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

Running Head:

Predictors of long-term MS outcomes

Vilija G. Jokubaitis, PhD; Department of Medicine and Melbourne Brain Centre at the Royal Melbourne Hospital, University of Melbourne, Australia; and Department of Neurology, Royal Melbourne Hospital, Melbourne, Australia

Tim Spelman, MBBS, MSc; Department of Medicine and Melbourne Brain Centre at the Royal Melbourne Hospital, University of Melbourne, Australia

Tomas Kalincik, MD, PhD; Department of Medicine and Melbourne Brain Centre at the Royal Melbourne Hospital, University of Melbourne, Australia; and Department of Neurology, Royal Melbourne Hospital, Melbourne, Australia

Johannes Lorscheider, MD; Department of Medicine and Melbourne Brain Centre at the Royal Melbourne Hospital, University of Melbourne, Australia; and Department of Neurology, Royal Melbourne Hospital, Melbourne, Australia

Eva Havrdova, MD, PhD; General Teaching Hospital; Dpt. of Neurology, First Medical Faculty, Charles University in Prague, Prague, Czech Republic

Dana Horakova, MD, PhD; General Teaching Hospital; Dpt. of Neurology, First Medical Faculty, Charles University in Prague, Prague, Czech Republic

Pierre Duquette, MD; CHUM, Hôpital Notre Dame, Montreal, Canada

Marc Girard, MD; CHUM, Hôpital Notre Dame, Montreal, Canada

Alexandre Prat, MD; CHUM, Hôpital Notre Dame, Montreal, Canada

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as an 'Accepted Article', doi: 10.1002/ana.24682

ANA-15-1538

Guillermo Izquierdo, MD; Hospital Universitario Virgen Macarena, Sevilla, Spain

Pierre Grammond, MD; Centre de réadaptation déficience physique Chaudière-Appalache, Levis, Canada

Vincent Van Pesch, MD, PhD; Cliniques Universitaires Saint-Luc, Brussels, Belgium

Eugenio Pucci, MD, PhD; Neurology Unit, ASUR Marche – AV3, Macerata, Italy

François Grand'Maison, MD; Neuro Rive-Sud, Hôpital Charles LeMoyne, Quebec, Canada

Raymond Hupperts, MD; Zuyderland Ziekenhuis, Sittard, The Netherlands

Franco Granella, MD; University of Parma, Parma, Italy

Patrizia Sola, MD; Nuovo Ospedale Civile S.Agostino/Estense, Modena, Italy

Roberto Bergamaschi, MD; C. Mondino National Neurological Institute, Pavia, Italy

Gerardo Iuliano, MD; Ospedali Riuniti di Salerno, Salerno, Italy

Daniele Spitaleri, MD; AORN San Giuseppe Moscati, Avellino, Italy

Cavit Boz, MD; Karadeniz Technical University, Trabzon, Turkey

Suzanne Hodgkinson, MD; Department of Neurology, Liverpool Hospital, NSW, Australia

Javier Olascoaga, MD; Hospital Donostia, San Sebastián, Spain

Freek Verheul, MD; Groene Hart ziekenhuis, Gouda, The Netherlands

Pamela McCombe, MBBS, PhD; Centre for Clinical Research, The University of Queensland, Brisbane, Australia

Thor Petersen, MD; Kommunehospitalet, Arhus C, Denmark

Csilla Rozsa, MD; Jahn Ferenc Teaching Hospital, Budapest, Hungary

Jeannette Lechner-Scott, MD, PhD; John Hunter Hospital, University of Newcastle, Newcastle, Australia

Maria Laura Saladino, MD; INEBA, Buenos Aires, Argentina

ANA-15-1538

Deborah Farina, MD; MS Center, Department of Neuroscience, Imaging and Clinical Sciences, University 'G. d'Annunzio', Chieti, Italy

Pietro Iaffaldano, MD; Department of Basic Medical sciences, Neuroscience and Sense Organs, University of Bari, Italy

Damiano Paolicelli, MD; Department of Basic Medical sciences, Neuroscience and Sense Organs, University of Bari, Italy

Helmut Butzkueven*, MBBS, PhD; Department of Medicine and Melbourne Brain Centre at the Royal Melbourne Hospital, University of Melbourne, Australia; Department of Neurology, Royal Melbourne Hospital, Melbourne, Australia and Department of Neurology, Box Hill Hospital, Monash University, Box Hill, Australia

Alessandra Lugaresi*, MD, PhD; Department of Biomedical and NeuroMotor Sciences (DIBINEM), Alma Mater Studiorum - Università di Bologna, Italy; IRCCS Istituto delle Scienze Neurologiche di Bologna, Italy

Maria Trojano*, MD; Department of Basic Medical sciences, Neuroscience and Sense Organs, University of Bari, Italy

On behalf of the MSBase Study Group[+].

