Predictors of Long-Term Disability Accrual in Relapse-Onset Multiple Sclerosis

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View this article online at wileyonlinelibrary.com. DOI: 10.1002/ana.24682

Received Nov 24, 2015, and in revised form Apr 28, 2016. Accepted for publication May 2, 2016.

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Objective: To identify predictors of 10-year Expanded Disability Status Scale (EDSS) change after treatment initiation in patients with relapse-onset multiple sclerosis.
Methods: Using data obtained from MSBase, we defined baseline as the date of first injectable therapy initiation. Patients need only have remained on injectable therapy for 1 day and were monitored on any approved disease-modifying therapy, or no therapy thereafter. Median EDSS score changes over a 10-year period were determined. Predictors of EDSS change were then assessed using median quantile regression analysis. Sensitivity analyses were further performed.
Results: We identified 2,466 patients followed up for at least 10 years reporting post-baseline disability scores. Patients were treated an average 83% of their follow-up time. EDSS scores increased by a median 1 point (interquartile range = 0–2) at 10 years post-baseline. Annualized relapse rate was highly predictive of increases in median EDSS over 10 years ($coeff = 1.14$, $p = 1.9 \times 10^{-22}$). On-therapy relapses carried greater burden than off-therapy relapses. Cumulative treatment exposure was independently associated with lower EDSS at 10 years ($coeff = -0.86$, $p = 1.3 \times 10^{-9}$). Furthermore, pregnancies were also independently associated with lower EDSS scores over the 10-year observation period ($coeff = -0.36$, $p = 0.009$).
Interpretation: We provide evidence of long-term treatment benefit in a large registry cohort, and provide evidence of long-term protective effects of pregnancy against disability accrual. We demonstrate that high annualized relapse rate, particularly on-treatment relapse, is an indicator of poor prognosis.

ANN NEUROL 2016;00:000–000

Multiple sclerosis is one of the most common causes of neurological disability in young adults globally.[1] It is a chronic degenerative illness, usually diagnosed in the third decade of life, and therefore carries a high economic and quality of life burden associated with it.[2–6] One of the principal objectives in the care of people with multiple sclerosis is, therefore, to reduce the irreversible accumulation of neurological disability.

Clinical trials provide evidence for clinical efficacy of disease-modifying therapies (DMTs) in reducing short-term disease burden[7–10]; however, clinical trials occur within well-controlled environments, with rigorous patient review, and therefore do not necessarily reflect real-world patient characteristics or behaviors. Importantly, the duration of follow-up is too short to assess persistent disability outcomes with certainty. Long-term treatment effectiveness in reducing disability accumulation remains controversial, because data from some observational studies provide evidence for short- to medium-term treatment efficacy,[11–13] whereas others show that treated patients derive no benefit over and above untreated patients.[14,15] One possible confounder is that long-term untreated patients represent an intrinsically benign group of patients, so that comparisons of treated versus untreated patients suffer from indication bias.

We sought to remove indication bias for evaluation of treatment effects by retrospectively defining the baseline of a large, prospectively followed cohort in the MSBase observational study as the time of first commencement of immune-modulatory therapy.

Our aim was to identify demographic, clinical, and treatment exposure predictors of long-term disability accrual, as assessed by Expanded Disability Status Scale (EDSS) score change over 10 years in a real-world multiple sclerosis registry cohort.

Patients and Methods

Ethics Statement

The MSBase Registry (registered with World Health Organization International Clinical Trials Registry Platform, ID ACTRN12605000455662) was approved by the Melbourne Health Human Research Ethics Committee and by the local ethics committees in all participating centers (or exemptions were granted, according to applicable local laws and regulations). Written informed consent was obtained from all enrolled patients participating in the registry in accordance with the Declaration of Helsinki.

Study Population

Data were extracted from the global MSBase Registry. Extracted data were recorded as part of routine clinical practice according to the MSBase observational protocol.[16] The MSBase protocol mandates minimum annual updates, where data entry is performed in real-time or near real-time at most participating centers.

Patients with relapse-onset multiple sclerosis prescribed interferon-β (IFNβ) or glatiramer acetate (GA) as a first DMT exposure were included in this study. Patients must have had an EDSS score recorded at baseline, defined as an EDSS score recorded within $\pm$12 months of first IFNβ/GA initiation. Additionally, study inclusion criteria required at least 1 EDSS score to be recorded within $\pm$12 months of the 10-year post-treatment initiation time point. All analyzed EDSS scores must have been recorded in the absence of a concurrent relapse, defined as occurrence of new symptoms or exacerbation of existing symptoms persisting for $>$24 hours, in the absence of concurrent illness or fever. EDSS scores recorded within 30 days of relapse onset were excluded from this analysis to eschew artificial inflation of median EDSS score changes over time.

