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TITLE PAGE

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Highly active immunomodulatory therapy ameliorates accumulation of disability in moderately advanced and advanced multiple sclerosis

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ABSTRACT

Objective: To evaluate variability and predictability of disability trajectories in moderately advanced and advanced multiple sclerosis (MS), and their modifiability with immunomodulatory therapy.

Methods: The epochs between Expanded Disability Status Scale (EDSS) steps 3-6, 4-6, and 6-6.5 were analysed. Patients with relapse-onset MS and having reached six-month confirmed baseline EDSS step (3/4/6) were identified in MSBase, a global observational MS cohort study. We used multivariable survival models to examine the impact of disease-modifying therapy, clinical and demographic factors on progression to the outcome EDSS step (6/6.5). Sensitivity analyses with varying outcome definitions and inclusion criteria were conducted.

Results: For the EDSS 3-6, 4-6, and 6-6.5 epochs, 1,560, 1,504, and 1,231 patients were identified, respectively. Disability trajectories showed large coefficients of variance pre- (0.92-1.11) and post-baseline (2.15-2.50), with no significant correlations. Probability of reaching the outcome step was not associated with pre-baseline variables, but was increased by higher relapse rates during each epoch (hazard ratios: 1.58-3.07; P<0.001). A greater proportion of each epoch treated with higher-efficacy therapies was associated with lower risk of reaching the outcome disability step (hazard ratios: 0.72-0.91 per 25%; P≤0.02). Three sensitivity analyses confirmed these results.

Conclusions: Disease progression during moderately advanced and advanced MS is highly variable and amnesic to prior disease activity. Lower relapse rates and greater time on higher-efficacy immunomodulatory therapy after reaching EDSS steps 3, 4, and 6 are associated with a decreased risk of accumulating further

disability. Highly-effective immunomodulatory therapy ameliorates accumulation of disability in moderately advanced and advanced relapse-onset MS.

TEXT

INTRODUCTION

Whether currently available immunomodulatory therapies may modify disability trajectories in patients with moderately advanced and advanced MS remains to be answered.[1,2]

Three large cohort studies have explored factors affecting the disability accrual at various stages of MS.[3-5] While many demographic and clinical features, including early relapse activity, age, and sex, have been implicated in the accumulation of disability in early disease, these studies were largely unable to explain the variation in disease progression in moderately advanced MS (defined in these as the period between Expanded Disability Status Scale[6] (EDSS) steps of 3 or 4, and 6). A small number of candidate predictors, such as early and late relapses,[5] prior disease duration,[5] and sex,[3] were inconsistent across these studies. It has therefore been suggested that disability accrual at later MS stages is primarily driven by neurodegeneration and is largely independent of inflammation.[4,7]

Prior studies did not assess the effects of immunomodulatory therapies, and their datasets preceded the use of novel and potentially more effective MS treatments, such as natalizumab,[8] fingolimod,[9] alemtuzumab,[10] dimethyl fumarate[11] and cladribine.[12] Although these therapies are known to prevent relapses and reduce first disability progression events, their effect on long-term disability accumulation, especially in the less inflammatory stages of MS, remains an important question that is still to be addressed.[1,13]

The objectives of our study were to evaluate variability and predictability of disability trajectories in MS, and to explore whether disability accrual in moderately advanced and advanced MS is modifiable with immunomodulatory therapy.

METHODS

Ethics Statement

The MSBase cohort study[14] (registered with WHO ICTRP, ID ACTRN12605000455662) was approved by both the Melbourne Health Research Ethics Committee and local ethics committees in all participating centres (or exemptions granted, as per local regulations). Where required, enrolled patients provided written informed consent.

Patient Population and Data Collection

Longitudinal data from 32,336 patients from 108 MS centres in 32 countries were extracted from MSBase in December 2014. Data quality procedures were applied as described elsewhere,[15] and only information from centres contributing ≥10 records to the MSBase cohort was used.

All data was recorded as part of routine clinical practice, with most centres practising near-real time data entry in relation to clinical visits. The MSBase protocol stipulates minimum annual updates of the dataset, although patients with less frequent visits were included. Data entry portal was either the iMed patient record system or the MSBase online data entry system. Only prospectively acquired data was included in the analysis, with the exception of date of disease onset, which is typically determined retrospectively. Prospective follow-up for each patient was defined by the dates of the first and last EDSS entry.

