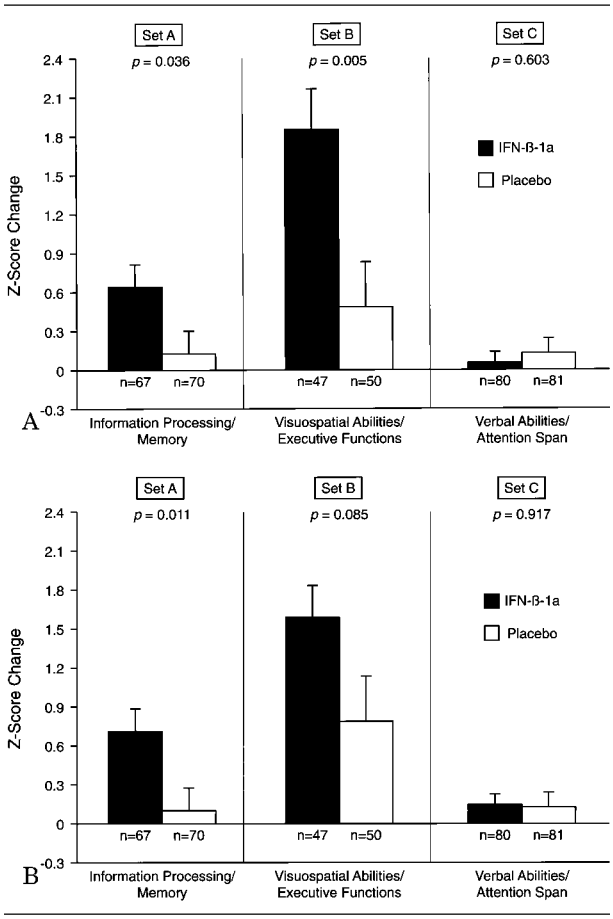

Fig 2. (A) Two-year change in Comprehensive Neuropsychological (NP) Battery performance (mean z score + SEM) for each treatment group (without baseline adjustment). (B) Two-year change in Comprehensive NP Battery performance (mean z score + SEM) for each treatment group (with baseline adjustment).

though the mean (±SD) slope of the IFNβ-1a group (0.021 ± 0.020) was greater than that of the placebo group (0.015 ± 0.023), this trend did not attain statistical significance ($F[1,146] = 2.46$, $p = 0.119$ without baseline as a covariate; $F[1,145] = 2.92$, $p = 0.090$ with baseline as a covariate). IFNβ-1a significantly lengthened time to onset of sustained deterioration in the PASAT processing rate (log-rank[1] = 5.19, $p = 0.023$), however, with fewer IFNβ-1a patients (19.5%) than placebo patients (36.6%) meeting criteria for sustained PASAT deterioration by the end of the treatment phase (Fig 4).

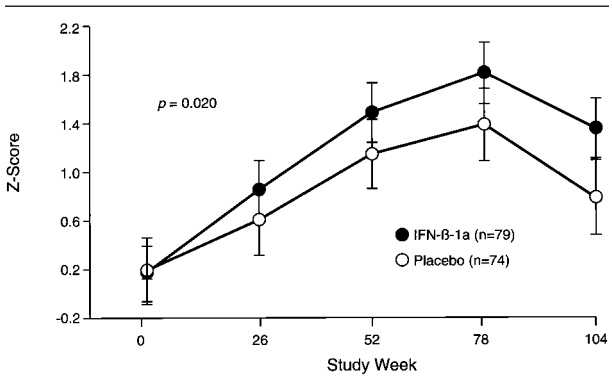

Fig 3. Brief Neuropsychological Battery composite performance (mean z score ± SEM) at each study visit by treatment group.

Discussion

Cognitive dysfunction is a common clinical problem in MS[5,6] even early in the disease when overall physical disability is mild to moderate.[10,46] Despite this, studies of the effects of disease-modifying medications on cognitive dysfunction have been limited. This is the first multicenter clinical trial in MS to prospectively assess NP outcomes across a wide range of cognitive functions. Relapsing MS patients treated with IFNβ-1a (Avonex) for 2 years performed significantly better than placebo patients on a composite of information processing and learning/recent memory measures (set A from the Comprehensive NP Battery). A similar trend was observed on a composite measure of visuospatial abilities and executive functions (set B) but not on the set C composite (verbal abilities and attention span). Thus, beneficial treatment effects were most apparent in cognitive domains commonly disrupted by MS.

