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

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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.


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 pathology4 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-
tional disease parameters (eg, relapse frequency and severity,18–21 time to sustained EDSS progression20–22) and MRI measures (eg, lesion activity,20,23–26 brain atrophy27,28). 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 EDSS32 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 Group33 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 published31; 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-
tory 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 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
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.

Secondary NP Outcome Analysis: PASAT Processing Rate
PASAT processing rates of both groups improved during the treatment phase, reflecting practice effects. Al-
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).

Discussion
Cognitive dysfunction is a common clinical problem in MS even early in the disease when overall physical disability is mild to moderate. 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.

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

<table>
<thead>
<tr>
<th></th>
<th>Interferon β-1a (n = 83)</th>
<th>Placebo (n = 83)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean years ± SD)</td>
<td>36.1 ± 6.4</td>
<td>36.2 ± 6.8</td>
<td>16–53</td>
</tr>
<tr>
<td>Education (mean years ± SD)</td>
<td>14.2 ± 2.2</td>
<td>14.7 ± 2.7</td>
<td>9–26</td>
</tr>
<tr>
<td>Disease duration (mean years ± SD)</td>
<td>6.7 ± 5.7</td>
<td>6.4 ± 5.1</td>
<td>0.7–26.5</td>
</tr>
<tr>
<td>EDSS (mean score ± SD)</td>
<td>2.3 ± 0.8</td>
<td>2.4 ± 0.9</td>
<td>1.0–3.5</td>
</tr>
</tbody>
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*Since symptom onset.
EDSS = Expanded Disability Status Scale.
include measures with demonstrated sensitivity to should focus on cognitive domains vulnerable to MS, functions. Outcome assessment in future MS trials ate analyses rather than in analyses of single cognitive simulations,50 NP effects were most evident in multivari- other clinical trials with cognitively heterogeneous pop- L. Boyle, BS, Revere P. Kinkel, MD, Janet E. Perryman, Sharon Treatment and Research, Cleveland Clinic Foundation: Acknowledgments: We thank all the research participants and center personnel in addition to the cited authors. Buffalo, NY—William C. Baird Multiple Sclerosis Research Center, Millard Fillmore Health System: Carol M. Brown- heidle, 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 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, change, and incorporate appropriate controls for demo- graphic 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 IFNß-1a group improved relatively more than that of the placebo group, however, an enhancement of cognitive function that could stem from IFNß-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 per- mit 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.5,46 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 IFNß-1a (Avonex).20,25,27,28 Pro- active treatment with disease-modifying therapy as recom- mended 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 respec- tive study personnel in addition to the cited authors.

Buffalo, NY—William C. Baird Multiple Sclerosis Research Center, Millard Fillmore Health System: Carol M. Brown- heidle, 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 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,
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