Patients classified as having secondary progressive multiple sclerosis (SPMS) at first IFNβ/GA treatment initiation, or those with incomplete data sets, were further excluded. The minimum data set required for study inclusion comprised date of birth, sex, clinic location, date of disease onset, clinical course, follow-up visit dates, EDSS scores recorded at visits,

dates of all relapses, start and end dates of all DMT commencements, and DMT identity.

Here we identified a phenotypically diverse patient population. All patients were included provided they met the above inclusion criteria and minimum data set requirements.

Data relating to reported pregnancies were also included. Available pregnancy data included confirmed conception date, termination date, birthdate, and number of live births.

Included patients commenced immunotherapy between January 1989 and August 2006.

Definitions

Ten-year EDSS score change was defined as the difference between the baseline EDSS score and EDSS scores recorded at 10 years post-baseline. To ensure standardized EDSS scoring and to reduce inter-rater variability, MSBase mandates that all participating neurologists have Neurostatus certification.

Annualized relapse rate (ARR) is defined as the number of relapses that occur per year of observation.

Statistical Analysis

Analysis was undertaken using Stata v12 (StataCorp, College Station, TX) or R (http://R-project.org). All analyses were 2-tailed, and $p < 0.05$ was considered significant.

Continuous variables were assessed for normality (Shapiro–Wilk normality test) and described using mean and standard deviation, or summarized using median and interquartile range (IQR) as appropriate. Categorical variables were summarized using frequencies. Kaplan–Meier estimates were used to assess median treatment persistence, as one-third of the cohort had not yet discontinued their first treatment commencement.

Predictors of 10-year EDSS change were assessed using unadjusted and adjusted quantile median regression. The EDSS change demonstrated significant departures from normality and was resistant to common transformations. Quantile median regression was preferred over simple linear regression of the mean to model the influence of baseline demographics, clinic location, within-interval IFNβ/GA treatment exposures, DMT identity, pregnancy events, baseline EDSS score, and relapse activity on 10-year EDSS change. Colinearity and interactions between model covariates were examined using a likelihood ratio test. The He and Zhu lack-of-fit test for quantile regression[17] was used to assess goodness of fit for each model. Competing quantile median regression models were compared, and the most parsimonious model was selected based on smallest model residuals.

A series of analyses were performed to evaluate the sensitivity of the study to inclusion criteria, and to differences in variable definitions. Sensitivity to inclusion criteria was tested by: comparing 10-year EDSS outcomes in a cohort in which EDSS scores must have been recorded within ±6 months of baseline and follow-up; comparing outcomes only in those patients with confirmed EDSS scores reported 3 to 15 months after the 10-year follow-up visit; and comparing 10-year EDSS outcomes only in those patients with no change or clinically significant changes according to a 3-step EDSS progression/regression paradigm (ie, a minimum 1.5-point EDSS score increase above a baseline score of 0, a minimum 1-point EDSS score increase/decrease if baseline EDSS score is between 1 and 5.5, and a minimum 0.5-point EDSS score increase/decrease if baseline EDSS score is 6 or above).[18] Sensitivity to the definition of variables was tested by: substituting cumulative treatment exposure on all DMTs (including IFNβ/GA, teriflunomide, fingolimod, dimethyl fumarate, cladribine, natalizumab, mitoxantrone, alemtuzumab, autologous stem cell transplantation, rituximab, ocrelizumab) for cumulative exposure to IFNβ/GA; substituting cumulative proportion of observation period spent pregnant for number of term-pregnancies, thereby incorporating all pregnancies, including those that were terminated early; substituting latitude for country; and substituting ARR disaggregated by 5-year intervals for overall ARR into the primary adjusted model to assess the effect of timing of relapses on EDSS outcomes.

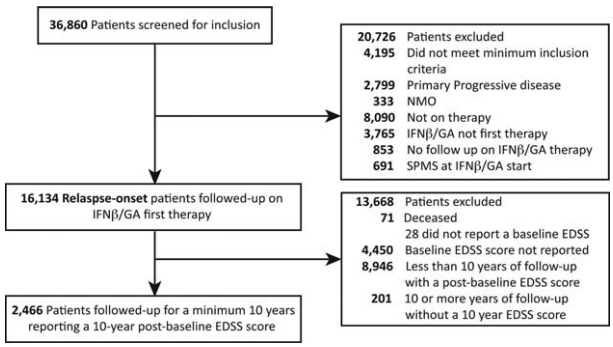

FIGURE 1: CONSORT (Consolidated Standards of Reporting Trials) flowchart for study inclusion. EDSS = Expanded Disability Status Scale; GA = glatiramer acetate; IFNβ = interferon-β; NMO = neuromyelitis optica; SPMS = secondary progressive multiple sclerosis.

To assess the impact of on-treatment relapses on EDSS outcomes, 2 additional adjusted quantile median regression models were run. In the first subanalysis, ARR was substituted with on- and off-treatment calculated ARR for the 10-year follow-up period (S1). In the second subanalysis, only those patients who were able to contribute to both on-treatment and off-treatment epochs were modeled (S2). Both models were adjusted for all model covariates included in the primary adjusted analysis.