Secondary outcome analyses of the Brief NP Battery support and extend these findings. The IFNβ-1a and placebo groups differed significantly in their mean slopes on the Brief NP Battery composite (plotted across the five time points from week 0–104), with the

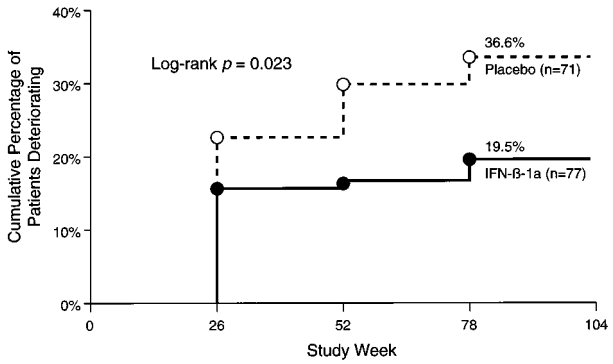

Fig 4. Cumulative percentage of patients in each treatment group with onset of sustained deterioration (>0.5 SD) in Paced Auditory Serial Addition Test processing rate at each study visit.

IFNβ-1a group outperforming the placebo group. IFNβ-1a also significantly lengthened time to sustained deterioration on a different Brief NP Battery measure, the PASAT processing rate: only 19.5% of IFNβ-1a patients had a sustained worsening in their PASAT processing rate by week 104 compared with 36.6% of placebo patients, reflecting a 46.7% reduction in the risk of cognitive deterioration. These NP findings are consistent with the main outcome of the trial, namely, that IFNβ-1a significantly lengthened time to sustained disability progression as assessed by the EDSS.[20]

Two previous relapsing MS trials have assessed NP outcomes, albeit in a more limited way. In the glatiramer acetate (Copaxone) trial,[30] no statistically significant treatment effects were observed. In the IFNβ-1b (Betaseron) study,[29] a beneficial treatment effect on a visual memory measure was reported. This finding is difficult to interpret given that this study had no pretreatment NP baseline, but it is consistent with our observation of beneficial treatment effects in learning/memory and information processing. We believe that IFNβ-1a (Avonex) exerts its beneficial effects on cognitive function via both short-term (inhibition of anti-inflammatory mediators)[47] and longer term (prevention of central nervous system tissue injury)[25,27,28] mechanisms.

Assessment of NP outcomes in MS clinical trials is challenging. MS-related cognitive dysfunction is inherently heterogeneous, affecting different cognitive domains to different degrees in different patients.[8] Furthermore, progression rates vary across patients and across cognitive domains.[46,48,49] In our trial and in other clinical trials with cognitively heterogeneous populations,[50] NP effects were most evident in multivariate analyses rather than in analyses of single cognitive functions. Outcome assessment in future MS trials should focus on cognitive domains vulnerable to MS, include measures with demonstrated sensitivity to change, and incorporate appropriate controls for demographic factors and baseline NP performance.[51]

Practice effects also complicate NP outcome assessment. In our trial, the Brief NP Battery performance of both groups improved over the first four testing sessions. The performance of the IFNβ-1a group improved relatively more than that of the placebo group, however, an enhancement of cognitive function that could stem from IFNβ-1a's anti-inflammatory effects. Although the sensitivity of NP outcome analyses may be improved by statistically modeling and controlling for practice effects as we did, establishment of a stable NP baseline before initiation of treatment would permit clearer interpretation of treatment effects.[51]

MS-related cognitive dysfunction can have a devastating impact on employment, social functioning, and the management of household responsibilities.[6,46] Once cognitive impairment is present, it is unlikely to remit to any significant extent, and it may worsen.[46,49] Extensive and irreversible cognitive impairment is most likely attributable to cerebral plaque accumulation and brain atrophy, both of which have been shown to be favorably affected by IFNβ-1a (Avonex).[20,25,27,28] Proactive treatment with disease-modifying therapy as recommended by the National Multiple Sclerosis Society (United States)[52] may forestall the development or worsening of MS-related cognitive dysfunction even when physical impairment is minimal.

Appendix

The Multiple Sclerosis Collaborative Research Group (MSCRG) consisted of the following sites and their respective study personnel in addition to the cited authors.

