Effect of Disease-Modifying Therapy on Disability in Relapsing-Remitting Multiple Sclerosis Over 15 Years

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Abstract

Objective

To test the hypothesis that immunotherapy prevents long-term disability in relapsing-remitting multiple sclerosis (MS), we modeled disability outcomes in 14,717 patients.

Methods

We studied patients from MSBase followed for ≥ 1 year, with ≥ 3 visits, ≥ 1 visit per year, and exposed to MS therapy, and a subset of patients with ≥ 15 -year follow-up. Marginal structural models were used to compare the cumulative hazards of 12-month confirmed increase and decrease in disability, Expanded Disability Status Scale (EDSS) step 6, and the incidence of relapses between treated and untreated periods. Marginal structural models were continuously readjusted for patient age, sex, pregnancy, date, disease course, time from first symptom, prior relapse history, disability, and MRI activity.

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MSBase Study group coinvestigators are listed at links.lww.com/WNL/B283.

Glossary

CI = confidence interval; EDSS = Expanded Disability Status Scale; HR = hazard ratio; MS = multiple sclerosis; NNT = number needed to treat.

Results

A total of 14,717 patients were studied. During the treated periods, patients were less likely to experience relapses (hazard ratio 0.60, 95% confidence interval [CI] 0.43–0.82, $p = 0.0016$), worsening of disability (0.56, 0.38–0.82, $p = 0.0026$), and progress to EDSS step 6 (0.33, 0.19–0.59, $p = 0.00019$). Among 1,085 patients with ≥ 15 -year follow-up, the treated patients were less likely to experience relapses (0.59, 0.50–0.70, $p = 10^{-9}$) and worsening of disability (0.81, 0.67–0.99, $p = 0.043$).

Conclusion

Continued treatment with MS immunotherapies reduces disability accrual by 19%–44% (95% CI 1%–62%), the risk of need of a walking aid by 67% (95% CI 41%–81%), and the frequency of relapses by 40–41% (95% CI 18%–57%) over 15 years. This study provides evidence that disease-modifying therapies are effective in improving disability outcomes in relapsing-remitting MS over the long term.

Classification of Evidence

This study provides Class IV evidence that, for patients with relapsing-remitting MS, long-term exposure to immunotherapy prevents neurologic disability.

Prevention of long-term disability accrual is currently the main goal of multiple sclerosis (MS) treatment. The available immunotherapies mitigate clinical and subclinical inflammation within the CNS.¹ Some of these therapies reduce disability accrual over the short term (≤ 3 years).^{2–5} Extension studies and randomized clinical trials suggested that timely immunotherapy may delay conversion to clinically definite MS,^{6–8} accumulation of disability,^{9,10} and death.¹¹ However, observational studies reported conflicting results. One study did not find differences in disability outcomes between interferon- β and no treatment (even though contrasting trends were seen when interferon- β was compared to historical and contemporary untreated controls).¹² Conversely, interferon- β and glatiramer acetate were shown to mitigate disability accrual over 10 years in the UK MS Risk Sharing scheme.^{13,14}

Proof of long-term effect of immunomodulation on the accumulation of MS-related neurologic disability is the key to establishing its disease-modifying properties. However, conclusive evidence is lacking and it is unlikely that it will arise from randomized trials.

We present a study from MSBase, the largest international MS registry, whose aim was to compare worsening and improvement of disability and incidence of relapses during periods of treatment vs no treatment with MS immunotherapies over more than 15 years of follow-up. We hypothesised that continued treatment is associated with substantially reduced cumulative hazard of disability worsening over the long term. Comparisons of observational data between treated and untreated patients are obfuscated by reverse causality, and randomized clinical trials that would address this question are neither feasible nor ethical. Therefore, this study used

information about relapses and worsening/improvement of disability from an MS registry analyzed with causal inference methods to adjust for time-dependent confounding and treatment indication bias in longitudinal data.

Methods

Study Design

This study compared long-term disability outcomes during periods under treatment and periods not under treatment recorded in an observational cohort of patients with MS and eligible for immunotherapy (Class IV evidence). The study estimated frequencies of relapses and disability accumulation or improvement events in patients who were hypothetically always exposed vs never exposed to disease-modifying therapies for MS. Because these 2 extreme scenarios are rarely directly observed, and if so, outcomes are usually strongly confounded by treatment indication bias, we have used a counterfactual framework (a statistical framework comparing outcomes of directly observed and counterfactual [potential] treatments in the same cohort) to estimate causal associations between long-term exposure to therapies and outcomes (confirmed worsening or improvement of disability, incidence of relapses, Expanded Disability Status Scale [EDSS] step 6). In the studied cohort, we have combined all observed periods on treatment into a treated pseudocohort (a hypothetical cohort derived from an observed cohort in the counterfactual framework) and all observed periods not on treatment into an untreated pseudocohort. The counterfactual framework enables an analyst to quantify the probability of reaching disease outcomes under hypothetical conditions when the observed cohorts would remain always treated vs never treated for the full duration of the follow-up period

(pseudocoorts; see figures 6 and 9, 10.5061/dryad.15dv41nt8), and continuously readjusted for confounders of outcomes with a marginal structural model (a class of statistical models using inverse probability of treatment weights to evaluate observed and counterfactual [potential] outcomes of observed and counterfactual [potential] interventions).¹⁵

Standard Protocol Approvals, Registrations, and Patient Consents

The MSBase registry is an international observational MS cohort, with contribution mainly from academic MS centers, registered with the WHO International Clinical Trials Registry Platform (ACTRN12605000455662).^{16,17} The study was approved by the Melbourne Health Human Research Ethics Committee and the site institutional review boards. Patients provided written informed consent, as required.

