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Title

Predictors of long-term disability accrual in relapse-onset multiple sclerosis

Running Head:

Predictors of long-term MS outcomes

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List of Abbreviations

ARR Annualised Relapse Rate

CIS Clinically Isolated Syndrome

DMT Disease Modifying Therapy

EDSS Expanded Disability Status Scale

GA Glatiramer Acetate

IFN β Interferon- β

SPMS Secondary Progressive Multiple Sclerosis

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Abstract

Objective: To identify predictors of ten year expanded disability status scale (EDSS) change after treatment initiation in patients with relapse-onset MS.

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 one 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. Annualised 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-annualised relapse rate, particularly on-treatment relapse, is an indicator of poor prognosis.

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Introduction

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 (DMT) 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 behaviours. 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 whilst 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 MS registry cohort.

Patients and Methods

● Ethics statement

The MSBase Registry (registered with WHO ICTRP, ID ACTRN12605000455662) was approved by the Melbourne Health Human Research Ethics Committee and by the local ethics committees in all participating centres (or exemptions 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 centres.

Patients with relapse-onset multiple sclerosis prescribed Interferon- β (IFN β) 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 +/- 12 months of first IFN β /GA initiation. Additionally, study inclusion criteria required at least one EDSS score to be recorded within +/- 12 months of the 10-year post-treatment initiation time-point. All analysed 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 IFN β /GA treatment initiation, or those with incomplete datasets were further excluded. The

● minimum dataset 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 dataset requirements.

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

Included patients commenced immunotherapy between January 1989 - 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 standardised EDSS scoring and to reduce *inter-rater* variability, MSBase mandates at all participating neurologists have Neurostatus[®] certification.

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

Statistical Analysis

Analysis was undertaken using Stata version 12 (StataCorp, College Station, Texas) or R (<http://R-project.org>). All analyses were two-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 summarised using median and inter-quartile range as appropriate. Categorical variables were summarised 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 IFN β /GA treatment exposures, DMT identity, pregnancy events, baseline EDSS score and relapse activity on 10-year EDSS change. Co-linearity and interactions between model covariates were examined using a likelihood ratio test. The He & Zhu Lack-Of-Fit test for Quantile Regression¹⁷ 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 3-15 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 (i.e. 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 1-5.5, and a minimum 0.5 point EDSS score increase/decrease if baseline EDSS score was 6 or above).¹⁸ Sensitivity to the definition of variables was tested by: substituting cumulative treatment exposure on all disease modifying therapies (including IFN β /GA, teriflunomide, fingolimod, dimethyl fumarate, cladribine, natalizumab, mitoxantrone, alemtuzumab, autologous stem cell transplantation, rituximab, ocrelizumab) for cumulative exposure to IFN β /GA; by substituting cumulative proportion of observation period spent pregnant for number of term-pregnancies, thereby incorporating all pregnancies, including those that were terminated early; by substituting latitude for country; and by substituting ARR disaggregated by 5-year intervals for overall ARR into the primary adjusted model to assess the timing of relapses on EDSS outcomes.

To assess the impact of on-treatment relapses on EDSS outcomes, two additional adjusted quantile median regression models were run. In the first sub-analysis, ARR was substituted with on and off-treatment calculated ARR for the 10-year follow-up period (S1). In the second sub-analysis, only those patients who were able to contribute to both on-treatment and off-treatment epochs were modelled (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 ten-year EDSS visit, unless stated otherwise.

Results

Primary Analysis

Patient characteristics

16,134 registry patients from 97 clinics across 27 countries recording IFN β or GA as first DMT were followed up for a median 6.7 years (IQR: 3.5, 10.8). Of these, 2,466 (15.3%) patients met the study inclusion criteria (Figure 1), that is, they were followed up for at least 10 years, recorded a 10-year post-baseline EDSS score, and met minimum dataset requirements. 2,302 (93.3%) of 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 CIS diagnosis, and had a shorter duration between symptom onset and therapy initiation.

The mean annualised relapse rate (ARR) was 0.36 (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 five years of follow-up post-baseline.