*These authors contributed equally to this work

[+]Co-investigators and Contributors are listed in the acknowledgements section – supplementary material

Corresponding Author

Vilija Jokubaitis; vilija.jokubaitis@unimelb.edu.au

ANA-15-1538

L4 Centre, Melbourne Brain Centre at the Royal Melbourne Hospital, Grattan St, Parkville, Victoria, Australia 3050; Ph: +61 3 9342 4404, Fax: +61 3 9342 8070

Word Count:

Title: 93 characters

Running head: 35 characters

Abstract: 231

Introduction: 261

Discussion: 1,399

Entire manuscript: 3,830

Figures: 3 (Colour Figures: 1)

Tables: 5

Supplementary Tables: 2

References: 45

Key words:

Prognosis, Disease modifying therapy, RRMS, relapse, MSBase

List of Abbreviations

ARR Annualised Relapse Rate

CIS Clinically Isolated Syndrome

DMT Disease Modifying Therapy

ANA-15-1538

EDSS Expanded Disability Status Scale

GA Glatiramer Acetate

IFNβ Interferon-β

SPMS Secondary Progressive Multiple Sclerosis

ANA-15-1538

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, $p=1.9\times10^{-22}$). 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, $p=1.3\times10^{-9}$). 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.

Words: 231

ANA-15-1538

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.

ANA-15-1538

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 (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 +/- 12 months of first IFNβ/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 IFNβ/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 form 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. Co-linearity and interactions between model covariates were examined using a likelihood ratio test. The He & 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 3-15 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

ANA-15-1538

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 IFNβ/GA, teriflunomide, fingolimod, dimethyl fumarate, cladribine, natalizumab, mitoxantrone, alemtuzumab, autologous stem cell transplantation, rituximab, ocrelizumab) for cumulative exposure to IFNβ/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 IFNβ 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 IFNβ/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 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 cumulative exposure to any IFNβ/GA

ANA-15-1538

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 INFβ/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 IFNβ/GA therapy was associated with reduced EDSS scores across the 10-year interval (*coeff* -0.86; 95% CI -1.13, -0.58; $p=1.3x10^{-9}$), 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 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).

ANA-15-1538

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; $p=5.3\times10^{-12}$). 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; $p=1.3\times10^{-5}$).

ANA-15-1538

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 ($p=6.5x10^{-19}$) 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 ($p=2.4x10^{-6}$) 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-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 DMT again confirmed the protective effect of DMT against disability accrual (*coeff* -0.87; $p=5.7x10^{-9}$; 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 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 (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

ANA-15-1538

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 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 IFNβ-1a IM MSCRG trial[9] 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

ANA-15-1538

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.

ANA-15-1538

Acknowledgements:

This investigator-initiated analysis was supported by a project grant from the NHMRC Project Grant [Grant ID 1032484], and an NHMRC Centre for Research Excellence Grant [Grant ID 1001216].

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, GIz, PG, EP, FGM, RB, FG, VvP, RH, GIu, 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, GIz, PG, VvP, EP, FGM, RH, FG, PS, RB, GIu, 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.

ANA-15-1538

References

1. World Health Organization., Multiple Sclerosis International Federation. Atlas : multiple sclerosis resources in the world 2008. Geneva: World Health Organization; 2008.

2. Castrop F, Haslinger B, Hemmer B, Buck D. Review of the pharmacoeconomics of early treatment of multiple sclerosis using interferon beta. Neuropsychiatric disease and treatment. 2013;9:1339-49.