Disability Milestones and Inclusion Criteria

This study consisted of three separate analyses, each addressing a distinct MS epoch defined by different neurological disability. The primary analysis concerned

the epoch between EDSS steps 3 (including step 3.5; moderate disability but unrestricted ambulation) and 6 (severe disability, unilateral assistance required to walk ≥100m). EDSS steps 3 and 3.5 were combined as in previous studies;[4,5] in addition, we have observed that the distributions of the pre- and post-baseline disability trajectories were consistent for both EDSS steps 3 and 3.5 (data not shown). Two secondary analyses addressed the epochs between EDSS steps 4 (moderate disability and/or walking distance >500m but not unrestricted) and 6, and between EDSS steps 6 and 6.5 (bilateral assistance required to walk ≥20m). For each epoch (EDSS 3-6, 4-6 and 6-6.5), a separate population of patients with clinically definite relapse-onset MS were selected using the following inclusion criteria:

Patients must have reached the initial EDSS step of the respective epoch (3 or 3.5 for the 3-6 epoch, 4 for the 4-6 epoch, or 6 for the 6-6.5 epoch), confirmed over ≥6 months without any interval regression (confirmation EDSS scores recorded within 30 days of a preceding relapse were excluded); this was defined as the study baseline. Patients had ≥12 months of prospective follow-up prior to baseline, and at least two post-baseline visits ≥3 months apart. A minimum required dataset consisted of year of birth, sex, date of the first clinical presentation of MS, disease course at onset, treatment and relapse information.

The EDSS 3-6 and 4-6 epochs were selected to emulate the natural history studies.[3-5] The EDSS 6-6.5 epoch was chosen as the smallest measurable change in disability during advanced disease, in order to maximise sensitivity of our study to the accrual of clinically significant disability.

Study Endpoints

The outcome of interest was the time from baseline to EDSS step 6 (for the EDSS 3-6 and 4-6 epochs) or 6.5 (for the EDSS 6-6.5 epoch), confirmed over ≥3 months with no interval regression (confirmation EDSS scores recorded within 30 days of a preceding relapse were excluded). The choice of confirmation time for both baseline and endpoint EDSS score was based on greater stability of disability progression events at higher EDSS scores.[16] Patients not attaining this outcome were censored at their last recorded EDSS score. Disability was scored by accredited scorers (online Neurostatus certification was required at each centre) using the EDSS.

The slopes of the EDSS trajectories prior to and following baseline were calculated with a linear regression over the pre-baseline EDSS scores or the post-baseline EDSS scores (including the baseline score in both).

Clinical Characteristics

Relapses were defined as the occurrence of new symptoms or exacerbation of existing symptoms persisting for ≥24 hours, in the absence of concurrent illness or fever, and occurring ≥30 days after a previous relapse.[17] Confirmation by increased EDSS was not required.

Annualised relapse rate and proportion of time on disease-modifying therapy were calculated for each of the three epochs and their respective pre-baseline periods. The overall proportion of time on disease modifying therapy, both prior to and during each epoch, was stratified according to the estimated higher-efficacy therapies (mainly represented by natalizumab and fingolimod, but also including alemtuzumab, dimethyl fumarate, cladribine, rituximab, and mitoxantrone) or lower-efficacy

therapies (mainly represented by interferon β preparations and glatiramer acetate, but also including teriflunomide).[8-11,18,19] Time on therapy was defined by recorded starting and termination dates; for disease-modifying therapies where extended effects are recognised, estimated effect duration was used to calculate time on therapy: mitoxantrone (three months from recorded treatment date), rituximab (six months), alemtuzumab (five years), and cladribine (twelve months).

Statistical Analysis

Statistical analysis was carried out by NL and TK using R version 3.1.0 (http://www.R-project.org). All hypotheses were tested at the two-tailed 0.05 level of statistical significance.

The variability in disease progression was examined through individual EDSS slopes for both the pre-baseline and post-baseline periods. Coefficient of variation was calculated as the ratio of slope standard deviation and mean. For each period, Pearson's r was calculated to evaluate the correlation between pre- and post-baseline slopes.

Median times to confirmed EDSS step 6 (for the EDSS 3-6 and 4-6 epochs) or 6.5 (EDSS 6-6.5 epoch) were estimated. The associations between the demographic (sex, age at baseline) and clinical patient characteristics (MS duration at baseline, annualised relapse rate pre-baseline and during the epoch, the proportion of time on higher- and lower-efficacy therapies pre-baseline and during the epoch, and rate of treatment initiations pre-baseline) and the time to the outcome EDSS step were analysed with multivariable Cox proportional hazard models. These models were designed based on the results of a series of univariate Cox models and were adjusted for total duration of recorded prospective follow-up and, in women, the

proportion of time pregnant. Where the assumption of the proportionality of hazards was violated as per statistical tests of Schoenfeld residuals, Weibull accelerated failure time models were applied instead. Continuous variables with non-normal distribution were transformed using Box-Cox transformations.

Each of the primary and two secondary analyses was accompanied by three sensitivity analyses, where: (1) in addition to the definition provided above, EDSS endpoint was required to be sustained without regression for the remainder of the available follow-up, (2) the inclusion criteria were altered to include patients reaching an EDSS step equal to or greater than the defined initial EDSS step for each epoch, and (3) the analysis used a nested model taking into account patients' country of residence.

Role of the funding source

The study was conducted separately and apart from the guidance of the sponsors.

RESULTS

Patients

Of the 32,336 patients in the MSBase cohort, the following number of patients with relapse-onset, clinically definite MS fulfilled the inclusion criteria for the EDSS 3-6, 4-6, and 6-6.5 epochs: 1,560, 1,504, and 1,231, respectively. These comprised 3,415 unique patients. The majority of the excluded patients have not yet reached moderately advanced MS or had insufficient pre-baseline follow-up. Of patients meeting the above criteria, 74-78% were included per epoch. Figure 1 details patient disposition information. The number of patients contributed per MSBase centre is

provided in Supplementary Table S2. Table 1 summarises demographic and clinical data for each epoch's cohort.