Disease-modifying therapy

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

initiation over the 10-year follow-up period was 0.79 (SD 0.27), indicating high intra-class 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). 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 (interquartile range (IQR): 0,2). We identified 839 (34%) individuals who improved or remained stable relative to baseline over the 10-year observation period. Table 2 summarises the proportion of patients reaching hard EDSS milestones at 10 years follow-up post-baseline.

Predictors of greater EDSS increase 10 years after initiating first INF β /GA on adjusted quantile regression modelling included older age at onset, longer disease duration at baseline and higher annualised relapse rate (ARR) (Table 3). Higher cumulative treatment exposure to IFN β /GA therapy was associated with reduced EDSS scores across the 10-year interval (*coeff* -0.86; 95% CI -1.13, -0.58; $p=1.3\times 10^{-9}$), translating into a prevention of 1 EDSS point increase for every 11.6-years of INF β /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 one pregnancy during the 10-year post-baseline period was associated with a median 0.36-point decrease in EDSS (95% CI: -0.62, -0.09).

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 either restricting inclusion criteria to only include patients whose EDSS scores were reported within +/- 6 months of baseline and 10-year follow-up, or to those patients whose 10-year EDSS scores were confirmed 3-15 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; 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.

Annualised relapse rate

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 one in the first 5 years of observation was associated with in a median 0.62-point EDSS score increase at 10-years (95% CI: 0.44, 0.79; p=5.3x10⁻¹²). Similarly, an ARR of one between years 5-10 was associated with a median 0.50-point EDSS score increase at 10 years (95% CI: 0.28, 0.72; p=1.3x10⁻⁵).

The effect of on and off-treatment relapses on 10-year EDSS change was assessed in two further sensitivity analyses. Of the 2,466 patients analysed in this study, 1,968 (79.8%) reported at least one on-treatment relapse, and 665 (27%) patients reported at least one 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; Figure 3- S1). Whereas, an off-treatment ARR of 1 was associated with a 0.05-point EDSS score increase ($p>0.05$). A second sub-analysis (S2) using only those patients who contributed to both on and off-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 (Figure 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-IFN β /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 DMT 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 modelling 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). Whereas, comparable exposure to INFB/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 (Table 5).

An additional adjusted sensitivity analysis substituting latitude for country failed to demonstrate an independent relationship between latitude (*coeff* per 10 degrees of latitude -0.002; 95% CI -0.16, 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 disease modifying therapy. 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 IFN β /GA therapy required to prevent 1 EDSS point increase.

Additionally, we found that the therapeutic effect of pregnancy was more than four-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 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 IFN β -1a IM MSCRG trial⁹ demonstrated that two 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 modelling, 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 two 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 indeed 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 Whilst limited relapse recovery data were available for this cohort, they nonetheless demonstrated that one of the key mechanisms driving disability accrual is the predisposition towards 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 towards 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 randomised 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 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 RCTs, demonstrating 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 post-partum.^{40, 41} Women with high disease activity prior to pregnancy are at greatest risk of post-partum 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 one pregnancy compared to nulliparous women^{45, 46}, or a reduced risk of reaching an EDSS 6 milestone only in those women with two or more pregnancies.⁴⁷ Here, we were able to examine the effect of pregnancy on long-term outcomes whilst adjusting for relapse rates, therapy use and other relevant covariates. We found that having at least one pregnancy within the first 10 years of first DMT initiation had a protective effect against the accumulation of disability, independent of relapse activity (including post-partum 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 whilst on therapy, suggesting that a large proportion of pregnancy decisions were not based solely on disease burden considerations.

The data analysed here were collected as part of a multinational cohort study, primarily in large tertiary referral centres. Further, 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 utilised an agreed minimum dataset to ensure consistency of collected data. Further, 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. Whilst other factors such as socioeconomic status, 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 both differences in healthcare systems and prescribing practices. Further 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 towards motor symptoms and subject to inter and intra-rater variability. To mitigate against this, we required that all investigators have Neurostatus certification. Further, the exclusion of EDSS scores recorded within 30 days of a relapse helped to mitigate against over-inflated scores driving sharp increases or decreases in observed long-term disability changes. Our analysis being conducted retrospectively on a prospectively acquired dataset

was free from reporting bias. Further, 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 disease modifying therapy against long-term disability accrual, particularly if used early in the disease course. We also demonstrate a potent therapeutic effect of pregnancy. Further, 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 disease-modifying therapy and pregnancy in patients with active relapsing-remitting multiple sclerosis, but further argue for treatment escalation in those patients relapsing on first-line therapy to protect against long-term disability accrual.

