Outcomes in a Modern Cohort of Treated Patients with Multiple Sclerosis from Diagnosis Up to 15 Years

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Background: Before disease-modifying therapies (DMTs) were available, the natural history of multiple sclerosis (MS) regarding attainment of accepted disability milestones was reported with fairly wide variance comparing outcomes across studies. The influence of DMTs on these outcomes is unknown. This study aimed to calculate attainment of disability milestones during the first 15 years after onset of DMT-treated relapsing forms of MS (RMS).

Methods: As a retrospective study, all available disability data (collected routinely) on all newly diagnosed patients with RMS seen and initially diagnosed in a single clinic between 1989 and 2006 were reviewed. Times from first symptoms and diagnosis until first treatment with DMTs were also reviewed. Time-to-event statistics were applied using disability milestones.

Results: Mean follow-up of 184 adult patients from symptom onset was 13.7 years. Of patients followed up for 15 years after onset, 16 of 86 (19%) reached an Expanded Disability Status Scale (EDSS) score of 6.0. Estimated median time to reach an EDSS score of 3.0 was 10.7 years and to reach an EDSS score of 4.0 was 18.1 years.

Conclusions: There were striking differences between the present results and older data sets and similar results to the few available modern data sets. This analysis of a modern treated RMS cohort provides outcomes data that may be compared favorably with the natural history of RMS. Int J MS Care. 2020;22:110-114.
lected outside the realm of controlled trials. We now add outcomes data from this retrospective analysis and the research questions generated at a single MS treatment center to the growing number of studies that aim to reveal the expected course of RMS in the treatment era, and we compare these results with those of natural history studies.

Methods

Participants and Methods

Inclusion and exclusion criteria for the 184 patients in this historical cohort were chosen for study by retrospective review of medical records and are also described in a previous report. All the patients attended the Allegheny MS treatment center, established in 1989, and met the McDonald criteria for a diagnosis of RMS. To longitudinally assess a “from-time-of-diagnosis” group, patients were included if they were evaluated within 12 months of a second disease-defining attack or had serial magnetic resonance imaging (MRI) changes leading to a diagnosis of MS while under our care. Onset of the disease (time zero) was determined by patients’ self-report of first symptoms that the examining physician deemed clearly related to RMS. Patients meeting this definition for newly diagnosed RMS were identified from patients seen consecutively between February 1, 1989, and December 31, 2006. All the patients had Expanded Disability Status Scale (EDSS) scores for at least year 5 after onset of symptoms, confirmed by repeated examination at least 6 months later. Approval was obtained by our internal institutional review board and ethics board (Allegheny Health Network Research Institute, Pittsburgh, PA). The need for informed consent was waived.

Definitions and Statistical Analysis

The EDSS measurements at the first visit were confirmed at least 6 months later. Changes in EDSS scores used for analyses were confirmed for each measurement at least 6 months later and were considered permanent. Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 24.0 (IBM Corp, Armonk, NY). Kaplan-Meier analyses were used to test for the effect of time-to-disability outcomes (EDSS scores 3.0, 4.0, and 6.0), and we conducted three separate Kaplan-Meier analyses using the same cohort with these end points. Patients were censored due to being lost to follow-up if not seen during at least 12-month intervals and if they reached the end of a follow-up period without an event.

Results

The 184 patients studied (age > 18 years) had a mean ± SD age at symptom onset of 35.4 ± 8.7 years; 140 were women and 44 were men (Table 1). Diagnosis was at a mean ± SD age of 37.05 ± 9.1 years. Mean ± SD follow-up from onset of symptoms was 13.7 ± 4.3 years, with 147 of 184 patients (80.0%) still being actively followed up at the time of the medical record review. Patients lost to follow-up were followed up for a mean ± SD of 11.6 ± 2.1 years from onset and were similar demographically to the entire group in age, sex, initial EDSS score, and time to first treatment. Most patients (140 of 184 [76%]) were examined at least yearly from diagnosis until 10 or more years after the onset of symptoms by a single examiner who rated EDSS score. A smaller percentage of patients, 86 of 184 (47%), completed EDSS measurements through 15 years or more after onset. Mean time from symptom onset until diagnosis was 2.3 years. Initial events were often retrospectively recalled by patients at the time of their first visit to a neurologist.

The estimated median time from first symptoms to an EDSS score of 3.0 was 10.7 (95% CI, 9.16-14.4) years, with the first quartile reaching an EDSS score of 3.0 in 4.7 years. An EDSS score of 4.0 was reached at a median of 18.1 (95% CI, 16.3-18.4) years, with the first quartile being reached in 9.9 years. For 25% of patients to reach an EDSS score of 6.0, the median estimated time was 16.3 years. Estimated time-to-event analyses using the Kaplan-Meier method are shown in Figure 1. Of patients still being followed up 15 years after symptom onset, only 16 of 86 (19%) reached an EDSS score of 6.0, and the median time to event was not calculated.