Patients

The inclusion criteria for this study were clinically isolated syndrome or definite MS.^{18,19} The minimum required data consisted of follow-up ≥ 1 year, ≥ 3 disability scores with ≥ 1 score recorded per year, a minimum dataset (to evaluate outcomes and adjust for confounders [see Procedures]), and exposure to MS immunotherapy during the recorded follow-up. This was to exclude patients with benign disease course, who are more likely to contribute only to the untreated cohort, and to assure that only contemporary controls are included.

Procedures

The data were recorded prospectively as part of clinical practice, mainly at academic MS centers, as governed by the MSBase Observational Plan. Rigorous automated quality assurance procedure was applied (table 5, 10.5061/dryad.15dv41nt8).¹⁷

The follow-up time was segmented into 3-month periods (to maximize the use of the information from patients followed more frequently than the median visit frequency), with potential confounders and intermediates of treatment effect captured in MSBase at each period (for a causal diagram, see figure 7, 10.5061/dryad.15dv41nt8). These consisted of time-dependent variables: treatment status (treated/untreated), treatment status during the preceding period, pregnancy status, pregnancy status during the preceding period, patient age, disease duration from the first MS symptom, disability score, change in disability score during the preceding 3 and 12 months, number of relapses during the preceding 3 and 12 months, the numbers of severe relapses, relapses with poor recovery and on-treatment relapses during the preceding 12 months, MRI activity during the preceding 12 months, and the date of the period end; and fixed variables: sex and 4 stabilizing variables: date of birth, date of first MS symptom, disease duration at first visit, pregnancy status at first visit. Periods with MS disease-modifying therapies recorded for ≥ 15 days were classified as treated. Where no MRI information was recorded during a 3-month period, the value

unavailable was allowed. Where no new disability data were recorded during a 3-month period, the last previously recorded disability score was carried over (disability was recorded during 2 consecutive 3-month periods at 84,226 time points; these values were highly correlated, with $r = 0.95$). At every time point, treatment status was a binary variable (treated/untreated). Each patient could contribute data to the treated and untreated pseudocoorts at different time points.

Relapses were recorded by treating neurologists, defined as new symptoms or exacerbation of existing symptoms persisting for ≥ 24 hours, in the absence of concurrent illness/fever, and occurring ≥ 30 days after a previous relapse. Disability was quantified with the EDSS, excluding scores obtained < 30 days after a relapse. Neurostatus EDSS certification was required at the participating centers.²⁰

Presence/absence of new or enlarging T2 hyperintense lesions or contrast-enhancing lesions on cerebral MRI was reported by treating neurologists.

Outcomes

The study endpoints were cumulative hazards of relapses, disability accumulation events, and disability improvement events. Disability accumulation was defined as an increase in EDSS by 1 step (1.5 steps if baseline EDSS = 0, 0.5 steps if baseline EDSS > 5.5) confirmed by subsequent EDSS scores over ≥ 12 months, as over 80% of such events translate into long-term disability worsening.²¹ Disability improvement was defined as a decrease in EDSS by 1 step (1.5 steps if baseline EDSS ≤ 1.5 , 0.5 steps if baseline EDSS > 6) confirmed over ≥ 12 months. No carryover EDSS scores were used in calculating confirmed disability endpoints. In addition, progression to EDSS step 6 confirmed over ≥ 12 months was evaluated in the primary analysis.

Statistical Analysis

Statistical analyses were conducted using R (version 3.0.3). In order to mitigate the effect of intermediates/confounders of treatment allocation and disease outcomes, marginal structural proportional hazards models were used.²² These models allowed comparison of counterfactual cumulative hazards of relapses, disability accumulation, disability improvement events, and EDSS 6 (recorded during discrete study periods) between pseudocoorts never treated vs always treated with immunotherapies for 15 years from their first recorded visit.²³

Marginal structural models estimated the probability of multiple events (Andersen-Gill²⁴) with the partial likelihood function modified with inverse probability-of-treatment weights.²⁵ Individual patient follow-up was right-censored at the last recorded EDSS score.

The stabilized nonnormalised inverse probability-of-treatment weights were calculated at each 3-month period, using the ratio of the probabilities of treatment assignment conditional on baseline, time-dependent, and stabilizing

variables (estimated with multivariable logistic regression models)²⁶:

$$w_{ij} = \prod_{k=0}^j \frac{P(A_{ik} = a_{ik} | A_{i(k-1)} = a_{i(k-1)}, S_i = s_i)}{P(A_{ik} = a_{ik} | A_{i(k-1)} = a_{i(k-1)}, F_i = f_i, T_{ik} = t_{ik}, S_i = s_i)}$$

Here, w_{ij} represents a stabilized weight for patient i at time j . A is the treatment status at time k , S represents stabilizing variables, F represents fixed confounding variables, and T represents time-dependent confounding variables (for the variables, see Procedures).