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Author Contributions:

Study conception and design: VGJ, TS, HB. Contributed substantially to data acquisition and analysis: VGJ, TS, TK, JL, PD, MG, AP, EH, DH, Glz, PG, EP, FGM, RB, FG, VvP, RH, Glu, DLS, PS, CB, TP, FV, JO, PMC, CR, JLS, SH, MLS, DF, PI, DP, HB, AL and MT. Drafted the manuscript and prepared the figures: VGJ.

Potential Conflicts of Interest:

Authors VGJ, TS, TK, JL, EH, DH, PD, MG, Glz, PG, VvP, EP, FGM, RH, FG, PS, RB, Glu, DS, CB, SH, JO, FV, TP, CR, JLS, DF, DP, HB, AL, and MT report conflicts of interest in relation to: advisory board membership, speakers 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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Figure Legends:**Figure 1:**

CONSORT Flowchart for study inclusion

Figure 2:

Figure shows change in EDSS score post-baseline at 2, 4, 6, 8 and 10-years (**A**). Figure further shows the number of patients receiving disease-modifying therapy at baseline (BL) and during each year of follow-up thereafter (**B**). Disease-modifying therapies included: all IFN β preparations, glatiramer acetate, natalizumab, fingolimod, dimethyl fumarate, teriflunomide, cladribine, alemtuzumab and rituximab, ocrelizumab, mitoxantrone and autologous stem cell transplantation.

Figure 3:

Contribution of on and off-therapy annualised relapse rate (ARR) to 10-year median EDSS changes (95% CI). Here the ARR is normalised to 1. This figure shows the results of two adjusted quantile median regression analyses. All analyses were adjusted for gender, age at baseline, disease duration, proportion of follow-up on first-line DMT, pregnancies, first DMT identity, baseline EDSS score and clinic country. Sub-analysis 1 (S1) includes all 2,466 patients from the primary analysis. Sub-analysis 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.

Table Legends:**Table 1:**

EDSS Expanded disability status scale; CIS Clinically Isolated Syndrome; RRMS Relapsing-remitting MS; SPMS Secondary Progressive MS; IFN β Interferon-beta; IM Intramuscular; SC Sub-cutaneous; GA Glatiramer Acetate; SD Standard Deviation; IQR Interquartile Range

Table 2:

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

Table 3:

Quantile median regression analysis.

#Adjusted modelling included adjustments for first DMT identity, baseline EDSS score and country.

EDSS Expanded disability status scale; CI Confidence Interval; DMT Disease Modifying Therapy; ARR Annualised Relapse Rate

Table 4:

Quantile median regression analysis.

*Adjusted modelling included adjustments for first DMT identity, baseline EDSS score and clinic country.

Adj: Adjusted; EDSS: Expanded Disability Status Scale; CI: Confidence Interval; ARR:

Annualised Relapse Rate; IFN β : Interferon-Beta; GA: Glatiramer Acetate; DMT: Disease

Modifying Therapy

Table 5:

● Quantile median regression analysis.

*Adjusted modelling included adjustments for first DMT identity, baseline EDSS score and clinic country.

y Analysis restricted to females only

Adj: Adjusted; EDSS: Expanded Disability Status Scale; CI: Confidence Interval; ARR:

Annualised Relapse Rate; IFN β : Interferon-Beta; GA: Glatiramer Acetate; DMT: Disease

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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, n(%)	1,830 (74.2)	
Age, mean (SD)	34.8 (9.3)	44.8 (9.3)
Disease duration years, 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		
CIS, n(%)	153 (6.2)	31 (1.3)
RRMS, n(%)	2,313 (93.8)	2,037 (82.6)
SPMS, n(%)	-	398 (16.1)
Pregnancies, n(% of females)	Pregnancies prior to baseline excluded	304 (12.3)
Pregnancies per female, mean (SD)	-	1.3 (0.55)
Disease modifying therapy, n(%)		Continuing on first BRACE therapy n(%)
IFN β -1a IM	720 (29.2)	196 (7.9)
IFN β -1b SC	580 (23.5)	206 (8.3)
IFN β -1a SC	834 (33.8)	225 (9.1)
GA	332(13.5)	123 (5.0)
Total	2466 (100)	750 (30.4)
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

