Disability Progression in a Clinical Trial of Relapsing-Remitting Multiple Sclerosis

Eight-Year Follow-up

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Objective: To investigate the value of Expanded Disability Status Scale (EDSS) worsening sustained for at least 6 months and other parameters as predictors for disability status.

Design: Retrospective analysis of the Multiple Sclerosis Collaborative Research Group study data.

Setting: The intramuscular interferon beta-1a pivotal trial was a double-blind, placebo-controlled phase 3 study.

Participants: Patients with relapsing-remitting multiple sclerosis who received at least 2 years of treatment and completed an EDSS evaluation 8 years postrandomization.

Intervention: Thirty micrograms of intramuscular interferon beta-1a or placebo once weekly during the 2-year clinical trial.

Main Outcome Measures: Positive predictive values for 6-month sustained progression during 2 years were calculated to determine the ability to predict disability status at 8 years. A multivariate logistic regression model was used to assess the relationship between predictors and EDSS milestones at follow-up.

Results: Forty-five patients had sustained 6-month EDSS progression during the clinical trial and 115 did not. Progression during the trial was the strongest predictor of reaching EDSS milestones at the follow-up visit, 8 years after randomization. Other independent predictors were treatment arm assignment and baseline EDSS score.

Conclusion: In this phase 3 clinical trial of intramuscular interferon beta-1a, compared with effects of treatment, baseline EDSS score, and number of relapses during the study, worsening of 1 point or more on EDSS from baseline lasting 6 months was the strongest predictor of clinically significant disability 8 years after randomization into the clinical trial.


Multiple Sclerosis (MS) is a chronic inflammatory disease of the central nervous system that is usually diagnosed in young adults, with a reported median age at onset of approximately 30 years. In approximately 85% of patients with MS, the disease is initially characterized by relapses and remissions that may be followed by a progressive worsening of neurologic function (secondary progressive MS). Disability in patients with relapsing-remitting MS (RRMS) may also be due to incomplete recovery from relapses or continuously progressive loss of neurological function. The variable clinical course of the disease in individual patients highlights the need for reliable predictors of long-term disability in RRMS.
been suggested that a change in EDSS score sustained for 3 months is suboptimal as a measure of permanent disability progression because, in a proportion of patients, it captures short-term changes in neurologic function that result from relapses. In an analysis of placebo arms of clinical trials in patients with MS, longer sustained disability was associated with reduced likelihood of reverting back to a lower EDSS score. Additionally, the performance of an EDSS-based disability measure will depend on accuracy and consistency when assigning scores over time. Most trials require that a single EDSS examiner assigns scores for any given patient over the course of a clinical trial to eliminate interobserver errors, and many have advocated training sessions to ensure that the EDSS is applied in a consistent manner across the study.

Despite these general measures, the optimal approach to capturing disability progression during RRMS is uncertain, principally because the relationship between EDSS score change during RRMS and long-term clinically relevant disability has not yet been established. Our objective was to determine the relationship between disability progression defined within an RRMS clinical trial and clinically significant disability after a significant time lag.

We used data from a 2-year phase 3 RRMS clinical trial to determine the relationship between sustained EDSS score worsening lasting at least 6 months and clinically relevant disability at 8-year follow-up. Data included in the analyses were from patients who previously participated in the Multiple Sclerosis Collaborative Research Group (MSCRG) study and had received at least 2 years of treatment. We also investigated the effects of treatment, baseline EDSS score, and number of relapses during the study on disability status at 8 years in this patient population. These additional covariates were included to assess the strength of their predictive value relative to the predictive value of disease progression when used in the same model.

**METHODS**

**PATIENT POPULATION AND DATA COLLECTION**

Patients in this analysis were enrolled in the MSCRG trial, a double-blind, placebo-controlled, multicenter phase 3 study in which 301 patients with RRMS were randomized to receive either 30 µg of intramuscular (IM) interferon beta-1a (IFNβ-1a) or placebo once weekly. Of 301 patients enrolled in the original study, 172 were assembled early enough to be followed up for 2 years and thus were eligible to participate in the 8-year follow-up. As long-term follow-up data were not available for the remaining 129 patients, comparisons of long-term predictive value between those patients and the patients with long-term follow-up data were not possible.