The weights reflect the probability of patients' treatment status at each period, depending on their demography and disease history, and were used to weigh contribution of a patient to a pseudocohort at any given period. Marginal structural models are inherently adjusted for all but the stabilizing variables, including the history of the time-dependent variables.²⁵ In addition to clustering by patient, the models were nested within study center and right-censored. The primary analysis combined follow-up periods from the first to the last recorded disability score for each eligible patient, with time 0 defined as the beginning of the prospective follow-up (first recorded EDSS). Each patient was allowed to contribute multiple treated and untreated periods to the analysis, depending on their treatment status at a given period (figure 6, 10.5061/dryad.15dv41nt8). Treatment was modeled as a time-dependent variable, relative to the time 0. For the summary of the study protocol, see table 4, 10.5061/dryad.15dv41nt8. As a confirmatory analysis, we have repeated the primary analysis in a subset of patients followed for ≥ 15 years from their first recorded visit.

Sensitivity Analyses

Eight sensitivity analyses were completed. Two analyses evaluated the effect of immunotherapy among patients with relapsing-remitting and progressive (primary and secondary) disease forms separately. A sensitivity analysis examined the effect of segmentation of recorded follow-up into study periods by extending the study periods to 6 months. A sensitivity analysis among patients with complete follow-up from MS onset restricted inclusion to the patients with EDSS recorded within 3 months from the first MS symptom. Another sensitivity analysis used the rigorously acquired prospectively recorded MSBASIS substudy, which requires prospective enrollment within 12 months from the first MS symptom and complete capture of EDSS functional system scores and MRI data.²⁷ We have generalized the analysis to cohorts defined by disease duration and patient age by using 2 alternative definitions of baseline (time 0): the first recorded MS symptom (i.e., clinical onset of MS) and date of birth. This experimental approach aimed to reconstruct disease trajectories over time, expressed as MS duration or patient age among patients with incomplete follow-up, and with left-truncation of the recorded follow-up. Finally, we analyzed the outcomes in a nonselective cohort, including patients irrespective of the frequency or the duration of their follow-up, frequency of EDSS assessments, or exposure to therapy.

Data Availability

The data analyzed in this study are the property of the individual contributing centers. They can be made available upon reasonable request for the purpose of replication of the analyses included in this study and at the discretion of the principal investigators.

Results

Study Population

Of the 34,007 patients enrolled in MSBase as of June 16, 2015, 14,717 patients fulfilled the inclusion criteria and 1,085 had ≥ 15 years of follow-up recorded from their first visit (figure 1, table 6, 10.5061/dryad.15dv41nt8). The most common reason for exclusion was the lack of sufficient follow-up required for the analysis. The excluded patients tended to be captured later in their disease and with shorter prospective follow-up than the included patients (table 1). Demographic information at first study visit was in keeping with the known epidemiology of MS (71% female, mean age 36 years, median disability EDSS step 2; table 2). Median visit interval was 6 months, similar to most

Figure 1 Patient Disposition

The data quality procedure excluded 147 patient records: 95 from centers with less than 10 enrolled patients, 49 with missing birth date or date of MS onset, and 3 with erroneous information about disease progression. The inclusion criteria were applied so that patients' follow-up is of sufficient duration to enable evaluation of at least short-term disability outcomes (≥ 1 year), with a minimum number of data points to ensure that individual hazard of confirmed disability worsening is non-zero (≥ 3 EDSS scores), sufficient data density to minimize the risk of disability events that were not captured, and to minimize recall bias (≥ 1 EDSS score per year). The minimum data set was required for calculation of the inverse probability of treatment weights and outcomes. Patients had to be exposed to an MS immunotherapy at least once in order to eliminate treatment indication bias, which is significant for untreated patients in countries where immunotherapies are commonly available. One third of patients excluded from the analysis due to insufficient data were enrolled in MSBase during the recent 2 years and did not yet accumulate sufficient follow-up information.

randomized clinical trials. Of the analyzed 426,544 study periods, 55% captured EDSS information, including 72% of the study periods recorded during the first year from the first study visit. Information about brain MRI during the preceding 12 months was available for 43% of the study periods. Patients were exposed to immunotherapies for 69% of the prospectively recorded cumulative follow-up of 102,978 patient-years (median per-patient follow-up of 6 years). The most represented therapies were interferon- β /glatiramer acetate (59% of follow-up time), followed by natalizumab (5%) and fingolimod (4%). Patient characteristics at the start of treated and untreated periods are shown in table 7, 10.5061/dryad.15dv41nt8. The patients with ≥ 15 -year follow-up were exposed to immunotherapies for 63% of the time over the median follow-up of 17 years. The time on higher-efficacy therapies was relatively less represented in this cohort compared to the full cohort, as natalizumab and fingolimod have only become available in 2006 and 2011, respectively.

Inverse Probability-of-Treatment Weights

Stabilized nonnormalized inverse probability-of-treatment weights for each patient and at each time point were built based on the probability of receiving immunotherapy at any given 3-month period conditional on patients' demographic information, MS history, and previous treatment exposure (for full list of baseline, time-dependent, and stabilizing variables, see Methods). The weights followed an expected distribution, centred around 1 and with only minor fluctuations over 15 years in both pseudocohorts, indicating good model specification (figure 8, 5061/dryad.15dv41nt8).

Disease Outcomes Among All Eligible Patients

In the full study cohort analyzed from the first visit, the pseudocohort treated continuously was less likely to

experience relapses than the untreated pseudocohort (annualized relapse rate 0.32 vs 0.46, respectively; hazard ratio [HR] 0.60, 95% confidence interval [CI] 0.43–0.82, $p = 0.0016$). Cumulative hazard of relapses in the treated vs untreated cohorts was estimated at approximately 5 vs 9 relapses at 15 years from first recorded visit, respectively (figure 2; the number needed to treat [NNT] to prevent 1 relapse over 15 years was 0.25). The difference between the treated and the untreated patients increased proportionally over time.