EDSS Expanded disability status scale; CIS Clinically Isolated Syndrome; RRMS Relapsing-remitting MS; SPMS Secondary Progressive MS; IFN β Interferon-beta; IM Intramuscular; SC Sub-cutaneous; GA Glatiramer Acetate; SD Standard Deviation; IQR Interquartile Range

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, n(%)	66	570	187	16	839 (34.0%)
Patients reaching EDSS ≥3, n(%)	48	629	550	42	1,269 (51.4%)
Patients reaching EDSS ≥4, n(%)	26	419	467	42	954 (38.7%)
Patients reaching EDSS ≥6, n(%)	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.

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Table 3. Predictors of median 10-year EDSS change, n=2,466

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

Quantile median regression analysis.

#Adjusted modelling included adjustments for first DMT identity, baseline EDSS score and country. EDSS Expanded disability status scale; CI Confidence Interval; DMT Disease Modifying Therapy; ARR Annualised Relapse Rate

Table 4: Results of Sensitivity Analyses relating to EDSS outcome measure

Outcome	β coefficient (95% CI)	adj p-value*
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, 0.35)	0.103
Age at onset (10 year units)	0.38 (0.27, 0.48)	3.6×10^{-12}
Disease duration at baseline (5 year units)	0.36 (0.28, 0.44)	4.2×10^{-18}
ARR during follow-up	1.31 (1.04, 1.58)	1.2×10^{-21}
Cumulative exposure to IFN β /GA	-0.94 (-1.27, -0.62)	1.5×10^{-8}
Number of pregnancies during follow-up		
Males	Excluded	-
0	Reference	-
≥ 1	-0.31 (-0.61, -0.02)	0.039
Predictors of median EDSS change: EDSS confirmed 3-15 months post-10 year follow-up		
Number of patients	1,300	
Gender		
Female	Reference	-
Male	0.14 (-0.07, 0.36)	0.191
Age at onset (10 year units)	0.40 (0.28, 0.52)	8.3×10^{-11}
Disease duration at baseline (5 year units)	0.38 (0.29, 0.47)	1.5×10^{-16}
ARR during follow-up	1.05 (0.75, 1.34)	8.6×10^{-12}
Cumulative exposure to IFN β /GA	-1.02 (-1.39, -0.66)	4.1×10^{-8}
Number of pregnancies during follow-up		
Males	Excluded	-
0	Reference	-
≥ 1	-0.46 (-0.81, -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, 0.47)	0.015
Age at onset (10 year units)	0.43 (0.31, 0.54)	5.6×10^{-13}
Disease duration at baseline (5 year units)	0.34 (0.25, 0.42)	4.8×10^{-14}
ARR during follow-up	1.26 (0.97, 1.54)	1.1×10^{-17}
Cumulative exposure to IFN β /GA	-0.86 (-1.20, -0.51)	1.4×10^{-6}
Number of pregnancies during follow-up		
Males	Excluded	-
0	Reference	-
≥ 1	-0.44 (-0.78, -0.10)	0.012

*Quantile median regression analysis. Adjusted modelling included adjustments for first DMT identity, baseline EDSS score and clinic country.

Adj: Adjusted; EDSS: Expanded Disability Status Scale; CI: Confidence Interval; ARR: Annualised Relapse Rate; IFN β : Interferon-Beta; GA: Glatiramer Acetate; DMT: Disease Modifying Therapy