One hundred sixty of 172 (93%) eligible patients were enrolled in the study; 137 were seen at a clinic and 16 provided self-reported assessments. Information provided by the families of 7 deceased patients was reviewed by a physician who estimated an EDSS score. Original inclusion criteria were definite MS for at least 1 year, a baseline EDSS score of 1.0 or 3.5 (inclusive), at least 2 documented relapses in the 3 years before enrollment, no relapses for at least 2 months before study entry, and age of 18 to 55 years. As previously described, relapses during the study were defined as appearance of new neurologic symptoms lasting for at least 48 hours in a patient who had been neurologically stable or improving for the last 30 days accompanied by an objective change on neurologic examination (worsening of 0.5 points on the EDSS or worsening of ≥1.0 points on pyramidal, cerebellar, brainstem, or visual functional system scores). If symptoms occurred between scheduled visits, patients were examined by the treating physician to determine if relapse criteria were met. Patients with chronic progressive MS were excluded. The protocol was approved by the respective institutional review boards and informed consent was obtained from all patients. Study visits were scheduled at baseline and at every 6 months. The present analysis included data from patients who completed an EDSS evaluation at 8 years postrandomization.

**ASSESSMENT OF DISABILITY PROGRESSION**

Neurologic disability was evaluated using the EDSS. The EDSS scores were determined at baseline, every 6 months for 2 years, and at 8 years. Sustained disability progression (referred to hereafter as disability progression) was defined as a 1-point or greater worsening from baseline sustained for at least 6 months.

**STATISTICAL ANALYSIS**

The proportion of patients reaching EDSS milestones at the follow-up evaluation (EDSS scores ≥4.0, ≥5.0, ≥6.0, and ≥7.0) was calculated for patients who experienced disability progression and those who did not during the 2-year clinical trial. The same data were calculated for number of relapses (≤1 or >1) during the 2-year clinical trial, treatment (IM IFNβ-1a or placebo), and baseline EDSS score (≥2.0 or >2.0). We selected the median number of relapses and baseline EDSS score as cutoffs for these analyses to balance the number of patients between the outcome comparison groups. The χ² and Fisher exact tests were used to assess the association between progression status, annualized relapse rate, treatment, baseline EDSS score, and disability status at 8-year follow-up. Positive predictive values (PPVs) were calculated to determine the probability of reaching each EDSS milestone at 8 years in patients who had 6-month sustained progression or 1 or more relapses during the 2-year clinical trial. A multivariable logistic regression model was used to assess the consistency of results across assigned treatment arms (IM IFNβ-1a or placebo), 2-year progression status, number of relapses, and baseline EDSS groups and to determine independent effects of each of these variables on reaching EDSS milestones at 8 years. Because the predictive value of these variables can be dependent on disease prevalence within a population, the likelihood ratio (test sensitivity/[1−test specificity]) was also calculated.

**RESULTS**

**PATIENTS**

One hundred sixty of the 172 eligible patients were enrolled in the 8-year follow-up study. Of the 160 patients, 79 were treated with IM IFNβ-1a and 81 were treated with placebo in the original clinical trial. After study completion, patients from the IM IFNβ-1a group were using disease-modifying therapies 46.6% of the time during the follow-up interval, and patients from the placebo group were using disease-modifying therapies for 55.8% of the time during follow-up. Further results from this study have been published elsewhere.
At the end of the original study, 45 of 160 (28%) eligible patients met the criteria for disability progression (18 of 79 [23%] originally randomized to IM IFNβ-1a and 27 of 81 [33%] originally randomized to placebo). Baseline demographics and patient characteristics by progression status are presented in Table 1. Baseline characteristics were similar between patients who met the criteria for disability progression and patients who did not progress, with the exception of T2 lesion volume. Patients who experienced disability progression had a significantly greater T2 lesion volume at baseline compared with patients who did not progress (21,257 vs 13,361; \(P=0.04\)). The number of baseline gadolinium-enhanced lesions was also greater in patients who progressed compared with those who did not, though the difference did not reach statistical significance (4.3 vs 1.8; \(P=0.05\)). Compared with patients who did not have disability progression during the clinical trial phase, patients with disability progression were more likely to reach all 4 EDSS milestones (\(P<.001\) for each milestone) at 8-year follow-up (Table 2). The PPV of disability progression at 2 years was high for EDSS scores of 4.0 or greater, 5.0 or greater, and 6.0 or greater at the 8-year follow-up (84%, 73%, and 67%, respectively). The PPV of disability progression at 2 years for EDSS scores of 7.0 or greater was lower (38%), likely because fewer patients reached this milestone.

