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Aggressive relapsing multiple sclerosis characterized by rapid disability progression

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Abstract
Background: Criteria for identifying relapsing multiple sclerosis (RMS) patients with aggressive disease, which would be useful for clinical decision making, are currently unavailable.
Objective: Identify RMS patients with aggressive disease characterized by rapid disability progression.
Methods: Data from a 2-year, phase 3, double-blind, placebo-controlled trial with long-term follow-up evaluations of RMS patients taking either intramuscular interferon beta-1a (IM IFNβ-1a, 30 μg) or placebo with baseline Expanded Disability Status Scale (EDSS) scores of 1.0–3.5 were retrospectively analyzed. Patients with a ≥2.0-point increase in EDSS score, resulting in a score ≥4.0 by study end, were considered to have aggressive RMS. The risk of a poor long-term outcome, defined as an EDSS score ≥8.0 at 8 years of follow-up, was calculated as an odds ratio from a logistic regression model comparing patients with and without aggressive RMS.
Results: Only 25 patients met the criteria for aggressive RMS. Among these patients, mean disease duration was 5.1±3.85 years, mean baseline age was 37.2±6.35 years, and mean baseline EDSS score was 2.8±0.74. Fewer IM IFNβ-1a-treated than placebo-treated patients met the criteria for aggressive RMS at 2 years (7% vs 22% on placebo, $p=0.0072$). Thirteen patients reached the EDSS milestone of ≥8.0 by the end of the 8-year follow-up. The odds ratio for attaining severe disability was 86.4 (95% CI, 10.3–726.4; $p<0.0001$) for patients with aggressive RMS compared to patients without aggressive RMS.
Conclusions: Defining aggressive RMS based on rapid EDSS progression was useful in identifying patients at risk for more severe disease course.

1. Introduction

Multiple sclerosis (MS) generally manifests as a progressive degenerative neurologic disorder. However, rates of progression vary greatly among patients and over time, and not all patients experience debilitating disease progression (Scalfari et al., 2010; Pittock and Rodriguez, 2008). Although some

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patients initially experience a slower, less aggressive disease course (Pittock and Rodriguez, 2008), MS disability progression may unexpectedly accelerate after this more indolent early course, and current models of MS progression cannot predict this increase in disease aggressiveness (Gholipour and Healy, 2011). It has been suggested that only the MS relapses that occur during the first few years after diagnosis, and not later relapses, can contribute to predictive models of long-term MS disability (Scalfari et al., 2010). However, the predictive utility of even these early relapses may depend on how they are characterized and recorded (Scott and Schramke, 2010; Lublin, 2011; Ebers et al., 2011).To date, there have been few reports attempting to define and classify severe MS subgroups (Scalfari et al., 2010; Tremlett, 2012; Confavreux et al., 2003; Weiner, 2009; Roxburgh et al., 2005), and these attempts have been largely unsuccessful in identifying predictive parameters. Validated criteria to identify relapsing MS (RMS) patients with aggressive disease could potentially facilitate improved clinical decision making and trial design, but no such validated criteria are currently available. Reaching an Expanded Disability Status Scale (EDSS) score of 4.0 is generally regarded as a turning point for most patients with MS, since at EDSS≥4.0, most, but not all, patients experience relatively constant, irreversible disability progression (Confavreux et al., 2000). It may be possible to identify subgroups of MS patients who are at risk for rapid disability progression based on their MS disease activity leading up to EDSS≥4.0.

In this study, patients with relatively rapid MS progression were identified in the large, long-term, prospectively collected Multiple Sclerosis Collaborative Research Group (MSCRG) database (Jacobs et al., 1996). This cohort was then evaluated for continuing rapid MS progression based on attainment of the EDSS milestone of 4.0 by a given assessment time period and on change in EDSS score over time. Using these data, we propose specific criteria for evaluating RMS that may predict an aggressive disease course in the long term.

2. Methods

Patient data for this study were from the MSCRG study, a phase 3, double-blind, placebo-controlled trial of intramuscular interferon beta-1a (IM IFNβ-1a) in patients with RMS (Jacobs et al., 1996). Patients were required to have a diagnosis of clinically definite MS (Poser et al., 1983) made at least 1 year earlier, a baseline EDSS score of 1.0 to 3.5 and at least two documented clinical exacerbations in the 3 years prior to study enrollment. Patients on study received IM IFNβ-1a 30 μg or placebo once weekly for up to 2 years, and EDSS data were collected at 6-month intervals.

Patients who completed MSCRG were eligible to enroll in an 8-year, open-label extension study (Rudick et al., 2005). A subset of these patients went on to participate in ASSURANCE, a multicenter, single-time-point, 15-year follow-up evaluation that measured treatment effects on patient disability and quality of life (Bermel et al., 2010). Patients were not required to continue IM IFNβ-1a therapy after MSCRG and were eligible for the 8-year and 15-year follow-up studies regardless of their current treatment or their treatment assignment in the MSCRG study.

Table 1 Disease progression risk categories.

Progression risk category	Definition
Less aggressive RMS (EDSS < 4.0)	EDSS < 4.0 at year 2
Less aggressive RMS (EDSS≥4.0)	EDSS≥4.0 at year 2 with a change in score of < 2.0 from baseline to year 2
Aggressive RMS	EDSS≥4.0 at year 2 with a change in score of ≥2.0 from baseline to year 2

EDSS, Expanded Disability Status Scale score; RMS, relapsing multiple sclerosis.

For the current analyses, patients were divided into three disease progression risk categories based on EDSS score at baseline and at year 2 in MSCRG (Table 1). Patients who reached EDSS≥4.0 at year 2 with a change in score of ≥2.0 from baseline to year 2 were defined as having aggressive RMS. Patients who reached EDSS≥4.0 at year 2 with a change in score of < 2.0 from baseline were included in the less aggressive RMS (EDSS≥4.0) cohort. The remaining patients were placed in the less aggressive RMS (EDSS < 4.0) cohort.

Disease progression rates were evaluated only for patients who had completed the 2-year MSCRG study. Differences among the three disease progression risk groups based on original MSCRG treatment assignment were analyzed using the chi-square test. Mean EDSS scores in each group at the 8-year and 15-year follow-up visits were analyzed using ***t*** tests. Changes in EDSS score were evaluated using analysis of variance (ANOVA). The proportion of patients in each group who reached EDSS≥8.0 by the 8-year or 15-year follow-up time points was evaluated using the Fisher exact test. Finally, long-term patient risk of developing severe disability, defined as EDSS≥8.0 by year 8 of follow-up, was calculated as an odds ratio from a logistic regression model. For comparison, the same outcome was also assessed in the 15-year follow-up data from the original MSCRG study.

3. Results

Patient baseline demographic and disease characteristics are presented in Table 2 by progression risk group. Patients with aggressive RMS as defined by their year 2 EDSS scores and EDSS progression over 2 years had a mean (SD) disease duration of 5.1 (3.9) years, a mean baseline age of 37.2 years and a mean (SD) baseline EDSS score of 2.8 (0.7). The majority of patients in MSCRG had less aggressive RMS with EDSS < 4.0 at 2 years (***n***=131). Among the 39 patients with EDSS≥4.0 at 2 years, only 25 patients met the criteria for aggressive RMS. The retrospective distribution of patients among these groups based on original MSCRG treatment assignment showed significantly more patients in the placebo group (22%) than in the IM IFNβ-1a group (7%) meeting the criteria for aggressive RMS at 2 years (***p***=0.0195).