3. Karampampa K, Gustavsson A, Miltenburger C, Eckert B. Treatment experience, burden and unmet needs (TRIBUNE) in MS study: results from five European countries. Mult Scler. 2012 Jun;18(2 Suppl):7-15.

4. Karampampa K, Gustavsson A, Miltenburger C, Kindundu CM, Selchen DH. Treatment experience, burden, and unmet needs (TRIBUNE) in multiple sclerosis: the costs and utilities of MS patients in Canada. Journal of population therapeutics and clinical pharmacology = Journal de la therapeutique des populations et de la pharamcologie clinique. 2012;19(1):e11-25.

5. Palmer AJ, Colman S, O'Leary B, Taylor BV, Simmons RD. The economic impact of multiple sclerosis in Australia in 2010. Mult Scler. 2013 Oct;19(12):1640-6.

6. Svensson J, Borg S, Nilsson P. Costs and quality of life in multiple sclerosis patients with spasticity. Acta neurologica Scandinavica. 2014 Jan;129(1):13-20.

7. Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. I. Clinical results of a multicenter, randomized, double-blind, placebo-controlled trial. The IFNB Multiple Sclerosis Study Group. Neurology. 1993 Apr;43(4):655-61.

8. PRISMS. Randomised double-blind placebo-controlled study of interferon beta-1a in relapsing/remitting multiple sclerosis. PRISMS (Prevention of Relapses and Disability by Interferon beta-1a Subcutaneously in Multiple Sclerosis) Study Group. Lancet. 1998 Nov 7;352(9139):1498-504.

9. Jacobs LD, Cookfair DL, Rudick RA, et al. Intramuscular interferon beta-1a for disease progression in relapsing multiple sclerosis. The Multiple Sclerosis Collaborative Research Group (MSCRG). Ann Neurol. 1996 Mar;39(3):285-94.

10. Johnson KP, Brooks BR, Cohen JA, et al. Copolymer 1 reduces relapse rate and improves disability in relapsing-remitting multiple sclerosis: results of a phase III multicenter, double-blind placebo-controlled trial. The Copolymer 1 Multiple Sclerosis Study Group. Neurology. 1995 Jul;45(7):1268-76.

11. Trojano M, Pellegrini F, Fuiani A, et al. New natural history of interferon-beta-treated relapsing multiple sclerosis. Ann Neurol. 2007 Apr;61(4):300-6.

12. Trojano M, Russo P, Fuiani A, et al. The Italian Multiple Sclerosis Database Network (MSDN): the risk of worsening according to IFNbeta exposure in multiple sclerosis. Mult Scler. 2006 Oct;12(5):578-85.

13. Jokubaitis VG, Spelman T, Kalincik T, et al. Predictors of disability worsening in clinically isolated syndrome. Annals of clinical and translational neurology. 2015 May;2(5):479-91.

14. 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 Jul 15;180(2):160-71.

15. 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 : the journal of the American Medical Association. 2012 Jul 18;308(3):247-56.

16. Butzkueven H, Chapman J, Cristiano E, et al. MSBase: an international, online registry and platform for collaborative outcomes research in multiple sclerosis. Multiple sclerosis. 2006 Dec;12(6):769-74.

17. He XM, Zhu LX. A lack-of-fit test for quantile regression. J Am Stat Assoc. 2003 Dec;98(464):1013-22.

18. Kalincik T, Cutter G, Spelman T, et al. Defining reliable disability outcomes in multiple sclerosis. Brain : a journal of neurology. 2015 Nov;138(Pt 11):3287-98.

19. Kappos L, Traboulsee A, Constantinescu C, et al. Long-term subcutaneous interferon beta-1a therapy in patients with relapsing-remitting MS. Neurology. 2006 Sep 26;67(6):944-53.

20. Ford CC, Johnson KP, Lisak RP, Panitch HS, Shifronis G, Wolinsky JS. A prospective open-label study of glatiramer acetate: over a decade of continuous use in multiple sclerosis patients. Mult Scler. 2006 Jun;12(3):309-20.

21. Confavreux C, Vukusic S, Adeleine P. Early clinical predictors and progression of irreversible disability in multiple sclerosis: an amnesic process. Brain. 2003 Apr;126(Pt 4):770-82.