In all analyses, patient follow-up was censored at the date of the 10-year EDSS visit, unless stated otherwise.

Results

Primary Analysis

PATIENT CHARACTERISTICS. A total of 16,134 registry patients from 97 clinics across 27 countries recording IFNβ or GA as first DMT were followed up for a median of 6.7 years (IQR = 3.5–10.8). Of these, 2,466 (15.3%) patients met the study inclusion criteria (Fig 1), that is, they were followed up for at least 10 years, recorded a 10-year post-baseline EDSS score, and met

TABLE 1. Cohort Demography and Characteristics

Characteristic	At Least 10 Years of Follow-up with a 10-year EDSS Score Recorded, n = 2,466	
	At Baseline	At Censoring
Female, No. (%)	1,830 (74.2)	
Age, mean [SD]	34.8 [9.3]	44.8 [9.3]
Disease duration, yr, median {IQR}	3.8 {1.5–8.3}	13.8 {11.5–18.3}
EDSS, median {IQR}	2 {1–3}	3 {1.5–4.5}
EDSS range	0–7	0–9.5
Disease course, No. (%)		
CIS	153 (6.2)	31 (1.3)
RRMS	2,313 (93.8)	2,037 (82.6)
SPMS	—	398 (16.1)
Pregnancies, No. (% of females)	Pregnancies prior to baseline excluded	304 (12.3)
Pregnancies per female, mean [SD]	—	1.3 [0.55]
Disease modifying therapy, No. (%)		
IFNβ-1a IM	720 (29.2)	196 (7.9)[a]
IFNβ-1b SC	580 (23.5)	206 (8.3)[a]
IFNβ-1a SC	834 (33.8)	225 (9.1)[a]
GA	332 (13.5)	123 (5.0)[a]
Total	2,466 (100)	750 (30.4)[a]
Number died subsequent to 10-year follow-up		39 individuals
EDSS score at 10-year follow-up for deceased patients		
Median {IQR}		6 {4–7}
Range		0-9.5

CIS = clinically isolated syndrome; EDSS = Expanded Disability Status Scale; GA = glatiramer acetate; IFNβ = interferon-β; IM = intramuscular; IQR = interquartile range; RRMS = relapsing–remitting multiple sclerosis; SC = subcutaneous; SD = standard deviation; SPMS = secondary progressive multiple sclerosis.
[a]Continuing on first IFNβ/GA therapy, No. (%).

minimum data set requirements. A total of 2,302 (93.3%) patients included in the analysis were followed-up in clinics within Italy, Canada, the Czech Republic, Spain, Australia, or Belgium (Supplementary Table 1). The baseline and follow-up characteristics of these cohorts are described in detail in Table 1 and Figure 2. Baseline characteristics of the 13,668 excluded patients (Supplementary Table 2) were largely comparable to the included cohort with the exception that a greater number of patients were first treated with a clinically isolated syndrome diagnosis, and had a shorter duration between symptom onset and therapy initiation.

The mean ARR was 0.36 (standard deviation [SD] = 0.33) over the 10-year follow-up period.

A total of 304 full-term pregnancies were reported for 226 (12.3%) females over the 10-year observation period, of which 134 (44.1%) were conceived on therapy; 128 (42.1%) pregnancies occurred in the first 5 years of follow-up post-baseline.

DMT. Of the 16,134 patients who initiated IFNβ/GA therapy, 9,425 (58.4%) patients discontinued treatment during the observation period after a median of 4.30 years (IQR = 1.83–8.90). Mean proportion of time on first IFNβ/GA therapy for the entire 16,134-patient cohort was 0.61 (SD = 0.44). Mean proportion of time on first IFNβ/GA therapy was 0.59 (SD = 0.36) for the 2,466-patient cohort with 10-year follow-up. Mean