Table 1: Characteristics of the study populations

	Study Epoch		
Characteristic	**EDSS 3-6**	**EDSS 4-6**	**EDSS 6-6.5**
Patients [number (% females)]	1,560 (71%)	1,504 (69%)	1,231 (67%)
Age at baseline, years [mean ± SD]	40.9 ± 9.9	43.0 ± 9.6	46.5 ± 10.2
Disease duration at baseline, years [median (IQR)]	9.4 (5.4, 14.5)	11.1 (6.5, 16.7)	14.0 (8.9, 19.9)
Total recorded follow-up, years [median (IQR)]	11.1 (7.9, 14.5)	10.9 (7.7, 14.3)	11.4 (8.2, 15.4)
Annualised relapse rate [mean, median (IQR)]			
- pre-baseline period	0.51, 0.38 (0.01, 0.76)	0.48, 0.36 (0.08, 0.69)	0.47, 0.33 (0.00, 0.71)
- during epoch	0.38, 0.23 (0.00, 0.52)	0.40, 0.19 (0.00, 0.57)	0.33, 0.00 (0.00, 0.41)
Pre-baseline therapy initiations per year [median (IQR)]	0.12 (0.00, 0.33)	0.14 (0.00, 0.32)	0.14 (0.00, 0.29)
Patients receiving disease modifying therapy, number (%)			
- pre-baseline period			
- total	1017 (65%)	1074 (71%)	877 (71%)
- lower-efficacy therapy	1005 (64%)	1052 (70%)	844 (69%)
- higher-efficacy therapy	82 (5.3%)	132 (8.8%)	212 (17%)
- during epoch			
- total	1218 (78%)	1166 (78%)	770 (63%)
- lower-efficacy therapy	1132 (73%)	1044 (69%)	639 (52%)
- higher-efficacy therapy	449 (29%)	440 (29%)	244 (20%)
Proportion of time on therapy [mean, median (IQR)]			
- pre-baseline period			
- total (%)	46%, 45% (0%, 92%)	51%, 59% (0%, 94%)	48%, 49% (0%, 89%)
- lower-efficacy therapy (%)	45%, 41% (0%, 91%)	48%, 51% (0%, 92%)	43%, 39% (0%, 83%)
- higher-efficacy therapy (%)	1%, 0% (0%, 0%)	2%, 0% (0%, 0%)	4%, 0% (0%, 0%)
- during epoch			
- total (%)	64%, 90% (20%, 100%)	66%, 90% (20%, 100%)	51%, 60% (0%, 100%)
- lower-efficacy therapy (%)	51%, 54% (0%, 100%)	50%, 49% (0%, 100%)	39%, 6% (0%, 100%)
- higher-efficacy therapy (%)	13%, 0% (0%, 9%)	16%, 0% (0%, 14%)	13%, 0% (0%, 0%)

SD: standard deviation. IQR: inter-quartile range

Disability Trajectories

Progression slopes (mean±standard deviation) for the pre-baseline period (EDSS 3/3.5: 0.34±0.38; EDSS 4: 0.38±0.39; EDSS 6: 0.56±0.51 EDSS steps/year) and for the post-baseline period (EDSS 3/3.5: 0.15±0.38; EDSS 4: 0.17±0.38; EDSS 6: 0.10±0.24 EDSS steps/year) were highly variable, as evidenced by large coefficients of variation (0.92-1.11 pre-baseline and 2.15-2.50 post-baseline; Figure 2A). No correlations were found between the pre- and post-baseline slopes (EDSS 3/3.5: r=0.01, P=0.57; EDSS 4: r=-0.001, P=0.97; EDSS 6: r=-0.03, P=0.37; Figure 2B).

Determinants of the Progression of Disability

Results of multivariable survival models are shown in Table 2. For all three epochs, higher annualised relapse rates during the epoch significantly increased the risk of reaching the EDSS endpoints (6 or 6.5), while increasing proportion of the epoch spent on higher-efficacy therapies significantly decreased this risk (illustrated in Figure 3). For the primary analysis (EDSS 3-6 epoch), no pre-baseline variables were associated with the probability of reaching EDSS step 6. For the EDSS 4-6 epoch, increased risk of reaching EDSS step 6 was associated with greater pre-baseline exposure to higher efficacy therapies, male sex, and shorter disease duration. For the EDSS 6-6.5 epoch, increased risk of reaching EDSS step 6.5 was associated with younger age at baseline, male sex and lower pre-baseline relapse rate.

For the EDSS 3-6, 4-6, and 6-6.5 epochs, median survival time to endpoints (years) was 17.3 (quartiles: 8.3-25.0), 11.4 (quartiles: 4.8-23.4), and 3.7 (quartiles: 1.7-7.2), respectively. The number (percentage) of patients reaching EDSS endpoints for each epoch was 296 (19%), 406 (27%), and 671 (55%), respectively.

