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Long-term Follow-up of Relapsing-Remitting Multiple Sclerosis

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Abstract

Background: Although many studies have shown short-term benefits of disease modifying drugs (DMDs) in reducing relapse rates in patients with multiple sclerosis (MS), the data about long-term effects is more scarce and less certain. The objective of this study was to determine the natural history of relapsing-remitting multiple sclerosis, both treated and untreated, in a real-world setting.

Methods: We analyzed relapse rates and disability scores in 891 patients in a specialized MS clinic followed in a longitudinal database for as long as 21 years. We compared 370 patients who never received treatment with 521 who had prolonged therapy with one of the various DMDs.

Findings: Most patients with relapsing-remitting disease did well, and accumulation of disability was slow regardless of treatment. Among patients followed 10 years or more, mean [median]Expanded Disability Status Scale scores were 3.0 [2.0] among untreated patients and 4.2 [4.3] among treated patients (p=0.0032).There was no correlation between number of relapses and disability.

Conclusion: Many patients have a mild course and accumulate little or no disability. Patients with more severe disease continue to worsen despite therapy but often still do well.

Keywords: Treatment; Disease-modifying drugs; Database; Longitudinal study; Natural history; Disability

Introduction

Randomized, placebo-controlled trials (RCTs) have consistently demonstrated a modest benefit for disease-modifying drugs (DMDs) in reducing relapse rates over short periods of time in patients with multiple sclerosis (MS) [1-3].The evidence that they can prevent long-term disability is controversial and less certain [4,5]. Rigorous, randomized, placebo-controlled trials extending over the many years required to measure long-term disability would be impractical to conduct and probably unethical [6]. Therefore, efforts to assess the effect of DMDs on ultimate disability have used other methods, especially open-label extensions of Phase III trials [7-9]. These studies are limited, however, since the original cohorts were often biased by selection for high attack rates, and problems during subsequent follow-up included loss of randomization, high dropout rates, small numbers of patients, and unblinding [10]. Another way to determine the long-term impact of DMDs is through longitudinal databases that follow large numbers of MS patients in real-world settings. Such prolonged observational studies, while not definitive, can provide valuable information on the behavior of large cohorts of patients over extended periods of time [11-15]. The purpose of this study is to analyze the natural history of relapsing-remitting MS, including the effects of long-term treatment with DMDs, for up to 21 years.

Methods

The Marshfield Clinic Multiple Sclerosis Center serves a predominantly rural population in Central Wisconsin, where there are few other neurologists and no other MS centers for a radius of 150 miles. Almost all patients with MS in this geographic area are seen at this center, resulting in very high attainment and very low referral bias. When the Food and Drug Administration approved beta-interferon-1b as the first DMD for MS in 1994, we established a database to evaluate response to therapy. Since then, each patient has been personally examined at each visit by the same neurologist (LAR) and their data entered into an on-going database including relapses, drug therapy, and Expanded Disability Status Scale (EDSS) scores. Relapses were defined as the abrupt onset of objective neurologic symptoms persisting greater than 24 hours and producing at least 1 point on the functional subsystem scale [16]. Almost all relapses were personally confirmed with an office visit. The dates patients started, switched, or stopped DMD therapy were recorded, along with the date of each relapse, and whether the relapse occurred while receiving a DMD. Most relapses were treated with a brief regimen of oral or intravenous corticosteroids. It was also recorded when patients entered a secondary progressive phase of their illness, defined as the sustained

progression of symptoms for 6 months or longer [16]. At each encounter, the EDSS score was also calculated for every patient. The data was, thus, constantly up-to-date.

All patients had a proven diagnosis of MS by the Poser or McDonald criteria, and had clinically isolated syndrome or relapsing-remitting course at disease onset [17,18]. These patients were evaluated personally (historical data was excluded) and had at least two EDSS measurements. Patients seen only once, with no follow-up, were excluded. All data were analyzed from the time the first DMD became available at the MS center in August 1994 until 22 years later in August 2016. During this span, most of the approved drugs were "platform" therapies with interferons or glatiramer and smaller numbers of patients accessed the later approved oral or infusion therapies. As in most clinical settings, treatment was decided in a shared decision making model between doctors and patient. All patients were offered treatment with a DMD as standard practice. Some chose not to receive therapy, either from fear of potential side effects, financial constraints, insurance coverage, planned pregnancy, needle phobia, convenience, a preference for non-pharmacologic treatment, or other real-world factors. To evaluate efficacy, treated patients were followed as long as they remained on therapy and excluded only if they were lost to follow up. They were compared against those patients who never received any treatment at any time during follow-up.