22. Tremlett H, Yousefi M, Devonshire V, Rieckmann P, Zhao Y. Impact of multiple sclerosis relapses on progression diminishes with time. Neurology. 2009 Nov 17;73(20):1616-23.

23. Confavreux C, Vukusic S, Moreau T, Adeleine P. Relapses and progression of disability in multiple sclerosis. The New England journal of medicine. 2000 Nov 16;343(20):1430-8.

24. Kalincik T, Vaneckova M, Tyblova M, et al. Volumetric MRI markers and predictors of disease activity in early multiple sclerosis: a longitudinal cohort study. PloS one. 2012;7(11):e50101.

25. Sormani MP, Bonzano L, Roccatagliata L, Mancardi GL, Uccelli A, Bruzzi P. Surrogate endpoints for EDSS worsening in multiple sclerosis. A meta-analytic approach. Neurology. 2010 Jul 27;75(4):302-9.

26. Lublin FD, Baier M, Cutter G. Effect of relapses on development of residual deficit in multiple sclerosis. Neurology. 2003 Dec 9;61(11):1528-32.

27. Rudick RA, Lee JC, Cutter GR, et al. Disability progression in a clinical trial of relapsing-remitting multiple sclerosis: eight-year follow-up. Arch Neurol. 2010 Nov;67(11):1329-35.

28. Bermel RA, You X, Foulds P, et al. Predictors of long-term outcome in multiple sclerosis patients treated with interferon beta. Ann Neurol. 2013 Jan;73(1):95-103.

29. Sormani M, Signori A, Stromillo M, De Stefano N. Refining response to treatment as defined by the Modified Rio Score. Mult Scler. 2013 Aug;19(9):1246-7.

30. Hirst C, Ingram G, Pearson O, Pickersgill T, Scolding N, Robertson N. Contribution of relapses to disability in multiple sclerosis. J Neurol. 2008 Feb;255(2):280-7.

31. Havrdova E, Galetta S, Stefoski D, Comi G. Freedom from disease activity in multiple sclerosis. Neurology. 2010 Apr 27;74 Suppl 3:S3-7.

32. Bevan CJ, Cree BA. Disease activity free status: a new end point for a new era in multiple sclerosis clinical research? JAMA neurology. 2014 Mar;71(3):269-70.

33. He A, Spelman T, Jokubaitis V, et al. Comparison of switch to fingolimod or interferon beta/glatiramer acetate in active multiple sclerosis. JAMA Neurol. 2015 Apr;72(4):405-13.

34. Spelman T, Kalincik T, Zhang A, et al. Comparative efficacy of switching to natalizumab in active multiple sclerosis. Annals of clinical and translational neurology. 2015 Apr;2(4):373-87.

35. Bermel RA, Weinstock-Guttman B, Bourdette D, Foulds P, You X, Rudick RA. Intramuscular interferon beta-1a therapy in patients with relapsing-remitting multiple sclerosis: a 15-year follow-up study. Mult Scler. 2010 May;16(5):588-96.

36. Rudick RA, Cutter GR, Baier M, et al. Estimating long-term effects of disease-modifying drug therapy in multiple sclerosis patients. Mult Scler. 2005 Dec;11(6):626-34.

37. PRISMS. PRISMS-4: Long-term efficacy of interferon-beta-1a in relapsing MS. Neurology. 2001 Jun 26;56(12):1628-36.

38. Uitdehaag B, Constantinescu C, Cornelisse P, et al. Impact of exposure to interferon beta-1a on outcomes in patients with relapsing-remitting multiple sclerosis: exploratory analyses from the PRISMS long-term follow-up study. Therapeutic advances in neurological disorders. 2011 Jan;4(1):3-14.

39. Kappos L, Kuhle J, Multanen J, et al. Factors influencing long-term outcomes in relapsing-remitting multiple sclerosis: PRISMS-15. J Neurol Neurosurg Psychiatry. 2015 Nov;86(11):1202-7.

40. Confavreux C, Hutchinson M, Hours MM, Cortinovis-Tourniaire P, Moreau T. Rate of pregnancy-related relapse in multiple sclerosis. Pregnancy in Multiple Sclerosis Group. N Engl J Med. 1998 Jul 30;339(5):285-91.