Buffalo, NY—*William C. Baird Multiple Sclerosis Research Center, Millard Fillmore Health System:* Carol M. Brownscheidle, PhD, Lynne M. Bona, Mayra E. Colon-Ruiz, BS, Nadine A. Donovan, RN, Sandra Bennett Illig, RN, MS, NP, Yvonne M. Kieffer, RN, BSN, Frederick E. Munschauer III, MD, Patrick M. Pullicino, MD, PhD, and Margaret A. Umhauer, RN, MS, CNS; *Department of Neurology, Buffalo General Hospital:* Colleen E. Miller, RN, MS, CNS; *Division of Developmental and Behavioral Neurosciences, Department of Neurology, Buffalo General Hospital:* Ayda K. Kilic, MS, Erica L. Sargent, BS, and Valerie Weider, PhD; *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, and Kathleen E. Michienzi, RT; *Department of Microbiology, Roswell Park Cancer Institute:* Michio Ito, MD, and Judith A. O'Malley, PhD; *Department of Social and Preventative Medicine, School of Medicine and Biomedical Sciences, State University of New York at Buffalo:* Maria A. Zielezny, PhD; *MSCRG Data Management and Statistical Center, Department of Neurology, Buffalo General Hospital:* Jean M. Brun, BS, Lydia A. Green, RRA, BS, and James A. Shelton, MS.

Cleveland, OH—*Mellen Center for Multiple Sclerosis Treatment and Research, Cleveland Clinic Foundation:* Sharon L. Boyle, BS, Revere P. Kinkel, MD, Janet E. Perryman,

Barbara G. Stiebeling, RN, MSN, and Bianca Weinstock-Guttman, MD; *Department of Diagnostic Radiology, Cleveland Clinic Foundation:* Jan F. Konescni, RT, and Jeffrey S. Ross, MD.

Denver, CO—*Department of Radiology/MRI, University of Colorado Health Sciences Center:* Kim S. Choi, MS, Cathy J. Gustafson, RT, Bobbie J. Quandt, and Ann L. Scherzinger, PhD.

Portland, OR—*Department of Neurology, Good Samaritan Hospital and Medical Center:* Debra A. Griffith, RN, and Michele K. Mass, MD; *Department of Neurology, Oregon Health Sciences University:* Jeanne M. Harris, BS, Ivan Mimica, PhD, Julie A. Saunders, RN, ANP, and Ruth H. Whitham, MD; *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, Jeffrey A. Kauffman, RTR, Karen E. Marberger, RTR, Jeff W. McBride, RTR, Lora L. Miller, RTR, and Gail K. Wright, RTR.

Washington, DC—*Department of Neurology, Walter Reed Army Medical Center:* David M. Bartoszak, MD, Jonathan Braiman, MD, Judith A. Brooks, RN, MSN, Herbert R. Brown, Michael E. Coats, MD, David S. Dougherty, MD, Maria E. Graves, RN, and Judith A. Schmidt, RN, DNSc; *Department of Neurology, Georgetown University Medical Center:* Stanley L. Cohan, MD, and Jacqueline W. Mothena, BSN, RN; *Cognitive Neuroscience Unit, National Institute of Neurological Disorders and Stroke, NIH (Bethesda, MD):* Mary K. Kenworthy, BA, and Margaret M. Morton, BS, MEd; *Department of Radiology, Walter Reed Army Medical Center:* Denise M. Brown, RT, and Douglas C. Brown, MD; *Department of Radiology, Georgetown University Medical Center:* Lucien M. Levy, MD, PhD.

Springfield, VA—*Department of Neurology, Kaiser Permanente Medical Center:* Barbara J. Scherokman, MD.

The following scientific consultants were involved in the planning of this clinical trial: Ernest C. Borden, MD (University of Maryland Cancer Center, Baltimore, MD), Richard M. Ransohoff, MD (Lerner Research Institute, Cleveland Clinic Foundation, Cleveland, OH), and Jan T. Vilcek, MD (Department of Microbiology, New York University Medical Center, New York, NY).

The National Institute of Neurological Disorders and Stroke Safety and Monitoring Committee consisted of John W. Griffin, MD (Chair), George W. Ellison, MD, Stephen L. Hauser, MD, John H. Noseworthy, MD, Steven Piantadosi, MD, PhD, A.P. Kerza-Kwiatecki, PhD, and Carl M. Leventhal, MD.

Support for this study was provided by National Institute of Neurological Disorders and Stroke (NINDS) grant RO1-26321, and Biogen (Cambridge, MA).

Portions of this article were presented at the 52nd Annual Meeting of the American Academy of Neurology, Minneapolis, MN, April 1998.