Table 5: Results of Sensitivity Analyses relating to therapeutic interventions

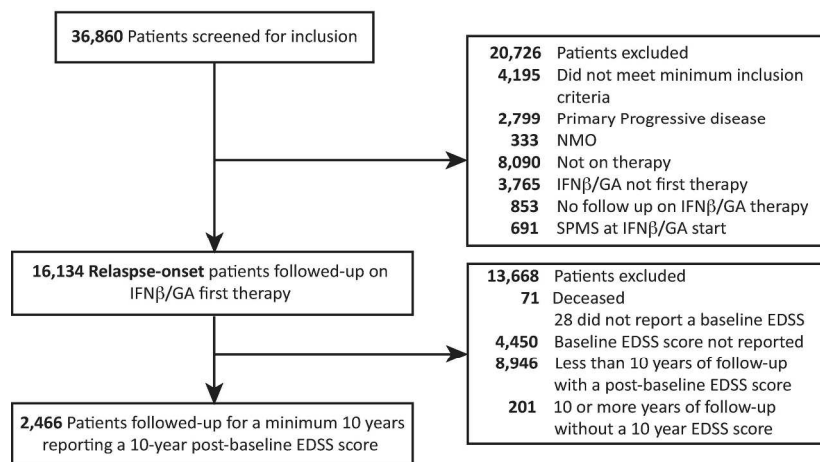
Outcome	β coefficient (95% CI)	adj p-value*
Predictors of median EDSS change: Cumulative exposure to all therapies		
Number of patients	2,466	
Gender		
Female	Reference	-
Male	0.14 (-0.02, 0.31)	0.086
Age at onset (10 year units)	0.41 (0.32, 0.50)	1.8×10^{-18}
Disease duration at baseline (5 year units)	0.35 (0.28, 0.42)	4.0×10^{-23}
ARR during follow-up	1.20 (0.98, 1.42)	9.2×10^{-26}
Cumulative exposure to all DMT:	-0.87 (-1.16, -0.58)	5.7×10^{-9}
Number of pregnancies during follow-up		
Males	Excluded	-
0	Reference	-
≥ 1	-0.34 (-0.61, -0.08)	0.011
Predictors of median EDSS change: Proportion of time spent pregnant over observation period^y		
Number of patients	1,830	
Age at onset (10 year units)	0.43 (0.32, 0.54)	7.52×10^{-15}
Disease duration at baseline (5 year units)	0.37 (0.29, 0.45)	3.1×10^{-19}
ARR during follow-up	1.21 (0.95, 1.47)	2.3×10^{-19}
Cumulative (100%) exposure to IFN β /GA	-0.71 (-1.03, -0.38)	2×10^{-5}
100% of observation period spent pregnant	-3.17 (-5.68, -0.67)	0.013

Quantile median regression analysis.

*Adjusted modelling included adjustments for first DMT identity, baseline EDSS score and clinic country.

^y Analysis restricted to females only

Adj: Adjusted; EDSS: Expanded Disability Status Scale; CI: Confidence Interval; ARR: Annualised Relapse Rate; IFN β : Interferon-Beta; GA: Glatiramer Acetate; DMT: Disease Modifying Therapy