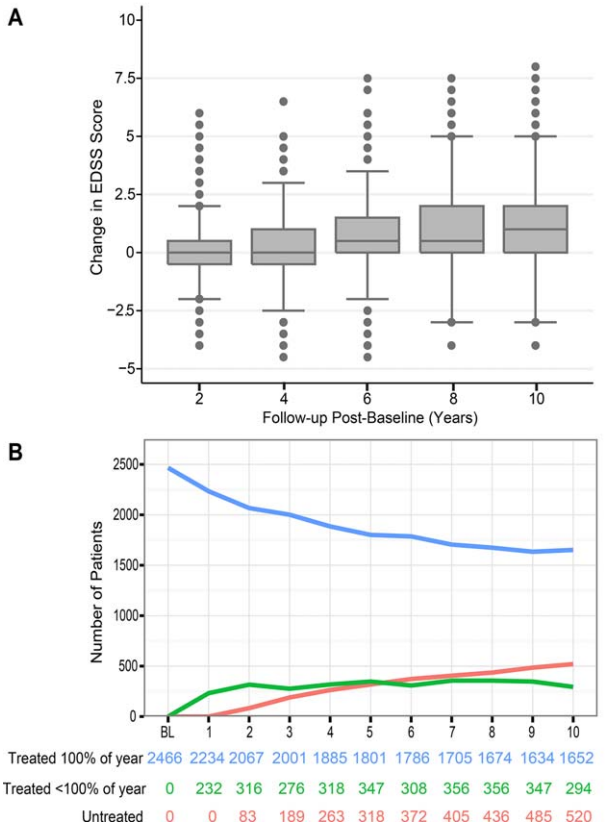

FIGURE 2: (A) Change in Expanded Disability Status Scale (EDSS) score at 2, 4, 6, 8, and 10-years post-baseline. (B) Number of patients receiving disease-modifying therapy at baseline (BL) and during each year of follow-up thereafter. Disease-modifying therapies included all interferon-β preparations, glatiramer acetate, natalizumab, fingolimod, dimethyl fumarate, teriflunomide, cladribine, alemtuzumab and rituximab, ocrelizumab, mitoxantrone, and autologous stem cell transplantation.

cumulative exposure to any IFNβ/GA initiation over the 10-year follow-up period was 0.79 (SD = 0.27), indicating high intraclass switching. Mean proportion of follow-up on oral therapies (including fingolimod, dimethyl fumarate, teriflunomide, and cladribine) during this period was 0.01 (SD = 0.06), and mean proportion of follow-up on high-efficacy therapies (principally natalizumab and mitoxantrone, but also encompassing alemtuzumab, autologous stem cell transplantation, rituximab, and ocrelizumab) was 0.03 (SD = 0.10). A total of 1,183 switches of therapy were reported for 932 (37.8%) patients. Median treatment gap was 36 days (IQR = 0–286) for all switches. Mean proportion of follow-up spent untreated was 0.19 (SD = 0.26) over 10 years.

LONG-TERM EDSS SCORE CHANGES AND THEIR PREDICTORS. Median EDSS point increase at 10 years post-baseline was 1.0 (IQR = 0–2). We identified 839 (34%) individuals who improved or remained stable relative to baseline over the 10-year observation period. Table 2 summarizes the proportion of patients reaching hard EDSS milestones at 10-year follow-up post-baseline.

Predictors of greater EDSS increase 10 years after initiating first INFβ/GA on adjusted quantile regression modeling included older age at onset, longer disease duration at baseline, and higher ARR (Table 3). Higher cumulative treatment exposure to IFNβ/GA therapy was associated with reduced EDSS scores across the 10-year interval ($coeff = -0.86$, 95% confidence interval [CI] $= -1.13$ to -0.58, $p = 1.3 \times 10^{-9}$), translating into a prevention of 1 EDSS point increase for every 11.6 years of INFβ/GA exposure. First-line DMT choice was not significantly associated with long-term outcomes ($p > 0.05$ for all comparisons, data not shown). In addition, at least 1 pregnancy during the 10-year post-baseline period was associated with a median 0.36-point decrease in EDSS (95% CI = −0.62 to −0.09).

TABLE 2. Summary of 10-Year EDSS Change Disaggregated by Baseline EDSS

	Baseline EDSS Score				Total, n = 2,466
	0, n = 261	1–2.5, n = 1,533	3–5.5, n = 629	≥6, n = 43	
Patients remaining stable or improved, No. (%)	66	570	187	16	839 (34.0)
Patients reaching EDSS ≥ 3, No. (%)	48	629	550	42	1,269 (51.4)
Patients reaching EDSS ≥ 4, No. (%)	26	419	467	42	954 (38.7)
Patients reaching EDSS ≥ 6, No. (%)	8	146	251	34	439 (17.8)

Number of patients remaining stable or improved, or reaching disability milestones over the 10-year observation period disaggregated by baseline EDSS score.
EDSS = Expanded Disability Status Scale.

TABLE 3. Predictors of Median 10-Year EDSS Change, n = 2,466

Predictor	Unadjusted Models		Adjusted Model[a]	
	β Coefficient (95% CI)	***p***	**β Coefficient (95% CI)**	***p***
Gender				
Female	Reference	—	Reference	—
Male	0.00 (−0.20 to 0.20)	0.999	0.14 (−0.02 to 0.31)	0.089
Age at onset, 10-year units	0.00 (−0.10 to 0.10)	0.999	0.41 (0.32 to 0.50)	5.8×10^{-18}
Disease duration at baseline, 5-year units	0.16 (0.10 to 0.23)	9.7×10^{-7}	0.36 (0.29 to 0.43)	1.8×10^{-23}
Post-baseline relapses, ARR in first 10 years of follow-up	1.11 (0.87 to 1.35)	4.1×10^{-19}	1.14 (0.91 to 1.37)	1.9×10^{-22}
Cumulative exposure to IFNβ/GA therapy	−0.73 (−1.03 to −0.43)	1.8×10^{-6}	−0.86 (−1.13 to −0.58)	1.3×10^{-9}
Number of pregnancies during follow-up				
Male	Excluded	—	Excluded	—
0	Reference	—	Reference	—
≥1	−0.50 (−2.18 to 1.18)	0.560	−0.36 (−0.62 to −0.09)	0.009

Quantile median regression analysis.
[a]Adjusted modeling included adjustments for first DMT identity, baseline EDSS score, and country.
ARR = annualized relapse rate; CI = confidence interval; EDSS = Expanded Disability Status Scale; GA = glatiramer acetate; IFNβ = interferon-β.