The PPVs of sustained disability progression at 2 years were moderate for all EDSS milestones when stratified by treatment group (\(P<.007\) for all EDSS scores; Table 2) or by baseline EDSS score (\(P<.008\) for all EDSS scores; Table 2). Multivariable logistic regression analyses showed significant association between 6-month sustained disability progression at 2 years and disability progression to all EDSS milestones at 8 years (all \(P<.001\)) after adjusting for treatment and baseline score. The relationship between 6-month sustained disability progression at 2 years and disability status at 8 years did not differ significantly across treatment groups or baseline EDSS groups (all logistic regression interactions' \(P>0.05\)).

### EFFECT OF TREATMENT ON 8-YEAR DISABILITY STATUS

Patients randomized to IM IFNβ-1a (n=79) were significantly less likely than patients randomized to pla-
cebo (n=81) to progress to an EDSS score of 4.0 or greater (44.3% vs 65.4%; P = .007) or 5.0 or greater (34.2% vs 54.3%; P = .01) at the 8-year follow-up assessment.

Compared with patients in the placebo group, a lower proportion of patients treated with IM IFNβ-1a progressed to EDSS scores of 6.0 or greater or 7.0 or greater; however, the difference did not reach statistical significance. Thus, while patients who began treatment later in their disease course may have derived some benefits, early treatment significantly reduced the probability of progression to EDSS milestones selected for this study.

IMPACT OF BASELINE DISABILITY ON 8-YEAR DISABILITY

At baseline, 82 patients had scores of 2.0 or less and 78 patients had EDSS scores greater than 2.0. At year 8, patients with baseline scores greater than 2.0 were significantly more likely than those with scores of 2.0 or less to reach a score of 4.0 or greater (74.4% vs 36.6%; P < .001), 5.0 or greater (60.3% vs 29.3%; P < .001), 6.0 or greater (50% vs 22%; P < .001), and 7.0 or greater (18% vs 6.1%; P = .02) (Figure 2). Of 88 patients who reported an EDSS score of 4.0 at the 8-year follow-up, 34 (38.6%) reached that milestone.

### Table 2. Patients Progressing to Specific EDSS Milestones at 8 Years

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>% of Patients Progressing to Specified EDSS Score at 8-Year Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≥4.0</td>
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<tr>
<td>Sustained Disability Progression at 2 y</td>
<td></td>
</tr>
<tr>
<td>Yes (n = 45)</td>
<td>84.4%</td>
</tr>
<tr>
<td>No (n = 115)</td>
<td>43.5%</td>
</tr>
<tr>
<td>Likelihood ratio</td>
<td>0.84%</td>
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<tr>
<td>P value</td>
<td>&lt;.001a</td>
</tr>
<tr>
<td>No. of Relapses Within 2 y</td>
<td></td>
</tr>
<tr>
<td>≤2 (n = 61)</td>
<td>73.8%</td>
</tr>
<tr>
<td>&gt;1 (n = 99)</td>
<td>43.4%</td>
</tr>
<tr>
<td>Likelihood ratio</td>
<td>0.74%</td>
</tr>
<tr>
<td>P value</td>
<td>&lt;.001a</td>
</tr>
<tr>
<td>Baseline EDSS Score</td>
<td></td>
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<tr>
<td>≤2 (n = 82)</td>
<td>36.6%</td>
</tr>
<tr>
<td>&gt;2 (n = 78)</td>
<td>74.4%</td>
</tr>
<tr>
<td>Likelihood ratio</td>
<td>2.37%</td>
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<tr>
<td>PPV of sustained disability progression at 2 y by baseline EDSS score</td>
<td></td>
</tr>
<tr>
<td>≤2</td>
<td>0.74%</td>
</tr>
<tr>
<td>&gt;2</td>
<td>0.96%</td>
</tr>
<tr>
<td>P value by EDSS score</td>
<td></td>
</tr>
<tr>
<td>≤2</td>
<td>&lt;.001a</td>
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<tr>
<td>&gt;2</td>
<td>.008b</td>
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<tr>
<td>Sustained Disability Progression at 2 y by Treatment</td>
<td></td>
</tr>
<tr>
<td>Intramuscular interferon beta-1a (n = 79)</td>
<td>72.2%</td>
</tr>
<tr>
<td>Placebo (n = 81)</td>
<td>92.6%</td>
</tr>
<tr>
<td>Likelihood ratio</td>
<td>3.26%</td>
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<tr>
<td>Intramuscular interferon beta-1a</td>
<td>6.61%</td>
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<tr>
<td>Placebo</td>
<td></td>
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<tr>
<td>P value</td>
<td>&lt;.001a</td>
</tr>
<tr>
<td>Intramuscular interferon beta-1a</td>
<td>.007a</td>
</tr>
<tr>
<td>Placebo</td>
<td>&lt;.001b</td>
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</tbody>
</table>

Abbreviations: EDSS, Expanded Disability Status Scale; PPV, positive predictive value.

a Chi-square test.

b Fisher exact test.
stone during the MSCRG study. At year 8, 10 of 57 (17.5%) patients who had an EDSS score of 6.0 and 2 of 19 (10.5%) patients who had a score of 7.0 reached those milestones during the 2-year study period.