Table 2: Determinants of progression to the confirmed outcome disability level

	Study Epoch					
	EDSS 3-6		EDSS 4-6		EDSS 6-6.5[a]	
	HR (95% CI)	P-value	HR (95% CI)	P-value	WAF (95% CI)	P-value
Sex (Male)	1.11 (0.86-1.43)	0.42	1.33 (1.08-1.63)	0.008	1.20 (1.04-1.37)	0.01
Age at baseline (per year)	1.01 (1.00-1.02)	0.19	1.01 (1.00-1.02)	0.07	0.99 (0.98-1.00)	0.02
Disease duration at baseline (per year)	0.99 (0.89-1.11)	0.93	0.91 (0.83-1.00)	0.05	0.96 (0.91-1.02)	0.21
Annualised Relapse Rate						
- Pre-baseline (per relapse/year)	0.92 (0.75-1.13)	0.41	0.93 (0.76-1.13)	0.44	0.79 (0.68-0.91)	0.001
- During epoch (per relapse/year)	3.07 (2.56-3.70)	<0.001	2.41 (2.05-2.84)	<0.001	1.58 (1.45-1.73)	<0.001
Rate of pre-baseline therapy initiation (per initiation/year)	1.07 (0.60-1.91)	0.81	1.10 (0.70-1.72)	0.69	0.93 (0.69-1.24)	0.60
Proportion of time on lower-efficacy therapies						
- Pre-baseline (per 25% increase)	1.01 (0.92-1.11)	0.88	0.97 (0.90-1.05)	0.51	1.04 (0.99-1.09)	0.15
- During epoch (per 25% increase)	0.98 (0.90-1.07)	0.61	1.00 (0.93-1.07)	0.92	1.02 (0.97-1.06)	0.49
Proportion of time on higher-efficacy therapies						
- Pre-baseline (per 25% increase)	0.74 (0.32-1.68)	0.47	1.59 (1.22-2.07)	<0.001	1.10 (0.94-1.28)	0.22
- During epoch (per 25% increase)	0.72 (0.59-0.89)	0.002	0.79 (0.69-0.91)	<0.001	0.91 (0.84-0.99)	0.02

Results of multivariable survival models for each epoch. Unless stated otherwise, Cox proportional hazard models were utilised.

[a]Weibull accelerated failure time models were utilised for this epoch.

CI: confidence interval; HR: hazard ratio; WAF: Weibull acceleration factor.

Sensitivity Analyses

Results of the sensitivity analyses are provided in Supplementary Tables S3-S5. Taking into account the country of residence had no significant effects on the results of the primary analysis. The associations between exposure to higher-efficacy therapies or the higher relapse rates during the studied epochs and the risk of attaining the EDSS endpoints were confirmed in full extent. The only exception was a lack of effect of annualised relapse rate within the sensitivity analysis including patients with EDSS step 6 or more at baseline for the EDSS 6-6.5 epoch. In addition, the sensitivity analyses including patients with EDSS steps 3/4/6 or higher at baseline showed that patients with greater exposure to lower-efficacy therapies during each epoch were less likely to reach the EDSS endpoints; however, this association was of smaller magnitude than that observed for higher-efficacy therapies. For the EDSS 4-6 analysis, the effect of greater pre-baseline time on higher efficacy therapy was supported by both sensitivity analyses, while neither demonstrated any effect of pre-baseline disease duration. Finally, the sensitivity analyses reproduced some of the effects of male sex, older age at baseline, and (for the EDSS 6-6.5 epoch) pre-baseline relapse rate, however, these observations were inconsistent.

DISCUSSION

Our study demonstrates that disability progression in moderately advanced and advanced MS is highly variable and, surprisingly, amnesic to prior disease activity. Features of early disease course, including relapses, disability trajectory, disease duration, or treatment status, largely do not predict the rate of progression during later epochs. Contrastingly, we have found that once patients develop moderately

severe and severe disability, lower relapse rates and greater persistence on highly effective immunomodulatory therapy significantly decrease the risk of further disability accrual. Together, this likely represents an effect of immunomodulatory therapy on relapse-dependent disability progression. This effect of immunomodulation is independent of other factors, including prior disease activity and treatment.

Previous studies have identified factors associated with early disease progression.[3-5] However, the ability to predict the course of more advanced MS has been limited and varied among these studies. These observations have led to a two-stage hypothesis, with the first stage representing a therapeutic window for modifying disease trajectory, which then becomes uniform in the second stage of disease.[4] Our results concur that the disability trajectory in moderately advanced and advanced disease is independent of earlier disease characteristics, including previous disability trajectory, relapse activity, or exposure to immunomodulatory therapy. As a milestone defining the two stages of MS course, EDSS step 3 was proposed,[4] but Confavreux and colleagues have reported a similar dichotomy between the epochs preceding and following EDSS steps 4 and 6.[3] In fact, we have observed this dichotomy at various time-points, including EDSS steps 3, 4, and 6. Amnesic disease trajectory therefore represents a more general MS characteristic, with clinical variables pertaining to any disease epoch affecting that epoch exclusively, with little effect on subsequent epochs.