Sensitivity Analyses

EDSS OUTCOME MEASURE. Sensitivity analyses evaluating the robustness of results based on inclusion criteria (Table 4) largely supported the primary analysis. All results of the primary analysis were replicated when restricting inclusion criteria to include either only patients whose EDSS scores were reported within ±6 months of baseline and 10-year follow-up, or only those patients whose 10-year EDSS scores were confirmed 3 to 15 months after the 10-year assessment.

Assessment of long-term outcomes in individuals who reported either no change in EDSS score, or a clinically significant change in EDSS score according to a 3-step EDSS progression/regression paradigm (n = 1,984) additionally found that male sex was predictive of a median 0.26-point higher EDSS score at 10 years post-baseline relative to females ($p = 0.015$; see Table 4). Here again ARR was the primary driver of disability accumulation, where an ARR of 1 resulted in a median 1.26-point increase in EDSS score over the 10-year observation period.

ARR. Given that ARR was the strongest independent clinical predictor of long-term outcome, we further sought to determine the impact of the timing of these relapses. We disaggregated relapses by those that occurred within the first 5 years of follow-up, and those that occurred thereafter. We found on adjusted analysis that an ARR of 1 in the first 5 years of observation was associated with a median 0.62-point EDSS score increase at 10 years (95% CI = 0.44–0.79, $p = 5.3 \times 10^{-12}$). Similarly, an ARR of 1 between years 5 and 10 was associated with a median 0.50-point EDSS score increase at 10 years (95% CI = 0.28–0.72, $p = 1.3 \times 10^{-5}$).

The effect of on- and off-treatment relapses on 10-year EDSS change was assessed in 2 further sensitivity analyses. Of the 2,466 patients analyzed in this study, 1,968 (79.8%) reported at least 1 on-treatment relapse, and 665 (27%) patients reported at least 1 off-treatment relapse. An on-treatment ARR of 1.0 was associated with a 0.86-point EDSS score increase ($p = 6.5 \times 10^{-19}$) over 10 years (equivalently, an on-treatment ARR of 0.3 was associated with a 0.26-point increase in EDSS over the 10-year period; Fig 3, S1). In contrast, an off-treatment ARR of 1 was associated with a 0.05-point EDSS score increase ($p > 0.05$). A second subanalysis (S2) using only those patients who contributed to both on- and off-

TABLE 4. Results of Sensitivity Analyses Relating to EDSS Outcome Measure

Outcome	β Coefficient (95% CI)	Adjusted p[a]
Predictors of median EDSS change: EDSS recorded within 6 months of baseline and follow-up		
Number of patients	2,001	
Gender		
Female	Reference	—
Male	0.16 (−0.03 to 0.35)	0.103
Age at onset, 10-year units	0.38 (0.27 to 0.48)	3.6×10^{-12}
Disease duration at baseline, 5-year units	0.36 (0.28 to 0.44)	4.2×10^{-18}
ARR during follow-up	1.31 (1.04 to 1.58)	1.2×10^{-21}
Cumulative exposure to IFNβ/GA	−0.94 (−1.27 to −0.62)	1.5×10^{-8}
Number of pregnancies during follow-up		
Males	Excluded	—
0	Reference	—
≥1	−0.31 (−0.61 to −0.02)	0.039
Predictors of median EDSS change: EDSS confirmed 3–15 months after 10-year follow-up		
Number of patients	1,300	
Gender		
Female	Reference	—
Male	0.14 (−0.07 to 0.36)	0.191
Age at onset, 10-year units	0.40 (0.28 to 0.52)	8.3×10^{-11}
Disease duration at baseline, 5-year units	0.38 (0.29 to 0.47)	1.5×10^{-16}
ARR during follow-up	1.05 (0.75 to 1.34)	8.6×10^{-12}
Cumulative exposure to IFNβ/GA	−1.02 (−1.39 to −0.66)	4.1×10^{-8}
Number of pregnancies during follow-up		
Males	Excluded	—
0	Reference	—
≥1	−0.46 (−0.81 to −0.11)	0.010
Predictors of median EDSS change: only including clinically significant EDSS changes according to 3-step EDSS progression strata		
Number of patients	1,984	
Gender		
Female	Reference	—
Male	0.26 (0.05 to 0.47)	0.015
Age at onset, 10-year units	0.43 (0.31 to 0.54)	5.6×10^{-13}
Disease duration at baseline, 5-year units	0.34 (0.25 to 0.42)	4.8×10^{-14}
ARR during follow-up	1.26 (0.97 to 1.54)	1.1×10^{-17}