41. Hughes SE, Spelman T, Gray OM, et al. Predictors and dynamics of postpartum relapses in women with multiple sclerosis. Mult Scler. 2013 Oct 9.

ANA-15-1538

42. Portaccio E, Ghezzi A, Hakiki B, et al. Postpartum relapses increase the risk of disability progression in multiple sclerosis: the role of disease modifying drugs. J Neurol Neurosurg Psychiatry. 2014 Jan 8.

43. Karp I, Manganas A, Sylvestre MP, Ho A, Roger E, Duquette P. Does pregnancy alter the long-term course of multiple sclerosis? Annals of epidemiology. 2014 Jul;24(7):504-8 e2.

44. Ramagopalan S, Yee I, Byrnes J, Guimond C, Ebers G, Sadovnick D. Term pregnancies and the clinical characteristics of multiple sclerosis: a population based study. J Neurol Neurosurg Psychiatry. 2012 Aug;83(8):793-5.

45. Runmarker B, Andersen O. Pregnancy is associated with a lower risk of onset and a better prognosis in multiple sclerosis. Brain. 1995 Feb;118 (Pt 1):253-61.

46. Verdru P, Theys P, D'Hooghe MB, Carton H. Pregnancy and multiple sclerosis: the influence on long term disability. Clinical neurology and neurosurgery. 1994 Feb;96(1):38-41.

47. D'Hooghe M B, Haentjens P, Nagels G, D'Hooghe T, De Keyser J. Menarche, oral contraceptives, pregnancy and progression of disability in relapsing onset and progressive onset multiple sclerosis. J Neurol. 2012 May;259(5):855-61.

ANA-15-1538

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 IFNβ 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.

ANA-15-1538

Table Legends:

Table 1:

EDSS Expanded disability status scale; CIS Clinically Isolated Syndrome; RRMS Relapsing-remitting MS; SPMS Secondary Progressive MS; IFNβ 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; IFNβ: 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.

γ Analysis restricted to females only

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

Table 1. Cohort Demography and Characteristics

	At least 10 years of follow-up with a 10-year EDSS score recorded, n = 2,466	
Characteristic	**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(%)
IFNβ-1a IM	720 (29.2)	196 (7.9)
IFNβ-1b SC	580 (23.5)	206 (8.3)
IFNβ-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; IFNβ 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				
	0 **n=261**	**1-2.5** **n=1,533**	**3-5.5** **n=629**	**≥6** **n=43**	**Total** **n=2,466**
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.

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

	Unadjusted models		#Adjusted model	
Predictor	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