**PREDICTIVE VALUE OF NUMBER OF RELAPSES DURING 2 YEARS**

Within the 2-year study period, 61 of the 160 patients had 2 or more relapses. Of the patients originally randomized to the IM IFNβ-1a group, 24 (31%) had 2 or more relapses vs 37 (71%) of the patients originally randomized to placebo. Compared with patients who experienced 1 or fewer relapses, patients who had 2 or more relapses within 2 years were more likely to reach an EDSS score of 4.0 or more, 5.0 or more, 6.0 or more, and 7.0 or more (P < .001 for all EDSS milestones) at the 8-year follow-up (Table 2). The PPV of number of relapses within 2 years was high for EDSS scores of 4.0 or more (74%); moderate for scores of 5.0 or more (62%) and 6.0 or more (56%); and low for scores of 7.0 or more (28%) at the 8-year follow-up. However, when adjusted for progression status as well as baseline EDSS score in the same multivariate logistic regression, number of relapses within 2 years was no longer a significant predictor of long-term disability at 8 years, nor was the interaction between number of relapses within 2 years and progression status at 2 years statistically significant.

**LIKELIHOOD RATIOS**

The likelihood ratio for sustained disability progression at 2 years was numerically higher (indicating a greater certainty of depicting disease progression) than those for number of relapses at 2 years or baseline disability for EDSS score of 4.0 or greater through EDSS score of 7.0 or greater at year 8. The likelihood ratio for initial treatment with IM IFNβ-1a was numerically higher than that of initial treatment with placebo for patients who reached an EDSS score of 5.0 and 6.0 or greater, but not for patients with an EDSS score of 4.0 or greater or 7.0 or greater at 8 years.

**COMMENT**

In this retrospective analysis, 6-month sustained EDSS worsening of 1.0 or more points from baseline during the 2-year MSCRG study was a significant predictor of progression to EDSS milestones of 4.0 or more, 5.0 or more, 6.0 or more, and 7.0 or more at the 8-year follow-up. Baseline EDSS scores, number of relapses in 2 years, and original treatment group assignment also correlated with disability status at 8 years. Patients randomized to placebo, patients with 2 or more relapses during the 2-year trial, and patients with baseline EDSS scores of 2.0 or more were more likely to reach EDSS scores of 4.0 or greater, 5.0 or greater, 6.0 or greater, or 7.0 or greater at 8 years. Notably, fewer than 20% of patients who reported an EDSS score of 6.0 at the 8-year follow-up reached that milestone during the MSCRG study period. In the final multivariable regression model, the factors that remained in-dependent predictors of the disability milestones, in order of the strength of the prediction, were progression status during the 2-year trial, baseline EDSS score, and initial treatment arm assignment. Number of relapses was no longer a significant independent predictor. These data indicate that the most favorable combination of factors, in terms of long-term outcome, were nonprogressor status during the clinical trial, baseline EDSS score of 2.0 or less, and assignment to the IFNβ-1a arm of the trial.

Many clinical studies have defined disability progression as 3-month sustained EDSS score worsening. We were unable to analyze this definition in the MSCRG trial, because visits were scheduled for every 6 months. However, different definitions of disability progression have been applied in retrospective analyses of patients in the placebo arms of clinical trials of subcutaneous (SC) IFNβ-1a (Prevention of Relapses and Disability by Interferon β-1a Subcutaneously in Multiple Sclerosis study; n = 187) and glatiramer acetate (n = 126). These different definitions consisted of confirmed progression, which included a 1.0-point increase in EDSS score at 3 months, a 2.0-point increase at 3 months, and a 2.0-point increase at 6 months, and resulted in PPVs of 48% to 55% for confirmed progression compared with sustained progression (defined as EDSS worsening sustained until the end of the 2-year study period). Consistent with our findings, the predictive value of confirmed progression, when defined as a 1.0-point worsening at 6 months, was somewhat higher at 67%. The value of 3-month sustained disability progression as a predictor of long-term patient outcomes has been questioned in some studies. For example, Ellison and colleagues studied 569 patients in an MS clinic population. In that study, of 63% of patients who worsened by 1.0 or more Disability Status Scale units, one-third returned to baseline. When the change was required to be sustained for at least 3 months in the same group of patients, 50% worsened, but 18% of these returned to the baseline EDSS score. In addition, analyses of the global MSBase data set showed that during a period of 6 years, up to 50% of patients with confirmed disability progression at 3 months improved back to baseline. Therefore, data reported from this study demonstrating EDSS score
worsening lasting at least 6 months cannot be extrapolated to disability progression defined as 3-month sustained worsening, as is commonly used in contemporary RRMS trials.