In contrast to the study of Leray and co-workers,[4] we have shown that disability trajectories in moderately advanced MS are highly variable. Determinants of this variability, such as relapse rate, provide opportunities to modify disease course even at later disease stages. Our observation of the highly significant deleterious effect of

greater relapse rates during each epoch contrasts some of the previous studies. While some studies only examined the effect of the presence/absence of relapses,[4,20] Scalfari and colleagues reported an unexpected association between a higher relapse count after the second year of disease and a reduced risk of disability progression.[5] Unlike relapse rate however, relapse count is confounded by time: patients with longer time to progression are exposed to a greater cumulative hazard of relapses. We have confirmed this assumption, by substituting annualised relapse rate with relapse count in our models. We have noted a reversal in the polarity of hazard ratios, creating an artifactual relationship similar to that reported by Scalfari and colleagues (data not shown). Thus, the previously reported association between higher relapse count and lower probability of disability progression is a result of confounding. Using relapse rates, which are by definition time-adjusted and less susceptible to bias, we have demonstrated that greater relapse activity is associated with worsening of disability during moderately advanced MS, which is in keeping with a similar association demonstrated in earlier disease.[21,22]

While a large body of evidence indicates that immunomodulatory therapy reduces relapse rate, studies of the treatment effect on disability trajectories once significant disability has been attained are largely lacking.[23-25] Our results demonstrate that sustained exposure to more effective immunomodulatory agents (here mainly represented by fingolimod and natalizumab) but not lower-efficacy agents (here mainly represented by interferon β preparations and glatiramer acetate) mitigates further accumulation of disability even after significant disability has been attained (here quantified as EDSS steps 3, 4, or 6). This observation is compatible with the outcomes of long-term follow-up extensions of randomised clinical trials in relapsing-

remitting MS, which reported long-term benefits of early treatment with interferon β preparations or glatiramer acetate.[23,26]

A recent study has shown an association between the number of relapses and the hazard of reaching EDSS step 6 after the onset of progressive disease (in both primary and secondary progressive MS).[13] Interestingly, this study has also reported a decreased hazard of EDSS step 6 among patients who received immunomodulatory therapy during the progressive stage of disease. Together with out findings, these observations imply that even at the more advanced stages of MS, inflammation, which may manifest with relapses, contributes to the accumulation of permanent disability. In fact, Frischer and colleagues showed that neurodegeneration in progressive MS is proportional to the magnitude of ongoing inflammatory activity.[27] This concept has important therapeutic implications, as it justifies immunomodulatory therapy in patients with more advanced MS.

The observational character of our data represents the main limitation of the present study. However, evaluation of long-term disability trajectories and their response to therapy in a randomised trial is impractical and unethical,[28,29] and all previous long-term follow-up studies in MS were based on observational cohorts. In order to minimise the impact of potential biases, we only utilised prospectively acquired data (mitigating recall bias), applied a rigorous data quality control procedure (reducing data entry errors, as described elsewhere[15]), defined a minimum required follow-up, adjusted the analyses for follow-up duration and used survival models with censoring (controlling attrition and selection biases), and modelled the outcomes in a series of two-step multivariable models adjusted for multiple potential confounders. Moreover, the independence of the main study outcomes (i.e. the effects of relapse rate and therapy on disability accrual) from the definition of sustained disability

accrual and the disability inclusion criteria was demonstrated by the sensitivity analyses. Our study was conducted in a large patient cohort representative of clinical practice at tertiary MS centres in multiple countries. This maximises the generalisability of our results given that treatment availability varies greatly across jurisdictions. In order to provide sufficient power to evaluate the effect of persistence on therapy, we grouped the available immunomodulatory therapies into two broad categories, based on the magnitude of their effects observed in randomised trials.[8-12,18,19] Up to 30% of patients were exposed to higher-efficacy disease-modifying therapies during the studied epochs. As a result, the distribution of the proportion of time on higher-efficacy therapies was markedly right-skewed and its mean and median values were relatively low. We also acknowledge that the crude stratification according to the estimated treatment efficacy precludes any conclusions regarding the efficacy of individual treatments. However, rather than compare the effect of individual preparations, our aim was to explore the class effect of immunomodulation on the accumulation of disability in moderately advanced disease.

Contrasting the previous studies,[4] our results suggest that disability accumulation in moderately advanced and advanced MS remains substantially driven by inflammatory activity. This hypothesis is supported by the observation that disability trajectories in moderately advanced and advanced relapse-onset MS are modifiable with immunomodulatory therapies. This observation, together with the general concept of the disease trajectory amnesic to the previous disease activity, lead us to conclude that prior disease activity should not preclude ongoing treatment, even when more advanced disability milestones have been reached (such as EDSS steps 3, 4, or 6). While we demonstrate an under-recognised benefit of therapy in more advanced MS, this must nonetheless be weighed against the risks of individual

immunomodulators in clinical decision-making. Our conclusion is highly relevant to the current debate resonating in the American MS community, concerning discontinuation of disease-modifying therapy in MS patients.[1,2] It also has important implications for the management of advanced disease, as well as treatment availability in jurisdictions where immunomodulatory therapies are only provided to patients with relatively mild disability.[30]