The treated cohort was less likely to experience 12-month confirmed disability accumulation events relative to the untreated cohort (HR 0.56, 95% CI 0.38–0.82, $p = 0.0026$). Cumulative hazard of disability accumulation in the treated vs untreated cohorts reached 0.9 vs 1.5 events at 15 years, respectively (figure 2; NNT 1.6). The difference between the treated and the untreated patients only became apparent at 3 years from the first recorded visit and tended to increase with time.

The probability of reaching 12-month confirmed EDSS step 6 was markedly lower in the treated than the untreated cohort (HR 0.33, 95% CI 0.19–0.59, $p = 0.00019$, figure 3). Within 15 years from the first visit, 13% of the treated cohort and 41% of the untreated cohort reached EDSS step 6 (NNT 3.5).

The probability of 12-month confirmed disability improvement events tended to be greater in the treated (0.21) than the untreated cohort (0.18) during the initial 4 years of follow-up. After year 4, the increment in the cumulative hazards was similar in the 2 pseudocohorts (figure 2). Therefore, this trend did not reach the defined threshold for statistically significant difference (HR 1.10, 95% CI 0.98–1.30, $p = 0.094$).

Table 1 Comparison of the Included and Excluded Cohorts

	Included	Excluded	Standardized difference (d)
Patients	14,717	19,290	
Female, n (%)	10,517 (71)	13,588 (70)	
Age at first recorded visit, y, mean $\pm$ SD	36 $\pm$ 10	40 $\pm$ 12	0.29
Disease duration at first visit, y, median (quartiles)	3.0 (0.7–8.2)	4.7 (1.0–11.8)	0.15
Prospective follow-up, y, median (quartiles)	6 (3.1–10)	4.5 (1.7–6.8)	0.68
Disability (1st visit), EDSS, median (quartiles)	2 (1.5–3.5)	2 (1.5–4)	0.00
MS course at last follow-up, n (%)			
Clinically isolated syndrome	996 (7)	4,630 (24)	
Relapsing-remitting	11,709 (80)	11,767 (61)	
Secondary progressive	1,654 (11)	2,315 (12)	
Primary progressive (inactive)	162 (1)	193 (1)	
Primary progressive (active)	196 (1)	386 (2)	

Abbreviations: EDSS = Expanded Disability Status Scale; MS = multiple sclerosis.

Table 2 Characteristics of the Study Cohort

	Full cohort	Patients with ≥15-year follow-up
Patients, n	14,717	1,085
Sex, female, n (%)	10,517 (71)	797 (73)
Age at first visit, y, mean ± SD	36 ± 10	33 ± 9
Age at MS onset, y, mean ± SD	30 ± 9	27 ± 8
Disease duration at first visit, y, median (quartiles)	3 (0.7–8.2)	3.2 (1.1–8)
Prospective follow-up, y, median (quartiles)	6 (3.1–10)	17 (15.6–18.8)
Relapses recorded per patient, n, median (quartiles)	4 (2–6)	8 (5–12)
EDSS scores recorded per patient, n, median (quartiles)	13 (7–21)	32 (24–43)
Study periods with recorded EDSS scores (%)	236,177 of 426,594 (55)	38,749 of 77,963 (50)
Disability at first visit, n (%)		
EDSS 0–3.5	11,960 (81)	919 (85)
EDSS 4–5.5	1821 (12)	129 (12)
EDSS 6–9.5	936 (6)	32 (3)
Disability at last visit, n (%)		
EDSS 0–3.5	9,655 (66)	464 (43)
EDSS 4–5.5	2,440 (17)	247 (23)
EDSS 6–10	2,622 (18)	374 (34)
Disease course at last follow-up, n (%)		
Clinically isolated syndrome	996 (7)	7 (1)
Relapsing-remitting	11,709 (80)	1,038 (96)
Secondary progressive	1,654 (11)	14 (1)
Primary progressive (inactive)	162 (1)	9 (1)
Primary progressive (active)	196 (1)	17 (2)
Visit interval, mo, median (quartiles)	6 (4–8)	7 (1%)
Patients with MRI recorded, n (%)	13,432 (91)	1,020 (94)
Exposure to immunotherapies (proportion of follow-up treated with any immunotherapy)	14,717 (69)	1,085 (63)
Interferon-β/glatiramer acetate, n (%)	12,879 (59)	1,061 (58)
Teriflunomide, n (%)	236 (0.2)	22 (0.1)
Dimethyl fumarate, n (%)	355 (0.2)	4 (0.02)
Fingolimod, n (%)	2,461 (4)	149 (2)
Cladribine, n (%)	52 (0.02)	0
Alemtuzumab, n (%)	22 (0.1)	0
Natalizumab, n (%)	2,520 (5)	142 (2)
Mitoxantrone, n (%)	751 (0.6)	135 (1)
Rituximab, n (%)	33 (0.02)	2 (0.01)

Abbreviations: EDSS = Expanded Disability Status Scale; MS = multiple sclerosis.

Figure 2 Incidence of Relapses, Disability Accumulation, and Improvement in the Treated and Untreated Pseudocohorts

(A) Relapses. (B) Disability accumulation. (C) Disability improvement. Cumulative hazards for unadjusted models (dotted) and marginal structural models adjusted with inverse probability of treatment weights (solid) are shown. Dashed lines show 95% confidence intervals (CIs). Numbers of patients contributing to the treated and untreated pseudocohorts are shown at multiple time points. HR = hazard ratio.