All but three patients were treated with DMTs (patient preference). Mean time from symptom onset and from diagnosis until first treatment was 37.5 months and 18.3 months, respectively. Patients were treated with either glatiramer or interferons (181 of 184 [98%]), and a small percentage were briefly exposed to natalizumab (40 of 184 [22%]), usually late in the disease and after reaching an EDSS score of 4.0. Only 24 patients were diagnosed before interferon beta became widely available for use in 1994, and these patients eventually received DMTs at the same rate as others (Table 1). We previously reported Kaplan-Meier analyses of individual risk factors for RMS.

Table 1. Cohort demographic characteristics

| Characteristic                  | Total group (N = 184) | Seen before 1994 (n = 24) | Seen after 1994 (n = 160) | Lost to follow-up (n = 34) |
|--------------------------------|-----------------------|---------------------------|---------------------------|---------------------------|
| Sex, M/F                       | 44/140                | 8/16                      | 36/124                    | 7/27                      |
| Sex ratio, F:M                 | 3.2:1                 | 2:1                       | 3.4:1                     | 3.9:1                     |
| Age at diagnosis, y            | 37.05 ± 9.14          | 34.98 ± 8.94              | 37.36 ± 9.16              | 38.5 ± 10.4               |
| Age at symptom onset, y        | 35.4 ± 8.71           | 34.2 ± 8.83               | 35.5 ± 8.71               | 37.6 ± 9.0                |
| First confirmed EDSS score     | 1.15 ± 1.17           | 0.925 ± 0.950             | 1.2 ± 1.2                 | 1.7 ± 1.1                 |
| First onset to treatment, mo   | 37.5 ± 42.81          | 26.4 ± 23.65              | 39.1 ± 44.80              | 14.6 ± 14.6               |

Note: Values are given as number or mean ± SD. Abbreviation: EDSS, Expanded Disability Status Scale.
characterizing a single-center experience of outcomes during the past 3 decades provides a similar profile of improvement in prognosis.10

We share our methods with the most frequently cited natural history studies by reporting outcomes in terms of time-to-event statistics.1,4,5 Using similar or identical methods, reported outcomes regarding time to attainment of disability have demonstrated wide variance, even before the development of DMTs (median of 15-28 years to reach an EDSS score of 6.0).1,4,5 Figure S1 and Table S1, which are published in the online version of this article at ijmsc.org, provide graphic and numerical comparisons of selected well-known previous studies.1-7,9,11,12,19,20 Natural history data sets, some of which are outlined in multiple publications, were obtained from patients generally entered for data collection between 1950 and 1990. These data sets are presented in terms of estimated median time to EDSS milestones, or, when only a small number of patients reach these milestones, frequency statistics are sometimes

Discussion

When we examine the outcomes data along with some of the most recent reports of other MS treatment centers, we note that, overall, the trends suggest potentially better outcomes compared with natural history studies. We are attempting to estimate the trajectory of disability in RMS in an era of a few decades that were likely heavily influenced by new definitions for diagnosis (ie, the MRI era) and new treatments (ie, DMTs). Disability milestones were reached in the present cohort at times from onset similar to the mildest natural history cohort from the pretreatment era, despite our patients being on average 5 years older at onset.4 Outcomes in our center predictably land between those of studies that included cohorts assembled before the DMT era and studies of treatment outcomes of patients with CIS receiving even earlier DMT use.11,12 A recent report

Figure 1. Kaplan-Meier time-to-event analyses (15 years). Time to Expanded Disability Status Scale scores of 3.0 (A), 4.0 (B), and 6.0 (C) in the 184 study participants.

Data are given as median (95% CI).
substituted (Table S2). Much of these data can be considered “pretreatment era,” although patients may have received intermittent corticosteroids, and at some centers a minority of patients received immunosuppressants such as azathioprine. More recent studies continue to use time-to-event analysis but also focus on the proportion of patients reaching milestones per decade (Figure S1). The median time for reaching disability levels of 3.0 and 6.0 (EDSS scores) became longer in more recent data sets.