Descriptive statistics including the mean and its standard deviation, the median, and the range for continuous measurements (e.g., age at onset of therapy, duration of therapy or follow-up); and the frequency and percentage for discrete data (e.g., gender) were calculated for treated versus untreated patients. The difference in frequency of relapse between treated and untreated patients for each drug was compared using Chi-Square or Fisher's Exact Test. For disability scores, comparisons were made between the median values among patients (untreated vs. treated) using Wilcoxon Rank Sum test. Kaplan-Meier curves were generated to assess differences in survival time to secondary progression (time to event was the number of years from disease onset until either end of follow-up or secondary progression occurred). To test for differences between the curves, we used the Log-Rank Test. Comparisons were also made using a multivariate accelerated failure time model and a linear regression model for cross-sectional data. All data analyses were carried out using commercially available statistical software. The research was approved by the Marshfield Clinic Institutional Review Board.

Results

Between August 1994 and August 2016, 891 patients meeting inclusion criteria were seen and enrolled in the database. On average, the 521 patients treated with one of the DMDs were slightly younger than the 370 untreated patients **(Table 1)**. They also had slightly higher disability scores when first evaluated (mean EDSS=2.9 compared to untreated patients mean EDSS=2.4,p=0.00014), although the clinical difference was small. However, there was no difference in annual relapse rates prior to initial evaluation and treatment (0.26 *vs*. 0.21, p=0.69). In general, treated patients were seen more frequently and had more EDSS measurements than untreated patients (mean of 12 visits versus 8 visits, p <0.0001). Some patients were followed for 21 years, but the mean follow-up was 7.1 years in the untreated group and 8.2 years for treated patients.

Table 1: Characteristics of patients seen at the Marshfield Multiple Sclerosis (MS) Center.

	Untreated	Treated	P-value
Number	370 (42%)	521 (58%)	-
Female	281 (76%)	376 (72%)	0.206
Mean Age of MS Onset (years)	33.7	31.7	0.007
Family History of MS	27 (7.3%)	36 (6.9%)	0.824
White Ethnicity	368 (99%)	517 (99%)	0.998
Initial EDSS	2.4	2.9	0.001
Final EDSS	3	4.2	0.003
Annualized Relapse Rate	0.26	0.21	0.69
Average Length of Follow up (years)	7.1	8.2	-
EDSS, Expanded Disability Status Scale			

Treatment was well-tolerated, and 471 (90.4%) treated patients remained on either the first or second DMD prescribed, including 171 patients treated with beta-interferon-1b (Betaseron), 167 treated with beta-interferon-1a weekly (Avonex), 41 treated with beta-interferon-1a thrice weekly (Rebif), 309 treated with glatiramer (Copaxone), 59 treated with mitoxantrone, and 25 treated with others(dimethyl fumarate, teriflunomide, nataluzimab, fingolimod, rituximab). Because there was no difference in EDSS scores or relapse rates among these drugs or patients switching drugs, data are presented as an aggregate of all treated patients [19].

Among the 370 untreated patients the average annual relapse rate was 0.13. The 571 treated patients had an average annual relapse rate of 0.26. Most relapses in both groups recovered well and produced little or no disability. There was no correlation between the number of relapses and the final EDSS scores (r=0.008 in the treated group and r=0.06 in the untreated group). The mean[median] EDSS score of all untreated patients followed 10 years or more was 3.0 [2.0].Whereas, the mean [median] EDSS scores in the treated cohort followed 10 years or more was 4.2 [4.3] (p=0.0032).This difference was more pronounced with longer follow-up as shown in **Figure 1a**.