The role of relapse as a prognostic factor for disability progression has varied in other studies and may be related to duration of disease or to the way relapses are defined. A study of a large (N = 1099) natural history cohort from Ontario, Canada, reported that in patients with early MS, a high relapse rate (≥5 relapses) within the first 2 years was strongly associated with disability progression. Similar results were seen in patients from 2 more recent natural history studies, 1 conducted in a population from Lyon, France, and 1 conducted in patients from the Lorraine Multiple Sclerosis population-based cohort. Like the Canadian study, both of these studies reported that a higher number of relapses in the first 5 years of disease predicted a more rapid progression to EDSS scores of 4, 6, and 7. However, analyses done by Young and colleagues on the Sylvia Lawry Centre for MS Research database (a database that contains data on the placebo arms from 20 randomized clinical studies) demonstrated that, in patients with late RMS, relapses during the study had no effect on subsequent progression of disability during a typical clinical study follow-up period. In addition, some of these studies reported that once an EDSS score of 4 was reached, the number of relapses was no longer indicative of disease progression. In the MSCRG trial, it is not surprising that the number of relapses during the study predicted subsequent disability milestones, as worsening on the EDSS scale was a required part of the definition for a relapse during the study. The effect of relapses during the study in predicting future EDSS milestones was weaker than the effect of EDSS worsening during the study, as demonstrated by the multiple-regression model.

Patients randomized to IM IFNβ-1a were less likely to progress to EDSS milestones after 8 years compared with patients randomized to placebo. Other long-term studies have also demonstrated a positive impact of early therapy in patients with MS. In a long-term follow-up of the pivotal study of SC IFNβ-1a, patients originally randomized to both the 22-µg and 44-µg doses of SC IFNβ-1a had sustained reductions in relapses and less disease progression compared with patients originally randomized to placebo. Time to confirmed EDSS progression was significantly prolonged in patients originally randomized to the 44-µg dose compared with patients originally randomized to placebo. Patients originally randomized to the higher dose of SC IFNβ-1a also had fewer confirmed EDSS changes compared with patients originally randomized to placebo and patients originally randomized to the 22-µg dose of SC IFNβ-1a. Although all patients received SC IFNβ-1a treatment by year 3 of the pivotal study (patients originally randomized to placebo were switched to either the 22- or 44-µg dose), the increased disability observed in patients for whom treatment was delayed was sustained, and suggests that delaying treatment for as little as 2 years may result in irreversible consequences. Although the impact of early treatment was evident in this study, it is still notable that sustained changes in EDSS predicted progression to EDSS milestones in both arms of the original trial.

When interpreting these results, it is important to consider that the predictive value of a test is dependent on the prevalence of the disease being evaluated, even if the sensitivity and specificity of the test is high. Therefore, PPV can vary depending on disease prevalence in a population. In the present study, calculating the likelihood ratio allows a comparison of the probability of disease progression to the specified milestone in a patient with worse disease during the initial clinical trial, compared with the likelihood of progression to that milestone in patients with more mild disease.

Results from this retrospective analysis of the MSCRG study suggest that 6-month sustained EDSS progression during 2 years is a meaningful intermediate clinical outcome measure that predicts clinically significant disability 8 years later. The disability classification worked in both arms of the clinical trial, which is an important attribute for any intermediate, or surrogate, clinical outcome measure. We recognize that the EDSS score at baseline will have an important impact on the likelihood of reaching the end point. An analysis of the size of that impact was beyond the scope of this analysis. In addition, some patients reached the 8-year clinically meaningful EDSS end point within the 2-year trial, so it is not surprising that these treatment failures predicted the 8-year outcome.

For the time being, EDSS remains the gold standard for observing progression in controlled trials. Results from this study suggest that this measure can be used to meaningfully identify disability progression in an RRMS population and to determine the effect of a disease-modifying therapy on disability progression at this early stage of MS. Caution is needed, however, in extrapolating results of this study to other settings, because of the specifics of the trial design, and it may be possible to design better outcome measures to define disability progression in early stages of MS in the future.

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REFERENCES


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