References

1. Adams RD, Victor M, Ropper AH. Principles of neurology. 6th ed. New York: McGraw-Hill, 1997
2. Arnold DL, Riess FT, Matthews PM, et al. Use of proton magnetic resonance spectroscopy for monitoring disease progression in multiple sclerosis. Ann Neurol 1994;36:76–82
3. Truyen L, van Waesberghe JHTM, van Walderveen MAA, et al. Accumulation of hypointense lesions ("black holes") on T1 spin echo MRI correlates with disease progression in multiple sclerosis. Neurology 1996;47:1469–1476
4. Trapp BD, Peterson J, Ransohoff RM, et al. Axonal transection in the lesions of multiple sclerosis. N Engl J Med 1998;338: 278–285
5. Heaton RK, Nelson LM, Thompson DS, et al. Neuropsychological findings in relapsing-remitting and chronic-progressive multiple sclerosis. J Consult Clin Psychol 1985;53:103–110
6. Rao SM, Leo GJ, Bernardin L, Unverzagt F. Cognitive dysfunction in multiple sclerosis: I. Frequency, patterns, and prediction. Neurology 1991;41:685–691
7. Rudick RA, Goodkin DE. Aspects of multiple sclerosis that relate to clinical trial design and treatment. In: Rudick RA, Goodkin DE, eds. Multiple sclerosis therapeutics. London: Martin Dunitz, 1999:3–15
8. Ryan L, Clark CM, Klonoff H, et al. Patterns of cognitive impairment in relapsing-remitting multiple sclerosis and their relationship to neuropathology on magnetic resonance images. Neuropsychology 1996;10:176–193
9. Fischer JS, Foley FW, Aikens JE, et al. What do we really know about cognitive dysfunction, affective disorders, and stress in multiple sclerosis? A practitioner's guide. J Neurol Rehabil 1994;8:151–164
10. van den Burg W, van Zomeren AH, Minderhoud JH, et al. Cognitive impairment in patients with multiple sclerosis and mild physical disability. Arch Neurol 1987;44:494–501
11. Beatty W, Goodkin DE, Hertsgaard D, Monson N. Clinical and demographic predictors of cognitive performance in multiple sclerosis: do diagnostic type, disease duration, and disability matter? Arch Neurol 1990;47:305–308
12. Rao SM, Leo GJ, Haughton VM, et al. Correlation of magnetic resonance imaging with neuropsychological testing in multiple sclerosis. Neurology 1989;39:161–166
13. Huber SJ, Bornstein RA, Rammohan KW, et al. Magnetic resonance imaging correlates of neuropsychological impairment in multiple sclerosis. J Neuropsychiatry Clin Neurosci 1992;4: 152–158
14. Swirsky-Sacchetti T, Mitchell D, Seward J, et al. Neuropsychological and structural brain lesions in multiple sclerosis: a regional analysis. Neurology 1992;42:1291–1295
15. Rovaris M, Filippi M, Falautano M, et al. Relation between MR abnormalities and patterns of cognitive impairment in multiple sclerosis. Neurology 1998;50:1601–1608
16. van Buchem MA, Grossman RI, Armstrong C, et al. Correlation of volumetric magnetization transfer imaging with clinical data in MS. Neurology 1998;50:1609–1617
17. Filippi M, Tortorella C, Rovaris M, et al. Changes in the normal appearing brain tissue and cognitive impairment in multiple sclerosis. J Neurol Neurosurg Psychiatry 2000;68:157–161
18. IFNβ Multiple Sclerosis Study Group. Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. I. Clinical results of a multicenter, randomized, double-blind, placebo-controlled trial. Neurology 1993;43:662–667
19. Johnson KP, Brooks BR, Cohen JA, et al. Copolymer 1 reduces relapse rate and improves disability in relapsing-remitting multiple sclerosis: results of a phase III multicenter, double-blind, placebo-controlled trial. Neurology 1995;45:1268–1276
20. Jacobs LD, Cookfair DL, Rudick RA, et al. Intramuscular interferon beta-1a for disease progression in relapsing multiple sclerosis. Ann Neurol 1996;39:285–294
21. PRISMS Study Group. Randomised double-blind placebo-controlled study of interferon beta-1a in relapsing/remitting multiple sclerosis. Lancet 1998;352:1498–1504