TABLE 4: Continued

Outcome	β Coefficient (95% CI)	Adjusted p[a]
Cumulative exposure to IFNβ/GA	−0.86 (−1.20 to −0.51)	1.4×10^{-6}
Number of pregnancies during follow-up		
Males	Excluded	—
0	Reference	—
≥1	−0.44 (−0.78 to −0.10)	0.012

Quantile median regression analysis.
[a]Adjusted modeling included adjustments for first disease-modifying therapy identity, baseline EDSS score, and clinic country.
ARR = annualized relapse rate; CI = confidence interval; EDSS = Expanded Disability Status Scale; GA = glatiramer acetate; IFNβ = interferon-β.

treatment epochs (n = 1,475) confirmed much weaker off-treatment relapse ($p > 0.05$) than on-treatment relapse ($p = 2.4 \times 10^{-6}$) effects (see Fig 3).

To further assess the impact of relapses on long-term EDSS outcomes, we identified those relapses for which categorical recovery data (complete, partial, none) were available. Recovery data were reported for 21% of all relapses that occurred during the 10-year follow-up period, corresponding to 33.7% of individuals in our cohort. When these data were disaggregated by clinically significant (3-step) EDSS changes, we found that a greater proportion of relapses failed to resolve (no or partial recovery) in those cases with clinically significant EDSS increases (58.1%), relative to those who remained stable (34.4%) or those whose EDSS scores significantly regressed (34.3%).

THERAPEUTIC INTERVENTION. Due to the very limited exposure of patients in this cohort to non-IFNβ/GA therapies (overall 1% for oral therapy, and 3% for high-efficacy therapies, as compared to 79% for injectable therapies), there was insufficient statistical power to disaggregate treatment effects by treatment class. However, an additional adjusted sensitivity analysis, combining all DMTs, again confirmed the protective effect of DMT against disability accrual (*coeff* = −0.87, $p = 5.7 \times 10^{-9}$; Table 5).

We further sought to interrogate the effect of pregnancy on long-term outcomes by modeling cumulative time spent pregnant over the observation period. We included all reported pregnancies, whether successfully delivered or prematurely terminated. Here we found that pregnancy was associated with a median 3.17-point lower EDSS score over 10 years (equivalently −0.32 points per 10% of time pregnant). In contrast, comparable exposure to INFβ/GA therapy was associated with a median 0.71-point (or −0.07 points per 10% of observation on therapy) lower EDSS score in the same context (see Table 5).

An additional adjusted sensitivity analysis substituting latitude for country failed to demonstrate an independent relationship between latitude (*coeff* per 10° of latitude = −0.002, 95% CI = −0.16 to 0.15, $p = 0.977$) and EDSS outcome (rest of model not shown).

Discussion

Our aim was to determine predictors of EDSS score change, including treatment effects, in a large, real-world, prospectively acquired cohort of multiple sclerosis patients who commenced injectable DMT. We found that EDSS score increases in this cohort were generally modest over the 10-year observation period, consistent with long-term extension arms of pivotal trials.[19,20] High relapse activity was the principal driver of 10-year post-baseline disability increase, with a smaller but equally significant effect of older age, and longer delay to treatment initiation. Cumulative treatment exposure to first-line DMTs was independently associated with decreased disability accrual in all models, with 11.6 years of exposure to INFβ/GA therapy required to prevent 1 EDSS point increase. Additionally, we found that the therapeutic effect of pregnancy was >4 times greater than that of first-line therapy in women within the first 10 years of DMT start.

The impact of relapses on long-term disability outcomes is still debated. Past studies have interrogated the effect of relapses on time to reach hard disability milestones, finding that very high relapse rates in the first 5 years of disease onset are associated with a more rapid progression to hard EDSS milestones, at least in the short term.[21,22] These studies have further argued that late relapses, particularly those in the progressive stages of the disease, have little or no influence on disability progression.[22,23] In contrast, we demonstrated a stronger relationship between relapses and EDSS score changes over time, consistent with other studies.[24–26] We have

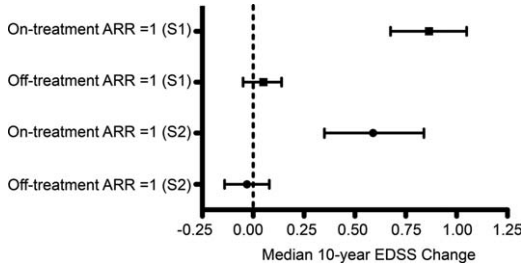

FIGURE 3: Contribution of on- and off-therapy annualized relapse rate (ARR) to 10-year median Expanded Disability Status Scale (EDSS) changes (95% confidence interval). Here the ARR is normalized to 1. This figure shows the results of 2 adjusted quantile median regression analyses. All analyses were adjusted for gender, age at baseline, disease duration, proportion of follow-up on first-line disease-modifying therapy (DMT), pregnancies, first DMT identity, baseline EDSS score, and clinic country. Subanalysis 1 (S1) includes all 2,466 patients from the primary analysis. Subanalysis 2 (S2) only models those patients who were able to contribute to both on-treatment and off-treatment epochs (n = 1,475). This figure demonstrates that on-treatment relapses have a profound effect on long-term EDSS increases, whereas off-treatment relapses have a marginal effect on disability outcomes.