CONSORT Flowchart for study inclusion
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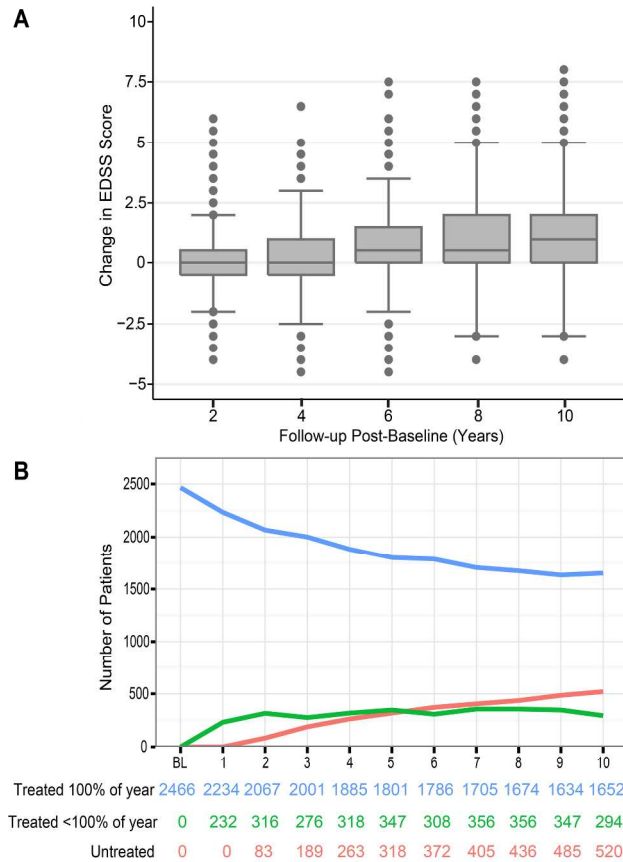
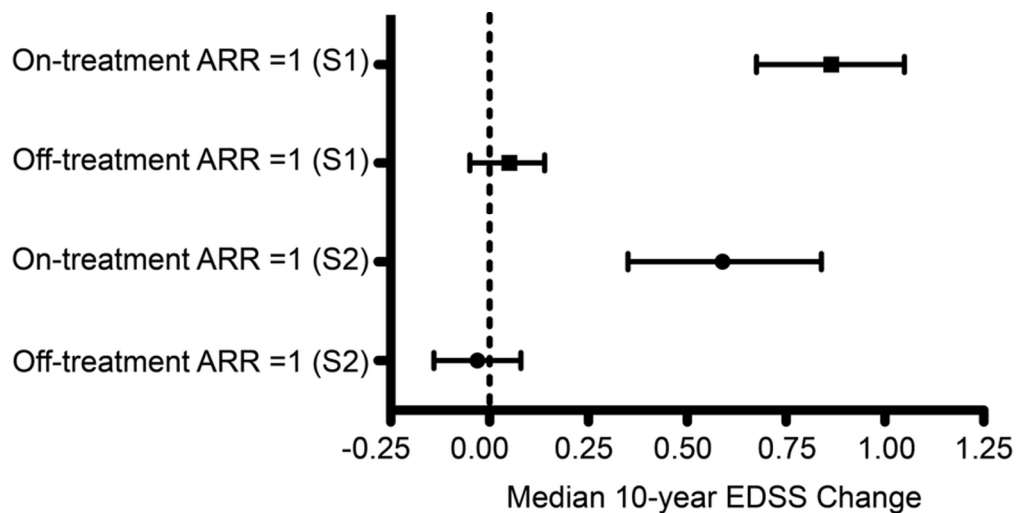


Figure shows change in EDSS score post-baseline at 2, 4, 6, 8 and 10-years (A). Figure further shows the number of patients receiving disease-modifying therapy at baseline (BL) and during each year of follow-up thereafter (B). Disease-modifying therapies included: all IFN β preparations, glatiramer acetate, natalizumab, fingolimod, dimethyl fumarate, teriflunomide, cladribine, alemtuzumab and rituximab, ocrelizumab, ASCT, mitoxantrone and autologous stem cell transplantation.

118x109mm (600 x 600 DPI)

AC



Contribution of on and off-therapy annualised relapse rate (ARR) to 10-year median EDSS changes (95% CI). Here the ARR is normalised to 1. This figure shows the results of two adjusted quantile median regression analyses. All analyses were adjusted for gender, age at baseline, disease duration, proportion of follow-up on first-line DMT, pregnancies, first DMT identity, baseline EDSS score and clinic country. Sub-analysis 1 (S1) includes all 2,466 patients from the primary analysis. Sub-analysis 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.

40x20mm (600 x 600 DPI)

Accept

ONLINE ONLY SUPPLEMENTAL MATERIAL

MSBase Study Group Co-investigators

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Supplementary Table 1

Supplementary Table 2

Number of included patients per centre

Baseline demography and characteristics of
excluded patients

Accepted Article

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From the MSBase Administration Ms Jill Byron, Ms Lisa Morgan and Ms Eloise Hinson.
From Rodanotech, Geneva, Switzerland; Mr Samir Mechaty, Mr Matthieu Corageoud, Mr Alexandre Bulla.