A very recent relative “snapshot” of patients with RMS with, on average, similar disease duration as the present cohort, followed closely and longitudinally in a single center, suggests that the reported natural history of MS will no longer be ascertainable. This overall view matches the impressions of most presently practicing clinicians who are old enough to remember the makeup of their MS clinics in the 1980s and 1990s (personal observations, T.F.S. and Robert M. Herndon, MD [verbal]). Patients studied in the present report were typically treated with DMTs within a few years of diagnosis, with almost all patients (98%) receiving either interferons or glatiramer, only a small group receiving natalizumab, and no patients receiving oral DMTs. Based on the present data, the improvement in the decade or two wherein most patients were treated early with interferons or glatiramer represents approximately a 2-decile improvement on the Multiple Sclerosis Severity Score. Early treatment of patients with CIS reported by others seems to produce greater improvement. Availability of the newest and most efficacious DMTs is expected to further change long-term outcomes. It may be reasonably predicted that other centers will soon document a marked increase in “benign MS” during each of the past 2 decades compared with previous periods; in fact, one large center has already succeeded in doing so.

There are several reasons why the previous changes in the long-term disability outcomes attributable to treatments are difficult to quantify; our center’s data are subject to these limitations (Table S3). For example, the use of historical data sets for comparison of outcomes, collected in a nonuniform manner across single centers, prompts the consideration of whether any data set gives outcomes that can be generalized worldwide (or must we reasonably limit interpretation to only region, era, and ethnic/genetic populations). Population-based studies claim a certain advantage in terms of accuracy but may not reflect the disease state across the world population and the real-world experience of practicing clinicians. Data from single centers, especially referral centers, may be prone to selection and investigator bias versus multicenter efforts, which can only partially overcome these limitations. In addition, there are limitations to our statistical models, which can be only partially overcome after adjustments such as propensity matching. We note that the studies in Table S1 have most of the same limitations as the present study.

Some of these limitations may be overcome by using much larger data sets collected through multicenter collaborations. Such studies can address more detailed questions concerning long-term treatment responses to multiple different medications but are thus far rare. Even single-center longitudinal studies such as ours, performed in the treatment era, remain rare and may reveal important changes in the real-world experience of MS care. The number of patients we studied may seem small compared with other similar efforts, but our seen-from-diagnosis design excluded most patients in our clinic, without creating any clear ascertainment bias. Although large multicenter registries will provide improved accuracy of disease behavior concerning large populations seen in multiple settings, we believe that carefully collected single-center experience will remain important in understanding this complex disease.

Concerning future similar studies, we would like to determine whether the newest treatments are more efficacious than initial DMTs (used as both first and second line), while recognizing that we do not fully know the effect of the earliest treatments. Until recently, there have been no long-term detailed data sets that

**PRACTICE POINTS**

- Expanded Disability Status Scale milestones during the first 15 years of MS in a cohort of 184 patients were ascertained.
- Long-term prognosis in this cohort seems improved compared with before the disease-modifying therapy era, similar to in other single-center studies.
- Multicenter studies of the changing natural history of relapsing MS can give more generalizable findings than single-center studies provided that the methods are uniform across centers (in ascertainment, management of comorbidities, and treatment bias).
are acceptable for the study of treatment outcomes, which should include a low dropout rate and multiple recorded examinations for many years after treatments. The pivotal trials of the earliest DMTs produced only a few examples of long-term follow-up with good retention rates.\textsuperscript{22,23} Even the newest studies presented herein may be hindered by ascertainment bias, questions of possible regional differences among populations, and methodological sources of bias (limitation of measurements, treatment bias, etc). However, the present results are in general agreement with those of other early reports and trends, and the overall conclusion is favorable for newly diagnosed patients with RMS. Despite the inherent difficulties in assessing the impact of the arrival of the DMTs, the interest level to clinicians and patients is high, and clear answers will help inform basic science researchers as well.

In conclusion, it has now been more than 2 decades since DMTs have been widely available. The long-term impact of DMTs may now be coming into focus as a new prognosis for RMS is unfolding. Although the present results seem favorable, measurement of the long-term effect of new treatments on the moving target of long-term prognosis still represents a daunting challenge. The availability of highly efficacious treatments will hopefully make this easier. □

**Financial Disclosures:** Dr Scott has received payments for research activities, advisory boards, promotional speaking, and consulting from Genentech, Teva Neuroscience, Biogen, Novartis, and Genzyme. Dr Elmalek has received honoraria for speaking from Biogen, EMD Serono, Novartis, and Sanofi Genzyme and has attended advisory board sessions for Genentech and Sanofi Genzyme. Dr Schramke and her spouse own more than $10,000 worth of Pfizer stock. The other authors declare no conflicts of interest.

**Funding/Support:** None.

**Prior Presentation:** This work was previously presented at the Annual Meeting of the American Academy of Neurology; April 21-27, 2018; Los Angeles, CA.

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