demonstrated that the effect of relapses on disability accrual in a modern-day, treated cohort of multiple sclerosis patients is profound, even for those relapses occurring some 14 or more years after disease onset. This held true even when adjusting for baseline EDSS score, treatment effects, and pregnancy. However, in concordance with past studies,[21,22] we did find that those relapses occurring earlier in the disease course had the greatest impact on long-term disability outcomes.

The 8-year follow-up of the IFNβ-1a IM MSCRG trial[9] demonstrated that 2 or more relapses in the first 2 years on treatment were predictive of disability score in the long term. However, this effect lost significance in adjusted modeling, most likely due to the relatively small cohort size of 160 participants.[27] The 15-year follow-up (ASSURANCE study) of this same pivotal trial, however, demonstrated that on-treatment relapses during the first 2 years of the MSCRG trial were correlated with severe EDSS worsening at 15 years.[28] We sought to confirm this observation and assessed the effect of on-treatment and off-treatment relapses on disability outcomes in a series of sensitivity analyses. We demonstrated that on-treatment relapses did have an independent and profound effect on 10-year EDSS score increases. We further found that the effect of off-treatment relapses on long-term outcomes was marginal. This result suggests that persistent relapse activity on first-line therapy is prognostic of future outcome, consistent with the modified Rio score.[29] Although limited relapse recovery data were available for this cohort, they nonetheless demonstrated that one of the key mechanisms driving disability accrual is the predisposition toward poor relapse recovery, consistent with prior studies.[26,30] In an era where numerous new therapeutic agents are available for the treatment of relapsing multiple sclerosis, and where treatment goals have shifted toward freedom from disease activity,[31,32] this result supports treatment escalation particularly in those patients relapsing on first-line therapy to mitigate permanent disability accrual.[33,34]

It has been demonstrated in a meta-analysis of 19 relapsing–remitting multiple sclerosis (RRMS) randomized controlled trials that efficacy of treatment in reducing the incidence of relapses is additionally correlated with decreases in short-term disability.[25] Similarly, data from observational cohort studies have shown that length of first-line treatment exposure significantly reduces the risk of disability progression in the short term, particularly if treatment is used early in the disease course.[12,13] Our data are consistent with and extend these studies, demonstrating that the influence of relapses and treatment exposure in RRMS extends to long-term disability changes, not just those in the acute phase. In contrast to past reports,[14,15] here we show that increasing cumulative treatment exposure over the observation period independently predicts better disability outcomes in the long-term. Our results are consistent with the extension phases of a number of pivotal randomized clinical trials, demonstrating that those patients exposed to treatment for longer periods have better long-term EDSS outcomes.[19,20,35–39] It is of course possible that we have identified treatment responders, whereas those who spent little time on therapy were poor responders with more aggressive disease. However, these results still provide confidence in the long-term effectiveness of first-line therapy in these patients.

It is now well established that relapse rates diminish during pregnancy, with relapse activity being lowest in the third trimester, and rebounding in the first 3 months postpartum.[40,41] Women with high disease activity prior to pregnancy are at greatest risk of postpartum disease activity.[41,42] However, the long-term effect of pregnancy on the accumulation of disability is less well understood, with studies reporting either acceleration to SPMS,[43] no effect of pregnancy on long-term outcomes,[44] longer time to wheelchair or progressive phase in women with at least 1 pregnancy compared to nulliparous women,[45,46] or a reduced risk of reaching an EDSS 6 milestone only in those women with 2 or more pregnancies.[47] Here, we were able to examine the effect of pregnancy on long-term outcomes while adjusting for relapse rates, therapy use, and other relevant covariates. We found that having at least 1 pregnancy within the first