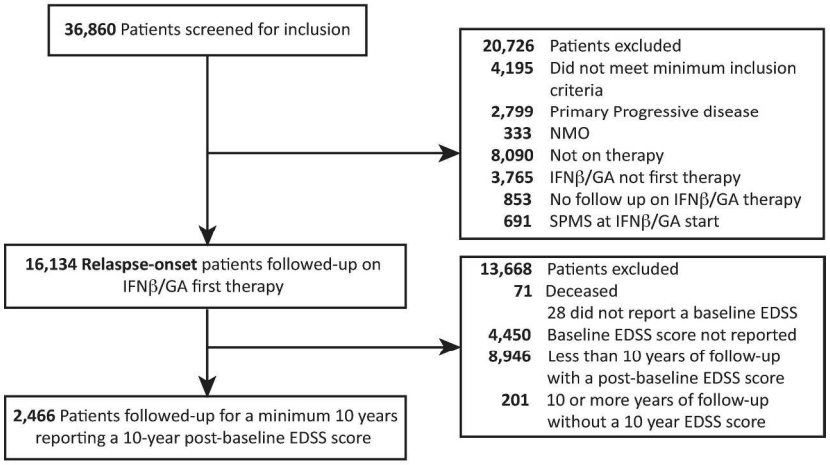
Outcome	β coefficient (95% CI)	adj p-value*
Predictors of median EDSS change: EDSS recorded within 6 months of baseline and follow-up		
Number of patients	2,001	
Gender		
Female	Reference	-
Male	0.16 (-0.03, 0.35)	0.103
Age at onset (10 year units)	0.38 (0.27, 0.48)	$3.6x10^{-12}$
Disease duration at baseline (5 year units)	0.36 (0.28, 0.44)	$4.2x10^{-18}$
ARR during follow-up	1.31 (1.04, 1.58)	$1.2x10^{-21}$
Cumulative exposure to IFNβ/GA	-0.94 (-1.27, -0.62)	$1.5x10^{-8}$
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)	$8.3x10^{-11}$
Disease duration at baseline (5 year units)	0.38 (0.29, 0.47)	$1.5x10^{-16}$
ARR during follow-up	1.05 (0.75, 1.34)	$8.6x10^{-12}$
Cumulative exposure to IFNβ/GA	-1.02 (-1.39, -0.66)	$4.1x10^{-8}$
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)	$5.6x10^{-13}$
Disease duration at baseline (5 year units)	0.34 (0.25, 0.42)	$4.8x10^{-14}$
ARR during follow-up	1.26 (0.97, 1.54)	$1.1x10^{-17}$
Cumulative exposure to IFNβ/GA	-0.86 (-1.20, -0.51)	$1.4x10^{-6}$
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; IFNβ: 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)	$1.8x10^{-18}$
Disease duration at baseline (5 year units)	0.35 (0.28, 0.42)	$4.0x10^{-23}$
ARR during follow-up	1.20 (0.98, 1.42)	$9.2x10^{-26}$
Cumulative exposure to all DMT:	-0.87 (-1.16, -0.58)	$5.7x10^{-9}$
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$^{\gamma}$		
Number of patients	1,830	
Age at onset (10 year units)	0.43 (0.32, 0.54)	7.5210^{-15}
Disease duration at baseline (5 year units)	0.37 (0.29, 0.45)	$3.1x10^{-19}$
ARR during follow-up	1.21 (0.95, 1.47)	$2.3x10^{-19}$
Cumulative (100%) exposure to IFNβ/GA	-0.71 (-1.03, -0.38)	$2x10^{-5}$
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.
γ Analysis restricted to females only
Adj: Adjusted; EDSS: Expanded Disability Status Scale; CI: Confidence Interval; ARR: Annualised Relapse Rate; IFNβ: Interferon-Beta; GA: Glatiramer Acetate; DMT: Disease Modifying Therapy



CONSORT Flowchart for study inclusion
194x284mm (300 x 300 DPI)

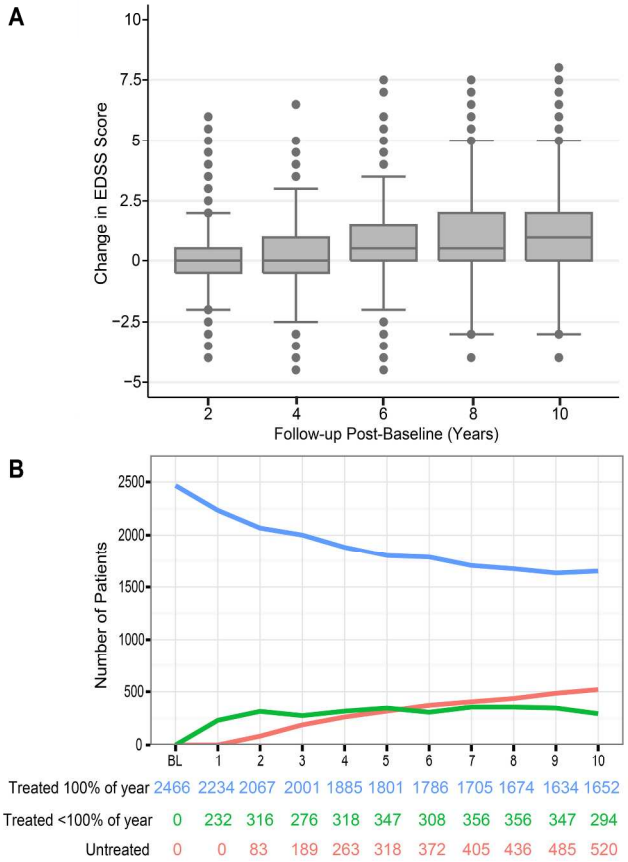
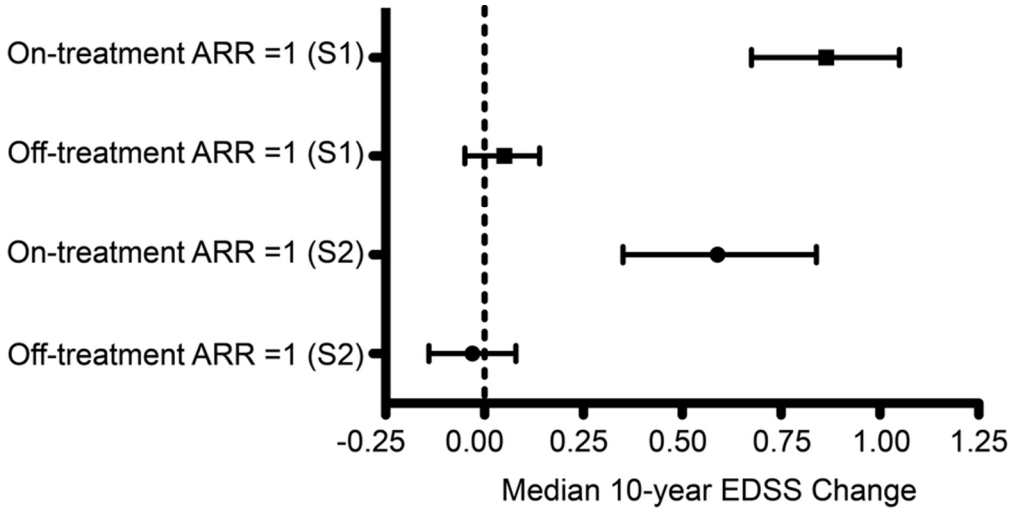