The analysis in relapsing-remitting MS-only confirmed the results of the primary analysis, demonstrating differences in relapse frequency (annualized relapse rate 0.35 vs 0.56; HR 0.49, 95% CI 0.42–0.58, $p < 10^{-16}$), disability accumulation (HR 0.68, 95% CI 0.52–0.88, $p = 0.004$), and disability improvement (HR 1.13, 95% CI 0.95–1.34, $p = 0.17$). On the contrary, the analysis in progressive disease forms did not find any differences in disability accumulation (HR 0.92, 95% CI

0.81–1.05, $p = 0.22$) or improvement (HR 1.38, 95% CI 0.85–2.26, $p = 0.19$) between the treated and untreated pseudocohorts.

The sensitivity analyses using 6-month study periods and including a larger, more inclusive cohort confirmed the results of the primary analysis (see table 8, 10.5061/dryad.15dv41nt8).

Figure 3 The Risk of Expanded Disability Status Scale (EDSS) 6

The risk of reaching EDSS 6 (patients use a single-point walking aid to walk ≥ 100 meters) in the treated and untreated pseudocohorts. Cumulative hazards for unadjusted models (dotted) and marginal structural models adjusted with inverse probability of treatment weights (solid) are shown. Dashed lines show 95% confidence intervals (CIs). Numbers of patients contributing to the treated and untreated pseudocohorts are shown at multiple time points. HR = hazard ratio.

Disease Outcomes Among Patients With ≥ 15 -Year Follow-Up

The results of the analyses among the 1,085 patients with ≥ 15 -year prospective follow-up from their first visit were in keeping with the results from the full study cohort. The treated pseudocohort was less likely to experience relapses than the untreated pseudocohort (annualized relapse rate 0.33 vs 0.44, respectively; HR 0.59, 95% CI 0.50–0.70, $p = 10^{-9}$). Confirmed disability progression events were less frequent in the treated pseudocohort (HR 0.81, 95% CI 0.67–0.99, $p = 0.043$). The probability of disability improvement did not differ between the treated and the untreated pseudocohorts (HR 0.91, 95% CI 0.69–1.2, $p = 0.54$).

Disease Outcomes Among Patients Followed From Disease Onset

The sensitivity analysis that included only patients with first EDSS follow-up recorded ≤ 3 months after the first MS symptom identified 2,194 eligible patients followed over 15,084 patient-years (69% female, mean age 31 years, median EDSS step 2, median follow-up 6 years, median visit interval 4 months). It replicated the results of the primary analysis for relapse incidence (showing lower hazard of relapses in the treated cohort, HR 0.51, 95% CI 0.38–0.68, $p = 10^{-5}$; figure 4) and disability accumulation (lower hazard of disability accumulation in the treated cohort, HR 0.59, 95% CI 0.39–0.88, $p = 0.011$). This sensitivity analysis also found a greater probability of disability improvement in the treated pseudocohort (HR 1.36, 95% CI 1.02–1.80, $p = 0.038$).

The sensitivity analysis using the prospective MSBASIS sub-study included 1,291 patients followed over 7,239 patient-years (69% female, mean age 31 years, median EDSS step 2, median follow-up 5.5 years, median visit interval 4 months). Similarly, this sensitivity analysis found superior outcomes in the treated cohort compared to the untreated cohort for relapse incidence (HR 0.39, 95% CI 0.31–0.50, $p = 10^{-13}$), disability accumulation (HR 0.47, 95% CI 0.24–0.93, $p = 0.031$), and disability improvement (HR 1.36, 95% CI 1.04–1.79, $p = 0.025$; figure 4).

Long-Term Disease Outcomes Throughout the Duration of MS and Life Span

When the time variable in the full study cohort was defined as the time from the first MS symptom (figure 9, 10.5061/dryad.15dv41nt8), the treated pseudocohort was less likely to experience relapses (annualized relapse rate 0.32 vs 0.47; HR 0.54, 95% CI 0.45–0.65, $p = 10^{-10}$; figure 5) and disability accumulation events (HR 0.69, 95% CI 0.55–0.85, $p = 0.0007$). No evidence of difference between the pseudocohorts in disability improvement was found (HR 1.20, 95% CI 0.96–1.50, $p = 0.1$).

Similarly, when the study follow-up was organized by patient age (figure 5), the treated pseudocohort experienced a lower frequency of relapses (annualized relapse rate 0.32 vs 0.46; HR 0.53, 95% CI 0.43–0.65, $p = 10^{-9}$) and disability accumulation events (HR 0.68, 95% CI 0.55–0.85, $p = 0.0006$). The probability of disability improvement did not differ between the compared pseudocohorts (HR 1.20, 95% CI 0.95–1.50, $p = 0.13$).

Discussion

This observational study in 14,717 patients from MSBase, including 1,085 patients with ≥ 15 -year recorded follow-up, demonstrated that continued immunotherapy reduces the risk of disability accrual in relapsing-remitting MS by 19%–44% (95% CI 1%–62%) and the risk of impaired gait requiring use of a walking aid by 67% (95% CI 41%–81%) over 15 years.

The reduction in accumulation of disability was observed on the background of a 40%–41% (95% CI 18%–57%) reduction in the frequency of MS relapses, an observation that is in keeping with previous knowledge.¹ Interestingly, we only observed a trend towards more likely improvement in disability in patients treated during early stages of MS. After a phase of accelerated disability improvement observed during the initial 4 years of follow-up, the probability of disability improvement became similar in the treated and untreated cohorts. This observation was confirmed statistically as a 36% (95% CI 2%–80%) higher chance of disability improvement among patients who were followed prospectively from disease onset.