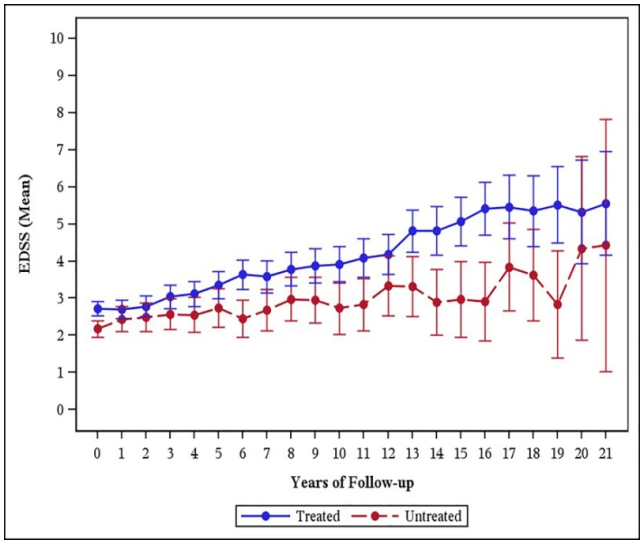

Figure 1a: Disability in treated and untreated patients with relapsing-remitting or clinically isolated MS.

We analyzed comparable subsets of both mild and more severely affected patients. **Figure1b** shows the cohort of treated (n=191) and untreated (n=178) patients whose EDSS was ≤ 1.5 at initial evaluation. These subset groups did not differ on initial EDSS scores (Z (two-sided) =-1.72, p=0.09). However, therapy did not prevent subsequent worsening disability. For example, after 10 years the mean EDSS among treated patients was 1.9 compared to 1.0 untreated, as shown in **Figure1b**. We then evaluated patients with more aggressive disease (198 treated and 102 untreated) who had an EDSS ≥ 3.0 when first seen. EDSS scores were again well matched at initial evaluation (Z (two-sided) =-0.17, p=0.86). Patients continued to accumulate disability at approximately the same rate regardless of therapy. For example, after 15 years the mean EDSS among these treated patients was 6.4 compared to 6.0 untreated (**Figure 1c**).

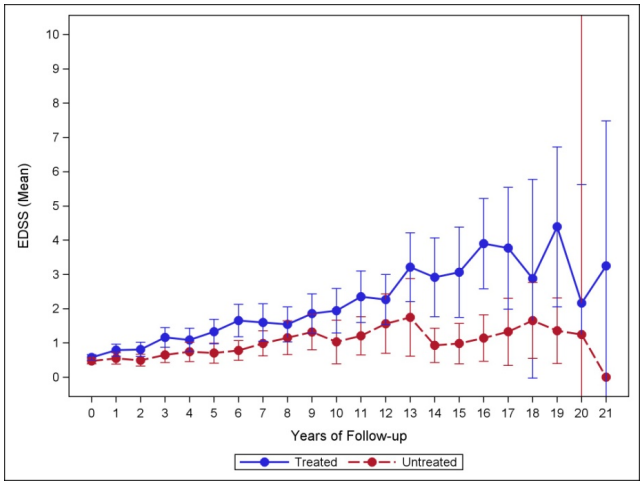

Figure1b: Disability in treated and untreated patients with mild disease at initial evaluation.

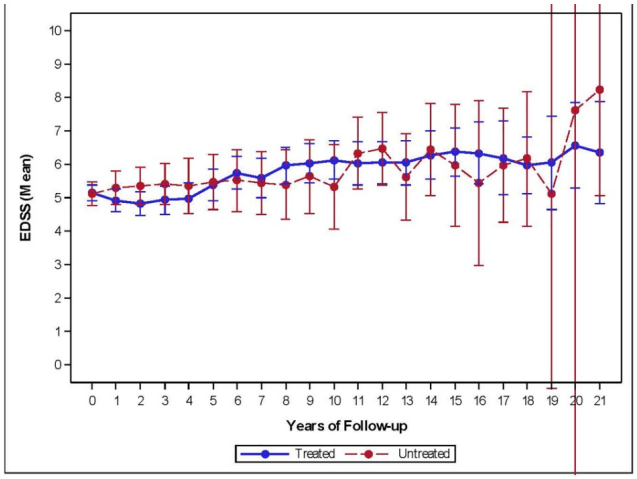

Figure 1c: Disability in treated and untreated patients with worse disease at initial evaluation.

An alternative to the EDSS as a measure of disease severity is the Multiple Sclerosis Severity Score (MSSS), which accounts for length of disease duration to assess disease severity, and allows a cross-sectional comparison of disease activity between groups over time [20]. **Figure 2** shows the mean MSSS for the treated and untreated groups across 29 years of disease (calculated from disease onset, not years of follow-up). By accounting for length of disease, disability as measured by the MSSS does not show as much increase over time as does the EDSS alone. In our treated cohort disability maintained a relatively constant, flat rate, with no slowing of progression. Conversely, the untreated group showed little change in severity for up to 14 years after onset.