Figure shows change in EDSS score post-baseline at 2, 4, 6, 8 and 10-years (A). Figure further shows the number of patients receiving disease-modifying therapy at baseline (BL) and during each year of follow-up thereafter (B). Disease-modifying therapies included: all IFNβ preparations, glatiramer acetate, natalizumab, fingolimod, dimethyl fumarate, teriflunomide, cladribine, alemtuzumab and rituximab, ocrelizumab, ASCT, mitoxantrone and autologous stem cell transplantation.
118x109mm (600 x 600 DPI)



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)

ONLINE ONLY SUPPLEMENTAL MATERIAL

MSBase Study Group Co-investigators
MSBase Study Group Contributors

Supplementary Table 1	Number of included patients per centre
Supplementary Table 2	Baseline demography and characteristics of excluded patients

MSBase study group co-investigators:
Dr Celia Oreja-Guevara ; Hospital Universitario La Paz, Madrid, Spain
Dr Ricardo Fernández-Bolaños; Hospital Universitario Virgen de Valme, Seville, Spain
Dr Murat Terzi ; 19 Mayis University, Medical Faculty, Samsun, Turkey
Dr Maria Edite Rio; Hospital São João, Porto, Portugal
Dr Shlomo Flechter; Assaf Harofeh Medical Center Beer-Yaakov, Israel
Dr Edgardo Cristiano; Hospital Italiano, Buenos Aires, Argentina
Dr Cristina Ramo; Hospital Germans Trias i Pujol, Badalona, Spain
Dr Richard Macdonell; Austin Hospital, Melbourne, Australia
Dr Stella Hughes; Royal Victoria Hospital and Craigavon Area Hospital, Belfast, United Kingdom
Dr Fraser Moore; The Jewish General Hospital, Montreal, Canada
Dr Mark Slee; Flinders Medical Centre and Flinders University
Dr Norma Deri; Hospital Fernandez, Buenos Aires, Argentina
Dr Neil Shuey; St Vincent's Hospital, Melbourne, Australia
Dr Tunde Csepany; University of Debrecen, Hungary
Dr Maria Pia Amato; University of Florence, Florence, Italy
Dr Carlos Vrech; Sanatorio Allende, Cordoba, Argentina
Dr José Luis Sánchez Menoyo; Hospital de Galdakao-Usansolo, Galdakao, Spain
Dr Orla Gray; South East Trust, United Kingdom
Dr Eniko Dobos; Szent Imre Hospital, Hungary
Dr Tatjana Petkovska-Boskova; JZU Clinic for Neurology, Skopje, Republic of Macedonia