In agreement with our conclusion, several previous studies showed reduced disability during treatment with

Figure 4 Sensitivity Analyses: Inception Cohorts

Comparisons of relapse frequency, disability accumulation, and improvement between treated and untreated pseudocohorts consisting of patients followed from disease onset; i.e., with the first disability recorded within 3 months from first presentation of multiple sclerosis (A) and the prospective MSBASIS cohort (B). Cumulative hazards for unadjusted models (dotted) and marginal structural models adjusted with inverse probability of treatment weights (solid) are shown. Dashed lines show 95% confidence intervals (CIs). Numbers of patients contributing to the treated and untreated pseudocohorts are shown at multiple time points. HR = hazard ratio.

Figure 5 Sensitivity Analyses: Treatment Effectiveness by Disease Duration and Patient Age

Sensitivity analyses: generalization of the analysis to follow-up by disease duration (A) and patient age (B). Incidence of relapses, disability accumulation, and improvement in the treated and untreated pseudocoorts are shown. Cumulative hazards for unadjusted models (dotted) and marginal structural models adjusted with inverse probability of treatment weights (solid) are shown. Dashed lines show 95% confidence intervals (CIs). Numbers of patients contributing to the treated and untreated pseudocoorts are shown at multiple time points. HR = hazard ratio.

immunotherapies.^{2,5} The results of our study are supported by a study of 5,610 patients enrolled in the UK Risk Sharing Scheme, which showed, using Markov and multilevel models, that treatment with interferon- β or glatiramer acetate was associated with a 24% decrease in disability accrual over up to 6 years.^{13,14} An MSBase study among 2,466 patients with relapsing-remitting MS suggested that continuous exposure to interferon- β or glatiramer acetate for 10 years was associated with slowing of disability accrual.²⁸ Re-assessment of the pivotal trial of interferon- β -1b at 16 years ($n = 372$), using recursive partitioning, showed that earlier exposure to interferon- β was associated with a decreased hazard of reaching significant disability or death.⁹ A propensity score-weighted analysis in 1,504 patients showed that patients treated with interferon- β were less likely to reach EDSS step ≥ 4 (restricted ambulatory capacity) than untreated patients over up to 7 years.²⁹ In keeping with our previous studies, we did not observe an overall effect of pooled immunotherapies in nonselectively treated cohorts with progressive disease forms.³⁰ However, this observation does not rule out the possibility that some therapies can slow down progression of disability in progressive MS, especially where episodic inflammatory activity is superimposed.^{31,32} In fact, clinical exacerbations in progressive MS may signal presence of a treatable target, and therefore may represent a positive prognostic marker among patients who commence immunotherapy.

In contrast to our results, a propensity score-matched analysis in 2,656 patients did not find any evidence of difference in the probability of reaching EDSS step ≥ 6 (use of unilateral support to walk ≥ 100 meters) between patients treated with interferon- β and those untreated. Interestingly, a trend favoring the treated cohort was observed when compared with historical controls, while an opposite trend was seen in a comparison against contemporary controls.¹² In the ensuing debate, the conflicting trends were attributed to the residual selection bias and the lack of readjustment for the ongoing decision process of choosing between treatment and no treatment, which occurs continuously throughout long-term follow-up. This problem of continuous confounding by treatment indication was also inherent in the other prior comparisons of longitudinal outcomes between treated and untreated patients.

Methodologic Considerations

The key problem in uncovering unbiased causal effect of immunotherapy on disability is that of time-dependent confounding by treatment indication.²³ Karim et al.³³ used a marginal structural Cox model³³ applied to a clinic-based cohort from British Columbia to assess the association between treatment and disability accrual. The model allowed the authors to construct pseudocohorts defined by their treatment status at any time point and readjusted for time-dependent confounders and intermediates of treatment allocation and study outcome.³⁴ The study demonstrated how a marginal structural model can effectively mitigate time-dependent confounding, and did not find an association between treatment with interferon- β and the risk of reaching

EDSS step ≥ 6 . In our present study, we have extended the methodology used by Karim et al.³⁴ to enable inclusive analysis of all treated patients, whereby the clinical follow-up in every patient consists of both treated and not treated periods. In this design, every patient may contribute study periods to either the treated or untreated group at different times—defined with respect to their first recorded visit, disease onset, or date of birth. Naturally, it is not possible to directly observe the outcomes of 2 mutually exclusive treatment states in a single cohort; therefore we have used a counterfactual framework that uses a well-defined statistical methodology, and have termed the compared groups “pseudocohorts”.^{13,15,22} This approach enabled us to compare cumulative hazards of disability and relapse events in pseudocohorts that were hypothetically treated or untreated for 15 years from their first visit (or throughout their disease duration or life span). The assumption of such an approach is that the effect of therapy does not attenuate over time. We have observed that the effect of therapy on relapses and worsening of disability was sustained throughout the 15-year follow-up (see figures 2 and 3). This observation supports the need for continued treatment with immunotherapies over an extended period of time. In contrast, the trend towards a difference in disability improvement was restricted to the initial years following the first presentation of MS and treatment start. This phenomenon is likely associated with functional compensatory mechanisms, which become exhausted with increasing cumulative inflammatory damage and age.³⁵ Such observation supports the notion that in order to facilitate recovery of neurologic function, immunotherapies should be commenced early after MS onset, when disability is more likely to be reversible.^{36,37}