22. Rudick RA, Goodkin DE, Jacobs LD, et al. Impact of interferon beta-1a on neurologic disability in relapsing multiple sclerosis. Neurology 1997;49:358–363
23. Paty DW, Li DKB, UBC MS/MRI Study Group, IFNβ Multiple Sclerosis Study Group. Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. II. MRI analysis results of a multicenter, randomized, double-blind, placebo-controlled trial. Neurology 1993;43:662–667
24. Li DKB, Paty DW, UBC MS/MRI Analysis Research Group, PRISMS Study Group. Magnetic resonance imaging results of the PRISMS trial: a randomized, double-blind, placebo-controlled study of interferon beta-1a in relapsing-remitting multiple sclerosis. Ann Neurol 1999;46:197–206
25. Simon JH, Jacobs LD, Campion M, et al. Magnetic resonance studies of intramuscular interferon beta-1a for relapsing multiple sclerosis. Ann Neurol 1998;43:79–87
26. Zhao GJ, Koopmans RA, Li DKB, et al. Effect of interferon β-1b in MS: assessment of annual accumulation of PD/T2 activity on MRI. Neurology 2000;54:200–206
27. Rudick RA, Fisher E, Lee J-C, et al. Use of the brain parenchymal fraction to measure whole brain atrophy in relapsing-remitting MS. Neurology 1999;53:1698–1704
28. Simon JH, Jacobs LD, Campion MK, et al. A longitudinal study of brain atrophy in relapsing multiple sclerosis. Neurology 1999;53:139–148
29. Pliskin NH, Hamer DP, Goldstein DS, et al. Improved delayed visual reproduction test performance in multiple sclerosis patients receiving interferon β-1b. Neurology 1996;47:1463–1468
30. Weinstein A, Schwid SR, Schiffer RB, et al. Neuropsychological status in multiple sclerosis after treatment with glatiramer acetate (Copaxone). Arch Neurol 1999;56:319–324
31. Jacobs LD, Cookfair DL, Rudick RA, et al. A phase III trial of intramuscular recombinant interferon beta as treatment for exacerbating-remitting multiple sclerosis: design and conduct of study and baseline characteristics of patients. Mult Scler 1995; 1:118–135
32. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an Expanded Disability Status Scale (EDSS). Neurology 1983; 33:1444–1452
33. Peyser JM, Rao SM, LaRocca NG, Kaplan E. Guidelines for neuropsychological research in multiple sclerosis. Arch Neurol 1990;47:94–97
34. Miller EN, Satz P, Visscher B. Computerized and conventional neuropsychological assessment of HIV-1–infected homosexual men. Neurology 1991;41:1608–1616
35. Ruff RR. Ruff Figural Fluency Test administration manual. San Diego: Neuropsychological Resources, 1988
36. Delis DC, Kramer JH, Kaplan E, Ober BA. California Verbal Learning Test: adult version. San Antonio: Psychological Corporation, 1987
37. Wechsler D. Wechsler Memory Scale-Revised (WMS-R) manual. San Antonio: Psychological Corporation, 1987
38. Heaton RK. Wisconsin Card Sorting Test manual. Odessa, FL: Psychological Assessment Resources, 1981
39. Lewis RF, Rennick PM. Manual for the Repeatable Cognitive-Perceptual-Motor Battery. Clinton Township, MI: Ronald F Lewis, 1979
40. Shallice T. Specific impairments of planning. In: Broadbent DE, Weiskrantz L, eds. The neuropsychology of cognitive function. London: Royal Society, 1982:199–209
41. Laine M, Butters N. A preliminary study of the problem-solving strategies of detoxified long-term alcoholics. Drug Alcohol Depend 1982;10:235–242
42. Wechsler D. Manual for the Wechsler Adult Intelligence Scale-revised. New York: Psychological Corporation, 1981
43. Gronwall D. Paced auditory serial addition task: a measure of recovery from concussion. Percept Mot Skills 1977;44:367–373
44. Floyd FJ, Widaman KF. Factor analysis in the development and refinement of clinical assessment instruments. Psychol Assess 1995;7:286–299
45. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958;53:457–481
46. Amato MP, Ponziani G, Pracucci G, et al. Cognitive impairment in early-onset multiple sclerosis: pattern, predictors, and impact on everyday life in a 4-year follow-up. Arch Neurol 1995;52:168–172
47. Rudick RA, Cookfair DL, Simonian NA, et al. Cerebrospinal fluid abnormalities in a phase III trial of Avonex (IFNβ1a) for relapsing multiple sclerosis. J Neuroimmunol 1999;93:8–14
48. Jennekens-Schinkel A, Laboyrie PM, Lanser JBK, van der Velde EA. Cognition in patients with multiple sclerosis: after four years. J Neurol Sci 1990;99:229–247
49. Kujala P, Portin R, Ruutiainen J. The progress of cognitive decline in multiple sclerosis: a controlled 3-year follow-up. Brain 1997;120:289–297
50. Sidtis JJ, Gatsonis C, Price RW, et al. Zidovudine treatment of the AIDS dementia complex: results of a placebo-controlled trial. Ann Neurol 1993;33:343–349
51. Fischer JS. Assessment of neuropsychological function. In: Rudick RA, Goodkin DE, eds. Multiple sclerosis therapeutics. London: Martin Dunitz, 1999:31–47
52. National Multiple Sclerosis Society. Disease management consensus statement. Clinical bulletin: information for health professionals. Available on-line at: http://www.nmss.org/publications/p-893283222/1998/oct/a-907774722.html (Accessed March 27, 2000)