ACKNOWLEDGEMENTS

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Study funding

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Author contributions

NL conducted the analysis, and drafted and revised the manuscript. TK edited the manuscript. AL, RA, JLS, MS, HB and TK conceptualised and designed the study, interpreted the analysis, and have revised and approved the manuscript. EH, DH, MT, GI, PD, MG, AP, PG, RH, FGM, PS, EP, RB, COG, VVP, CR, DS, GI, CB, FG, JO, FV, CR, EC, SF, SH, MPA, ND, VJ, and TS, contributed substantially to data acquisition, interpretation of the analysis, and have revised and approved the manuscript. NL and TK had full access to all the data in the study, conducted the analysis and take responsibility for the integrity of the data and the accuracy of the analysis.

Conflict of Interest Disclosures

The authors report no disclosures relevant to the manuscript. Full disclosures are reported in the online supplement.

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FIGURE LEGENDS

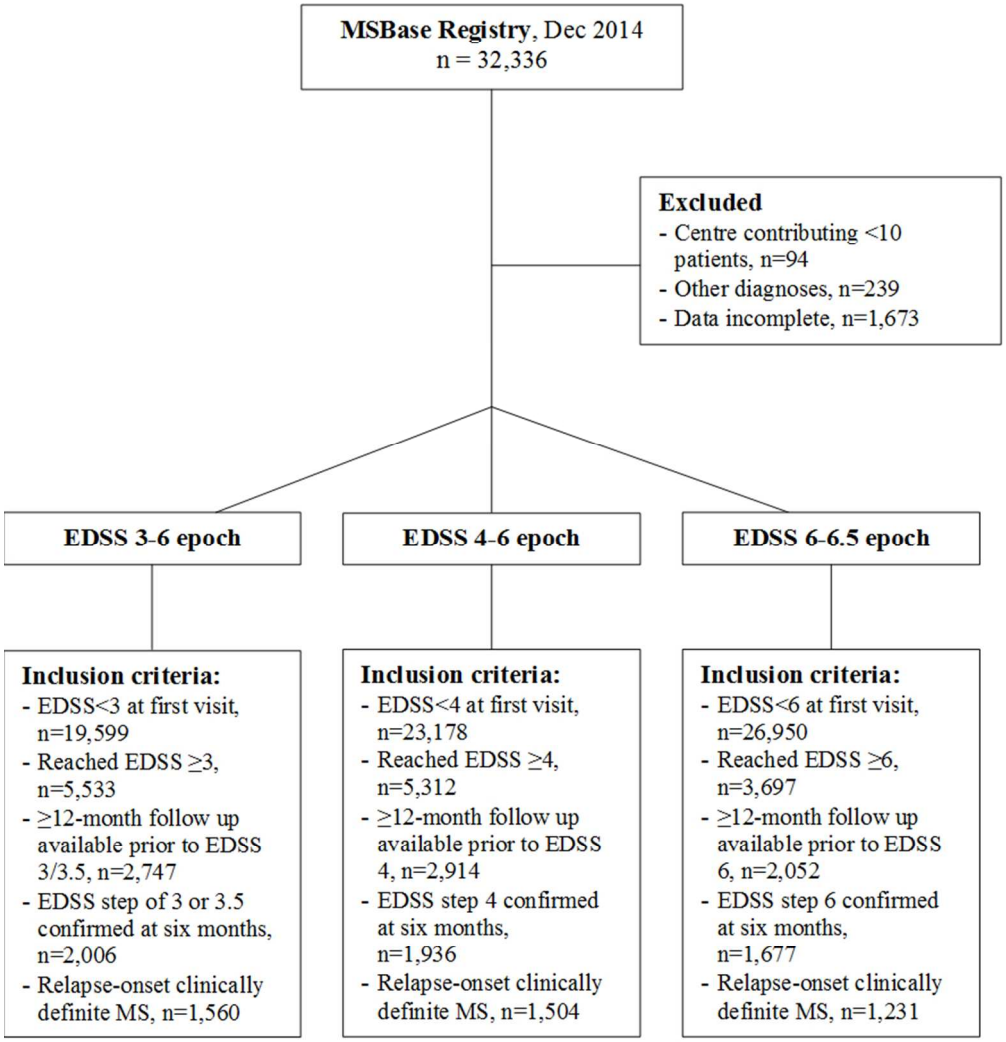
Figure 1: CONSORT diagram of patient disposition

Figure 2: Disability trajectories pre- and post-EDSS steps 3, 4 and 6

EDSS trajectories between first recorded EDSS and baseline, and between baseline and last recorded EDSS for the three studied epochs: (A) baseline EDSS of 3 or 3.5, (B) baseline EDSS of 4 and (C) baseline EDSS of 6. (D) Scatterplot of pre- and post-baseline disability trajectory slopes. No correlations were found between pre- and post-baseline slopes.