To avoid the need for left-truncation, the primary analysis evaluated patients with time 0 defined as their first recorded visit. In order to ensure stability of the observed associations over the long term, we have replicated the primary analysis in a subcohort with ≥ 15 years of recorded continuous follow-up. Furthermore, we have modeled the disability and relapse outcomes over the full disease duration and patient age. Using the first clinical presentation of MS or birth date as study baseline, respectively, these 2 sensitivity analyses have replicated the results of the primary analyses in full. While this suggests that combining observed periods to reconstruct disease outcomes over time that was not observed continuously is a feasible strategy, further mathematical justification of such an approach is required. In order to eliminate the scenario when treated and untreated cohorts are not comparable (due to strong indication bias that would lead to the allocation of patients with benign MS to the untreated cohort) and to fulfil the assumption of positivity, we have restricted inclusion to only those patients who qualified for at least one immunotherapy during the course of their disease.³⁸ The study cohort was exposed to injectable therapies for 59% of the studied time, to more potent therapies for 9% of the time, and was untreated for 31% of the time. In contrast with blinded randomized clinical trials, sequencing of therapies

driven by patient response and clinical reasoning in routine practice would maximize the true effectiveness of therapy.³⁹ It is therefore not surprising that our observed effects are greater than the effects reported by clinical trials. The marginal structural models enabled us to draw inference about causal associations between current treatment status and the probability of recurrent disability and relapse events, while accounting for measured confounders and intermediates of treatment allocation and disease outcomes.⁴⁰ Thus, the results presented can be considered free from measurable treatment indication bias.

The main limitation of this study is inherent in the observational nature of the analyzed data that originated from a large multicenter clinical cohort. We have mitigated the impact of intercenter variability by applying a rigorous data quality procedure and nesting the models within study centers. Generalizability of the presented results may be restricted to patients followed in academic MS centers. While we have extended the analytical methodology to enable comparison of cumulative hazards of recurrent events, in its present form, the models do not allow us to evaluate delayed treatment effects, such as delayed disability worsening and improvement, whose risk could be modulated by treatment exposure in the immediate or distant past, or directly compare outcomes between multiple therapies. However, the models were adjusted for prior treatment status (whether immediately preceding each 3-month period or the overall cumulative treatment history), relapses, disability accumulation, and improvement. Due to our inclusive definition of treated period (≥ 15 days on treatment), classification of exposure to immunosuppressants as untreated time, and pooling of low- and high-efficacy immunotherapies, the true differences between the treated and untreated pseudocohorts may be underestimated. It is therefore reassuring that clinically meaningful and consistent differences in relapse and disability outcomes were shown despite our conservative study design. While we have mitigated the risk of measured confounding by including a large number of potential confounders in the models of inverse probability-of-treatment weights and by completing 8 sensitivity analyses, propensity score-based methods can be subject to unmeasured confounding. This may include missingness-not-at-random of disability and MRI information. Finally, many of the assumptions of marginal structural models are unmeasurable. Therefore, consistency of the results across the primary and the sensitivity analyses—among patients with different definitions of baseline and study period—provides additional assurance with respect to the robustness of the used models.

This study provides Class IV evidence that long-term exposure to immunotherapy not only reduces relapse activity but also lowers the risk of decline in neurologic function by at least a fifth in patients with relapsing-remitting MS. In early MS, accelerated recovery from previously accrued disability can be observed early after commencing immunotherapy. Therefore, sustained, long-term immunotherapy from early stages of MS

is advisable as a strategy to preserve patients' neurologic capacity over the long-term.

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Appendix (continued)