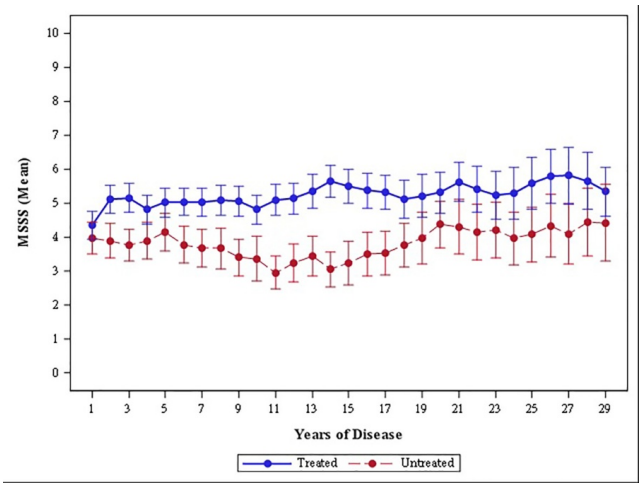

Figure 2: Multiple sclerosis severity scores in treated and untreated patients.

Across the entire cohort, secondary progressive disease developed in 101 (27.3%) untreated patients and182 (34.9%) treated patients p=.0158). Treatment did not prevent or delay secondary progression, as seen in **Figure 3**.According to the

Kaplan-Meier curves, the treated patients achieved secondary progression faster than untreated patients, throughout the entire disease course. The median survival time to secondary progression among treated patients was at 22.9 years after disease onset; whereas, the median survival time to reach secondary progression for the untreated cohort was 29.4 years ($p< 0.0001$). We analyzed the mild and severe disability subsets again, in terms of time to secondary progression. For the mild subset (initial EDSS ≤1.5), very few patients reached secondary progression in either treatment group (27 out of 191 or 14.1% for treated; 11 out of 178 or 6.2% for untreated). Unfortunately, these low numbers for the event of interest produced inadmissible Kaplan-Meier curves (not reported). However, for the severe disability subset (initial EDSS ≥3.0), secondary progression occurred more often in both groups (125 out of 198 or 63.1% for treated; 71 out of 102 or 69.6% for untreated). The median survival time to secondary progression among treated patients in the severe subset was 21.5 years; the same outcome for untreated patients was 26.7 years ($p<0.001$).

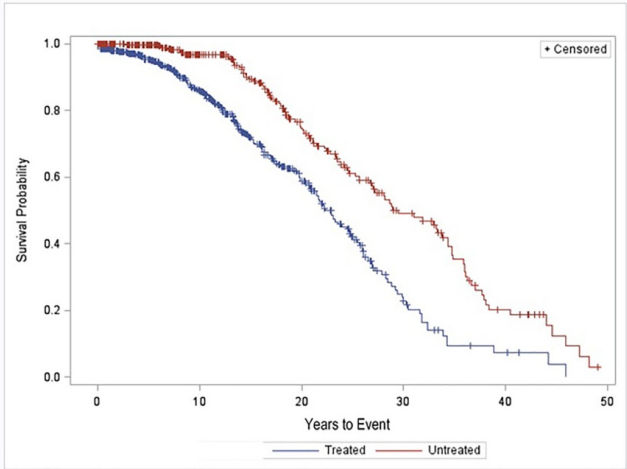

Figure3: Kaplan-Meier analysis of time to reach secondary progression in treated and untreated patients.

To account for selection bias in the treated group, we used a Weibull accelerated failure time model for time to EDSS ≥ 3 as a function of treatment. We adjusted for median EDSS in the first year of evaluation, gender, age at MS onset, and age at initial evaluation. Adjusting for these covariates was done to address the bias in the treatment cohort resulting from the non-randomized sample. This analysis showed that the average time to worsened disability for treated patients was 0.86 that of untreated patients ($p=0.002$, 95% CI 0.77- 0.94), so treatment did not show a decelerating effect on disability progression. Results showed that older age of MS onset and greater initial disability were poor prognostic factors: at onset, a patient's time to reach EDSS ≥3 decreases by 5% for each year older, and by 14% for each EDSS point higher. However, because the validity of estimating the effect of treatment on the rate of worsening disability in such a failure time model can be skewed due to the more frequent visits among treated patients, we also used a cross-sectional approach to address selection bias. We again adjusted for median EDSS in the first year, gender, age at MS onset, and age at initial evaluation. The results were similar: measured at 10 years of follow-up, treated patients had EDSS scores that were on average one point higher than untreated patients ($p=0.0002$). This worse outcome was still present at 15 years. Initial EDSS was again a significant predictor of more future disability.