TABLE 5. Results of Sensitivity Analyses Relating to Therapeutic Interventions

Outcome	β Coefficient (95% CI)	Adjusted p[a]
Predictors of median EDSS change: cumulative exposure to all therapies		
Number of patients	2,466	
Gender		
Female	Reference	—
Male	0.14 (−0.02 to 0.31)	0.086
Age at onset, 10-year units	0.41 (0.32 to 0.50)	1.8×10^{-18}
Disease duration at baseline, 5-year units	0.35 (0.28 to 0.42)	4.0×10^{-23}
ARR during follow-up	1.20 (0.98 to 1.42)	9.2×10^{-26}
Cumulative exposure to all DMTs	−0.87 (−1.16 to −0.58)	5.7×10^{-9}
Number of pregnancies during follow-up		
Males	Excluded	—
0	Reference	—
≥1	−0.34 (−0.61 to −0.08)	0.011
Predictors of median EDSS change: proportion of time spent pregnant over observation period[b]		
Number of patients	1,830	
Age at onset, 10-year units	0.43 (0.32 to 0.54)	7.5210^{-15}
Disease duration at baseline, 5-year units	0.37 (0.29 to 0.45)	3.1×10^{-19}
ARR during follow-up	1.21 (0.95 to 1.47)	2.3×10^{-19}
Cumulative [100%] exposure to IFNβ/GA	−0.71 (−1.03 to −0.38)	2×10^{-5}
100% of observation period spent pregnant	−3.17 (−5.68 to −0.67)	0.013

Quantile median regression analysis.
[a]Adjusted modeling included adjustments for first DMT identity, baseline EDSS score, and clinic country.
[b]Analysis restricted to females only.
ARR = annualized relapse rate; CI = confidence interval; DMT = disease-modifying therapy; EDSS = Expanded Disability Status Scale; GA = glatiramer acetate; IFNβ = interferon-β.

10 years of first DMT initiation had a protective effect against the accumulation of disability, independent of relapse activity (including postpartum relapse activity spikes) and therapy use. Interestingly, when comparing proportion of time spent pregnant (irrespective of pregnancy outcome) to proportion of time on first-line therapy, we found that the therapeutic effect of pregnancy was much larger than that of therapy, thus demonstrating that pregnancy is largely beneficial in women with relapse-onset multiple sclerosis. It is conceivable that women with lower disease burden are those more likely to attempt pregnancy. However, in our study, approximately half of the pregnancies were conceived while the patient was on therapy, suggesting that a large proportion of pregnancy decisions were not based solely on disease burden considerations.

The data analyzed here were collected as part of a multinational cohort study, primarily in large tertiary referral centers. Furthermore, a number of patients who initiated first-line therapy were excluded from this study as they did not meet inclusion criteria (length of follow-up, or availability of EDSS scores), and therefore this study is subject to selection bias. However, we utilized an agreed minimum data set to ensure consistency of collected data. Furthermore, we demonstrated that excluded patients were largely comparable to our included cohort at baseline, with the exception that patients more recently diagnosed tend to access treatment sooner. Although other factors such as socioeconomic status and vitamin D levels may also influence outcomes, these data were not available for analysis. We did, however, adjust for clinic country in all models to account for differences in both

healthcare systems and prescribing practices. Furthermore, a sensitivity analysis adjusting for latitude found no association with EDSS outcomes.

An additional limitation of our study is intrinsic in the use of the EDSS, which is weighted toward motor symptoms and subject to inter- and intrarater variability. To mitigate against this, we required that all investigators have Neurostatus certification. Furthermore, the exclusion of EDSS scores recorded within 30 days of a relapse helped to mitigate against overinflated scores driving sharp increases or decreases in observed long-term disability changes. Our analysis, being conducted retrospectively on a prospectively acquired data set, was free from reporting bias. Furthermore, we removed indication bias from this study by defining use of first injectable therapy as the baseline for this analysis.

Conclusions

In a large contemporary, real-world cohort, we provide evidence of a strong protective effect of DMT against long-term disability accrual, particularly if it is used early in the disease course. We also demonstrate a potent therapeutic effect of pregnancy. Furthermore, we demonstrate a direct relationship between inflammation and the accumulation of long-term disability. Our results demonstrate that high relapse activity, particularly early on-treatment relapse activity, is an indicator of poor prognosis. Together, these results provide evidence and confidence in the long-term benefits of DMT and pregnancy in patients with active RRMS, but further argue for treatment escalation in those patients relapsing on first-line therapy to protect against long-term disability accrual.

Acknowledgment

This investigator-initiated analysis was supported by a project grant from the National Health and Medical Research Council (NHMRC; 1032484) and an NHMRC Centre for Research Excellence grant (1001216).

Author Contributions

H.B., A.L., and M.T. contributed equally to this work. Study conception and design: V.G.J., T.S., H.B. Contributed substantially to data acquisition and analysis: all authors. Drafted the manuscript and prepared the figures: V.G.J.

Potential Conflicts of Interest

V.G.J., T.S., T.K., J.L., E.H., D.H., P.D., M.G., G.Iz., P.G., V.V.P., E.P., F.G.'M., R.H., F.G., P.S., R.B., G.Iu., D.S., C.B., S.H., J.O., F.V., T.P., C.R., J.L.-S., D.F., D.P., H.B., A.L., and M.T. report conflicts of interest in relation to advisory board membership, speaker honoraria, travel support, research grants, consulting fees, or clinical trial participation with the following companies: Bayer Schering, Biogen, Genzyme, Merck, Novartis, Sanofi, Teva, and their local affiliates. Please refer to supplementary material for full disclosures.

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