Figure 3: Probability of reaching disability endpoints per epoch

Kaplan-Meier curves of the proportion of patients reaching disability endpoints during each epoch, stratified by exposure to therapy during the epoch. The strata reflect the highest efficacy of the administered therapy (here visualised as a categorical variable). Top: EDSS 3-6 epoch; middle: EDSS 4-6 epoch; bottom: EDSS 6-6.5 epoch.



CONSORT diagram of patient disposition
Figure 1
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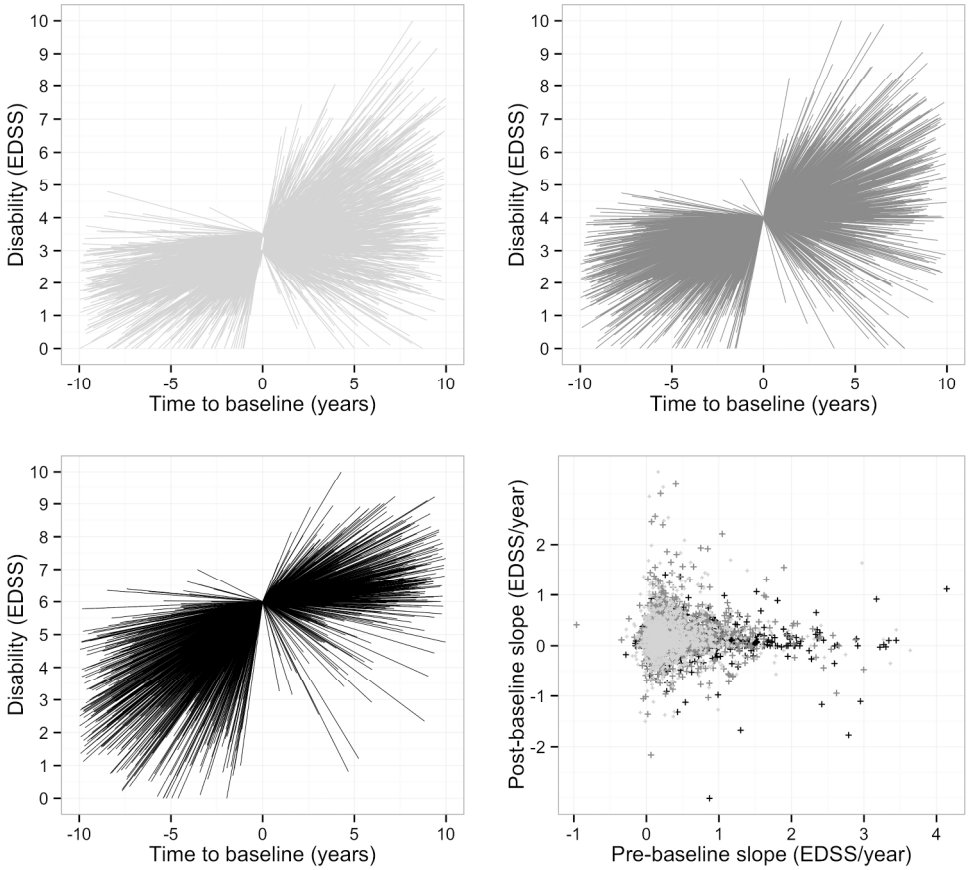
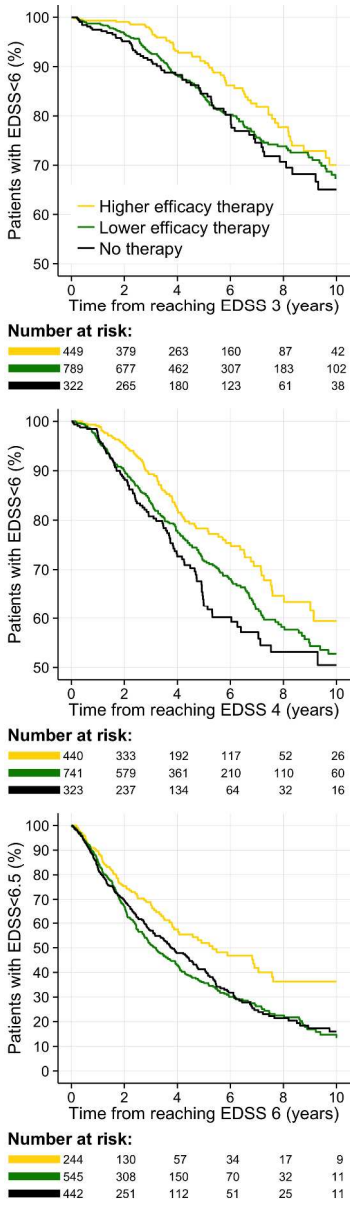


Disability trajectories pre- and post-EDSS steps 3, 4 and 6
EDSS trajectories between first recorded EDSS and baseline, and between baseline and last recorded EDSS for the three studied epochs: (A) baseline EDSS of 3 or 3.5, (B) baseline EDSS of 4 and (C) baseline EDSS of 6. (D) Scatterplot of pre- and post-baseline disability trajectory slopes. No correlations were found between pre- and post-baseline slopes.
Figure 2
833x749mm (72 x 72 DPI)