Discussion

Because MS is a chronic disease with great variability, it has been impossible to design and implement a perfect therapeutic study. However, clinicians treating patients can obtain useful guidance from prolonged observation of therapeutic response in a real world setting, such as in this database [21, 22]. From the first day treatment with DMDs became available for MS (beta-interferon-1b in 1994), data from every patient at every encounter was entered in real time. The result is a consistent (one institution), representative (minimal referral bias) cohort of a large number (n=891) of patients followed longitudinally over a long period of time (up to 21 years).

Many patients had a benign course. Long after their disease onset, among patients followed 10 to 21 years, most had no significant disability (mean EDSS of 4.2 or less). Patients whose initial symptoms were mild were more likely to continue a mild course, often without secondary progression or later disability. Severe initial disability predicted higher rates of secondary progression and a worse course. This was true regardless of treatment. The only other feature associated with a poor outcome was older age of onset.

The relationship between treatment of relapses and prevention of disability either short-term or long-term has been controversial and vexed by conflicting findings. Some data have suggested that treatments for relapsing-remitting MS improve long-term prognosis [23]. Conversely, other studies have shown that relapses have little or no correlation with permanent disability [24, 25]. In our study, the number of relapses was not associated with ultimate disability.

In this large, unselected cohort of patients followed for a long period of time, the relapse rates and disease activity were generally milder than in most randomized treatment trials, which usually are smaller, shorter, and enroll patients with more aggressive disease. However, our data are consistent with other long-term studies of relapsing-remitting MS that showed good recovery from most relapses and slow disability progression of approximately 1 EDSS score per decade [26-29].

Although all patients were offered DMDs regardless of disease status, our cohort of treated patients did worse than untreated patients on several parameters. Various factors could account for this. This could result from measurement bias since their more frequent evaluations and EDSS assessments might detect progression earlier than in the untreated patients who were not assessed as often. Also, it is possible some treated patients may have done worse because prolonged use of DMDs can cause medical complications and side effects that produce more disability [30]. Another concern

is selection bias, since in the real-world, patients with severe, aggressive disease may be more likely to begin and continue therapy than patients with milder disease. We employed several analyses to address this bias and make the two groups as matched and identical as possible including adjusting for variables that could account for more severe disease in the treated group such as gender, age of onset, age of initial evaluation and initial degree of disability. Definitive conclusions cannot be drawn from open, real-world studies, but after adjusting for potential confounding variables and known prognostic factors we were not able to determine that there were long term benefits of DMDs on disability progression.

Our results are concordant with some smaller studies that also failed to find significant improvement in patients treated with DMDs. A similar longitudinal study limited to interferon showed no difference in disability between treated and untreated patients [31]. A shorter study employing the MSSS also showed lack of a major impact of DMDs upon disease severity [32]. Other open studies lasting as long as a decade or more have also shown little difference between treated and untreated patients and a generally benign course with low rates of disability [33-35].

Our study has limitations. Although evaluation by a single neurologist at one institution eliminates inter-observer variability and improves reliability, it could potentially introduce personal biases and errors. The fact that the data agree with findings from other studies suggests these are not significant confounding factors, however. Another limitation is that our population is rural and white and may not be representative of urban, ethnic, or other MS patients. The study was also not designed to determine if DMDs could be beneficial for symptoms not assessed by the EDSS, such as fatigue or cognitive dysfunction. Also, some of the 16 DMDs were approved only recently, or were not used by our patients, so firm conclusions cannot be made about long-term efficacy of all drugs. Despite these considerations, our large, long longitudinal study provides information difficult to obtain by any other method. Given the impossibility of prolonged randomized blinded trials, a recent recommendation has advocated assessing treatments using a design of observational studies in single-center cohorts, such as ours [36].

Conclusion

Our results show that the natural history of relapsing-remitting MS is mild in many patients throughout their disease course, and many avoid disability. This should be reassuring to patients and physicians especially those with limited access to drugs. Disability is not related to relapse rate. Late age of onset and severe initial symptoms are predictors of a future worse course. Therefore physicians and patients should discuss appropriate therapeutic decisions on an individual basis.

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