MSBase study group contributors:
Dr Jose Antonio Cabrera-Gomez; CIREN, Havana, Cuba
Dr Giorgio Giuliani and Dr Elisabetta Cartechini; Generale Provinciale Macerata, Italy
From University Hospital Nijmegen, Netherlands, Dr Cees Zwanikken.
Dr Giovanna De Luca, Dr Valeria Di Tommaso, Dr Daniela Travaglini, Dr Erika Pietrolongo, Dr Maria di Ioia and Dr Luca Mancinelli; Department of Neuroscience and Imaging, University 'G. d'Annunzio', Italy
Dr Mark Marriott, Dr Anneke Van der Walt, Dr John King, and Dr Katherine Buzzard; The Royal Melbourne Hospital, Australia
Ms Elaine Roger and Mr Pierre Despault; CHUM, Montreal, Canada
Ms Jodi Haartsen; Monash University, Melbourne, Australia
Dr Vita Direnzo and Dr Mariangela D'Onghia; Department of Basic Medical Sciences, Neuroscience and Sense Organs, University of Bari, Italy
Dr Juan Ignacio Rojas and Dr Liliana Patrucco; Hospital Italiano, Buenos Aires, Argentina
Dr David Williams and Dr Lisa Dark; John Hunter Hospital, Newcastle, Australia
Dr Ilya Kister; New York University Langone Medical Center, New York, USA
Dr Steve Vucic; Westmead Hospital, Sydney, Australia
Dr Cameron Shaw; Geelong Hospital, Geelong, VIC, Australia
Dr Carmen-Adella Sirbu; Central Clinical Emergency Military Hospital, Bucharest, Romania
Dr Gabor Rum; Petz A County Hospital, Hungary
Dr Anita Trauninger; University of Pécs, Pécs, Hungary
Dr Tunde Erdelyl; Josa Andras Hospital, Hungary
Dr Krisztian Kasa; Jahn Ferenc Teaching Hospital
Dr Bhim Singhal; Bombay Hospital Institute of Medical Sciences, Mumbai, India
Dr John Parratt; Royal North Shore Hospital, NSW, Australia
Dr Imre Piroska; Veszprem Megyei Csolnoky Ferenc Korhaz, Veszprem, Hungary
Dr Tunde Erdelyi; Josa Andras Hospital, Nyiregyhaza, Hungary
Dr Magdolna Simo; Semmelweis University, Budapest, Hungary

Dr Kristina Kovacs; Peterfy Sandor Hospital, Budapest, Hungary
Dr Erik van Munster; Jeroen Bosch Ziekenhuis, Den Bosch, The Netherlands
Dr Carmen-Adella Sirbu; Central Clinical Emergency Military Hospital, Bucharest, Romania
Dr Gabor Rum; From Petz A. County Hospital, Gyor, Hungary
Dr Carolyn Young; The Walton Centre for Neurology, Liverpool, United Kingdom
Dr Ernest Butler; Monash Medical Centre, Melbourne, Australia
Dr Vladimir Bojkovski; Clinical Centrar - Neurology, Skopje, Macedonia.
Dr Seyed Aidin Sajedi; Golestan, Ahvaz, Iran
Dr Dheeraj Khurana; PGIMER, Chandigarh, India
Dr Elizabeth Alejandra Bacile- Bacile; Instituto de Neurociencias, Cordoba, Argentina
Dr Walter Oleschko Arruda; Hospital Ecoville, Brazil
Dr Eli Skromne; Hospital Angeles de las Lomas, Mexico City, Mexico
Dr Norbert Vella; Mater Dei Hospital, Msida, Malta
Dr Vahid Shaygannejad; Al-Zahra Hospital, Isfahan University of Medical Sciences, Isfahan, Iran
Ms Leontien Den Braber-Moerland; Franciscus Ziekenhuis, Netherlands
Dr Santiago Vetere; HIGA Gral. San Martin La Plata, La Plata, Argentina,
From the MSBase Administration Ms Jill Byron, Ms Lisa Morgan and Ms Eloise Hinson.
From Rodanotech, Geneva, Switzerland; Mr Samir Mechati, Mr Matthieu Corageoud, Mr Alexandre Bulla.

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 Mayis 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

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