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Continued

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References

- Tramacere I, Del Giovane C, Salanti G, D'Amico R, Filippini G. Immunomodulators and immunosuppressants for relapsing-remitting multiple sclerosis: a network meta-analysis. *Cochrane Database Syst Rev* 2015;9:Cd011381.
- Coles AJ, Compston DA, Selman KW, et al. Alemtuzumab vs. interferon beta-1a in early multiple sclerosis. *N Engl J Med* 2008;359:1786–1801.
- Polman CH, O'Connor PW, Havrdova E, et al. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. *N Engl J Med* 2006;354:899–910.
- Kappos L, Radue E-W, O'Connor P, et al. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. *N Engl J Med* 2010;362:387–401.
- Hauser SL, Bar-Or A, Comi G, et al. Ocrelizumab versus interferon beta-1a in relapsing multiple sclerosis. *N Engl J Med* 2017;376:221–234.
- Kappos L, Edan G, Freedman MS, et al. The 11-year long-term follow-up study from the randomized BENEFIT CIS trial. *Neurology* 2016;87:978–987.
- Kinkel RP, Kollman C, O'Connor P, et al. IM interferon beta-1a delays definite multiple sclerosis 5 years after a first demyelinating event. *Neurology* 2006;66:678–684.
- Comi G, Martinelli V, Rodegher M, et al. Effects of early treatment with glatiramer acetate in patients with clinically isolated syndrome. *Mult Scler* 2013;19:1074–1083.
- Goodin DS, Jones J, Li D, et al. Establishing long-term efficacy in chronic disease: use of recursive partitioning and propensity score adjustment to estimate outcome in MS. *PLoS One* 2012;6:e22444.
- Kavaliunas A, Manouchehrinia A, Stawiarz L, et al. Importance of early treatment initiation in the clinical course of multiple sclerosis. *Mult Scler* 2017;23:1233–1240.
- Goodin DS, Reder AT, Ebers GC, et al. Survival in MS: a randomized cohort study 21 years after the start of the pivotal IFNbeta-1b trial. *Neurology* 2012;78:1315–1322.
- Shirani A, Zhao Y, Karim ME, et al. Association between use of interferon beta and progression of disability in patients with relapsing-remitting multiple sclerosis. *JAMA* 2012;308:247–256.
- Palace J, Duddy M, Bregenzer T, et al. Effectiveness and cost-effectiveness of interferon beta and glatiramer acetate in the UK Multiple Sclerosis Risk Sharing Scheme at 6 years: a clinical cohort study with natural history comparator. *Lancet Neurol* 2015;14:497–505.
- Palace J, Duddy M, Lawton M, et al. Assessing the long-term effectiveness of interferon-beta and glatiramer acetate in multiple sclerosis: final 10-year results from the UK multiple sclerosis risk-sharing scheme. *J Neurol Neurosurg Psychiatry* 2019;90:251–260.
- Maldonado G, Greenland S. Estimating causal effects. *Int J Epidemiol* 2002;31:422–429.
- Kalincik T, Butzkueven H. The MSBase registry: informing clinical practice. *Mult Scler* 2019;25:1828–1834.
- Kalincik T, Kuhle J, Pucci E, et al. Data quality evaluation for observational multiple sclerosis registries. *Mult Scler* 2017;23:647–655.
- Polman CH, Reingold SC, Edan G, et al. Diagnostic criteria for multiple sclerosis: 2005 revisions to the “McDonald Criteria.” *Ann Neurol* 2005;58:840–846.
- Polman CH, Reingold SC, Banwell B, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. *Ann Neurol* 2011;69:292–302.
- D'Souza M, Yaldizli O, John R, et al. Neurostatus e-Scoring improves consistency of Expanded Disability Status Scale assessments: a proof of concept study. *Mult Scler* 2017;23:597–603.
- Kalincik T, Cutter G, Spelman T, et al. Defining reliable disability outcomes in multiple sclerosis. *Brain* 2015;138:3287–3298.
- Robins JM, Hernan MA, Brumback B. Marginal structural models and causal inference in epidemiology. *Epidemiology* 2000;11:550–560.
- Hernan MA. A definition of causal effect for epidemiological research. *J Epidemiol Community Health* 2004;58:265–271.
- Andersen PK, Gill RD. Cox's regression model for counting processes: a large sample study. *Ann Stat* 1982;10:1100–1120.
- van der Wal WM, Geskus RB. ipw: an R package for inverse probability weighting. *J Stat Softw* 2011;43:23.
- Imai K, Ratkovic M. Robust estimation of inverse probability weights for marginal structural models. *J Am Stat Assoc* 2015;110:1013–1023.
- Jokubaitis VG, Spelman T, Kalincik T, et al. Predictors of disability worsening in clinically isolated syndrome. *Ann Clin Transl Neurol* 2015;2:479–491.
- Jokubaitis VG, Spelman T, Kalincik T, et al. Predictors of long-term disability accrual in relapse-onset multiple sclerosis. *Ann Neurol* 2016;80:89–100.
- Trojano M, Pellegrini F, Fuiani A, et al. New natural history of interferon-beta-treated relapsing multiple sclerosis. *Ann Neurol* 2007;61:300–306.
- Lorscheider J, Jokubaitis VG, Spelman T, et al. Anti-inflammatory disease-modifying treatment and short-term disability progression in SPMS. *Neurology* 2017;89:1050–1059.
- Hughes J, Jokubaitis V, Lugaresi A, et al. Association of inflammation and disability accrual in patients with progressive-onset multiple sclerosis. *JAMA Neurol* 2018;75:1407–1415.
- Lizak, et al. Association of sustained immunotherapy with disability outcomes in patients with active secondary progressive multiple sclerosis. *JAMA Neurol* 2020;77:1–11.
- Sterne JA, Hernan MA, Ledergerber B, et al. Long-term effectiveness of potent antiretroviral therapy in preventing AIDS and death: a prospective cohort study. *Lancet* 2005;366:378–384.
- Karim ME, Gustafson P, Petkau J, et al. Marginal structural Cox models for estimating the association between beta-interferon exposure and disease progression in a multiple sclerosis cohort. *Am J Epidemiol* 2014;180:160–171.
- Lassmann H, van Horssen J, Mahad D. Progressive multiple sclerosis: pathology and pathogenesis. *Nat Rev Neurol* 2012;8:647–656.
- He, et al. Timing of high-efficacy therapy for multiple sclerosis: a retrospective observational cohort study. *Lancet Neurol* 2020;19:307–316.
- Ontaneda, et al. Early highly effective versus escalation treatment approaches in relapsing multiple sclerosis. *Lancet Neurol* 2019;18:973–980.
- Kalincik T, Butzkueven H. Observational data: understanding the real MS world. *Mult Scler* 2016;22:1642–1648.
- Trojano M, Pellegrini F, Paolicelli D, Fuiani A, Di Renzo V. Observational studies: propensity score analysis of non-randomized data. *Int MS J/MS Forum* 2009;16:90–97.
- Bodnar LM, Davidian M, Siega-Riz AM, Tsiatis AA. Marginal structural models for analyzing causal effects of time-dependent treatments: an application in perinatal epidemiology. *Am J Epidemiol* 2004;159:926–934.