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Supplementary Table 1: Number of included patients per centre

Centre	City	Country	Patients
University of Bari	Bari	Italy	400
Charles University in Prague	Praha	Czech Republic	375
CHUM - Hopital Notre Dame	Montreal	Canada	304
Hospital Universitario Virgen Macarena	Sevilla	Spain	268
Centre de Réadaptation déficience Physique Chaudière-Appalache	Levis, PQ	Canada	232
Ospedale Clinizzato (Ss. Annunziata)	Chieti	Italy	149
Cliniques Universitaires Saint-Luc	Brussels	Belgium	82
ASUR Marche – AV3	Macerata	Italy	69
Neuro Rive-Sud	Greenfield Park	Canada	60
Hospital Universitario La Paz	Madrid	Spain	50
Zuyderland Ziekenhuis	Sittard	Netherlands	43
University of Parma	Parma	Italy	38
Nuovo Ospedale Civile S.Agostino/Estense	Modena	Italy	36
The Royal Melbourne Hospital	Melbourne	Australia	34
National Neurological Institute C. Mondino	Pavia	Italy	31
Box Hill Hospital	Melbourne	Australia	30
Ospedali Riuniti di Salerno	Salerno	Italy	30
AORN San Giuseppe Moscati Avellino	Avellino	Italy	27
Hospital Universitario Virgen de Valme	Seville	Spain	25
KTU Medical Faculty Farabi Hospital	Trabzon	Turkey	17
Hospital São João	Porto	Portugal	16
19 Mayıs University, Medical Faculty	Samsun	Turkey	15
Liverpool Hospital	Liverpool	Australia	14
Assaf Harofeh Medical Center	Beer-Yaakov	Israel	14
Hospital Donostia	San Sebastián	Spain	13
Groene Hart Ziekenhuis	Gouda	Netherlands	13
University Hospital Nijmegen	Nijmegen	Netherlands	11
The University of Queensland	Brisbane	Australia	9
Kommunehospitalet	Arhus C	Denmark	6
Hospital Italiano	Buenos Aires	Argentina	6
Hospital Germans Trias i Pujol	Badalona	Spain	6
Austin Health	Melbourne	Australia	5
Royal Victoria Hospital	Belfast	United Kingdom	5
INEBA	Buenos Aires	Argentina	4
Jewish General Hospital	Montreal	Canada	4
Jahn Ferenc Teaching Hospital	Budapest	Hungary	4
John Hunter Hospital	New Lambton	Australia	3
Flinders Medical Centre	Adelaide	Australia	3
Hospital Fernandez	Buenos Aires	Argentina	2
St Vincent's Hospital	Melbourne	Australia	2
Craigavon Area Hospital	Portadown	UK	2
University of Debrecen	Debrecen	Hungary	2
University of Florence	Florence	Italy	2

Sanatorio Allende	Cordoba	Argentina	1
Szent Imre Hospital	Budapest	Hungary	1
Hospital de Galdakao-Usansolo	Usansolo	Spain	1
South East Trust		UK	1
JZU Clinic for Neurology	Skopje	Macedonia	1
Total			2,466

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Supplementary Table 2: Baseline demography and characteristics of excluded patients

Characteristic	Included Patients n=2,466	Excluded Patients n=13,668
Female, n(%)	1,830 (74.2)	9,851 (72.1)
Age at BL (years), Mean (SD)	34.8 (9.3)	35.2 (10)
Disease duration at BL (years), Median (IQR)	3.8 (1.5, 8.2)	2.4 (0.8, 6.8)
EDSS at BL, median (IQR)	2 (1,3)	2 (1, 2.5)*
EDSS at BL, range	0-7	0-8.5*
ARR 1 year prior to BL, median (IQR)	1 (1,2)	1(0,2)
Disease Course		
CIS, n(%)	153 (6.2)	1,801 (13.2)
RRMS, n(%)	2,313 (93.8)	11,867 (86.8)
Pre-baseline pregnancies n(% of females)	447 (9.9)	1,771 (10.2)
Pre-baseline pregnancies per female, mean (SD)	1.8 (0.93)	1.7 (0.88)
Patients who died prior to 10-year follow-up		n=71
Baseline EDSS of deceased patients, Median (IQR)		n=43 with reported scores 3 (2,5)
Baseline EDSS of deceased patients, range		0-8

BL: Baseline; SD: Standard Deviation; IQR: Interquartile Range; ARR: Annualised Relapse Rate; EDSS: Expanded Disability Status Scale

*available for 9190 (67.2%) patients