Probability of reaching disability endpoints per epoch
Kaplan-Meier curves of the proportion of patients reaching disability endpoints during each epoch, stratified by exposure to therapy during the epoch. The strata reflect the highest efficacy of the administered therapy (here visualised as a categorical variable). Top: EDSS 3-6 epoch; middle: EDSS 4-6 epoch; bottom: EDSS 6-6.5 epoch.
Figure 3
416x1449mm (72 x 72 DPI)

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Table S1:
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The following collaborators contributed to data acquisition:
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The following collaborators contributed to the administration of the MSBase cohort study:
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From Rodanotech, Geneva, Switzerland; Mr Samir Mechati, Mr Matthieu Corageoud, Mr Alexandre Bulla.

Table S2:

Patients included per MSBase centre

Centre	City	Country	Patients
General University Hospital	Praha	Czech Republic	624
University of Bari	Bari	Italy	373
Hospital Universitario Virgen Macarena	Sevilla	Spain	304
CHUM - Hopital Notre Dame	Montreal	Canada	269
Ospedale Clinizzato (Ss. Annunziata)	Chieti	Italy	264
Centre de Réadaptation déficience Physique Chaudière-Appalache	Levis	Canada	209
Zuyderland Ziekenhuis	Sittard	Netherlands	102
Neuro Rive-Sud	Quebec	Canada	92
Nuovo Ospedale Civile Sant'Agostino/Estense	Modena	Italy	83
ASUR Marche - AV 3	Macerata	Italy	79
National Neurological Institute C. Mondino	Pavia	Italy	75
Hospital Universitario La Paz	Madrid	Spain	69
Cliniques Universitaires Saint-Luc	Brussels	Belgium	68
Royal Melbourne Hospital	Melbourne	Australia	65
Box Hill Hospital	Melbourne	Australia	61
University Hospital Nijmegen	Nijmegen	Netherlands	60
Centro Internacional de Restauracion Neurologica	Havana	Cuba	51
Hospital Germans Trias i Pujol	Badalona	Spain	49
AORN San Giuseppe Moscati Avellino	Avellino	Italy	41
Kommunehospitalet	Aarhus C	Denmark	40
Hospital Universitario Virgen de Valme	Sevilla	Spain	35
Ospedali Riuniti di Salerno	Salerno	Italy	35
Hospital São João	Porto	Portugal	32
Farabi Hospital	Trabzon	Turkey	32
Ospedale di Parma	Parma	Italy	31
John Hunter Hospital	Newcastle	Australia	28
Hospital Donostia	Donostia	Spain	21
Groene Hart Ziekenhuis	Gouda	Netherlands	21
Jahn Ferenc Teaching Hospital	Budapest	Hungary	19
19 Mayis University	Samsun	Turkey	17
Flinders Medical Centre	Adelaide	Australia	16
Hospital Italiano de Buenos Aires	Buenos Aires	Argentina	13
Liverpool Hospital	Sydney	Australia	13
Assaf Harofeh Medical Center	Beer-Yaakov	Israel	13
University of Florence	Florence	Italy	12
Hospital Fernández	Buenos Aires	Argentina	10
Hospital de Galdakao-Usansolo	Galdakao	Spain	9
Jewish General Hospital	Montreal	Canada	8
INEBA	Buenos Aires	Argentina	6
St Vincent's Hospital	Melbourne	Australia	6
Westmead Hospital	Sydney	Australia	5
Royal Brisbane and Women's Hospital	Brisbane	Australia	5
Hôpital régional de Saint-Jérôme	Saint-Jérôme	Canada	5
Al-Zahra Hospital	Isfahan	Iran	5
Amiri Hospital	Kuwait City	Kuwait	5
Brain and Mind Research Institute	Camperdown	Australia	4
Craigavon Area Hospital	Craigavon	Northern Ireland	4
Royal Hobart Hospital	Hobart	Australia	3
Nemocnice Jihlava	Jihlava	Czech Republic	3
Petz A. County Hospital	Gyor	Hungary	3
Szent Imre Hospital	Budapest	Hungary	3
Geelong Hospital	Geelong	Australia	2
Bombay Hospital Institute of Medical Sciences	Mumbai	India	2
Francicus Ziekenhuis	Roosendaal	Netherlands	2
Central Clinical Emergency Military Hospital	Bucharest	Romania	2
Sir Charles Gairdner Hospital	Perth	Australia	1
The Alfred	Melbourne	Australia	1
Semmelweis University Budapest	Budapest	Hungary	1
University of Debrecen	Debrecen	Hungary	1
Péterfy Sandor Hospital	Budapest	Hungary	1
Neurology Clinical Center	Skopje	Macedonia	1
New York University Langone Medical Center	New York	United States	1

Table S3:
Sensitivity model 1 – outcome sustained for all available follow-up

	Study Epoch					
	EDSS 3-6		EDSS 4-6		EDSS 6-6.5	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Sex (Male)	1.10 (0.84-1.44)	0.48	1.31 (1.05-1.63)	0.02	1.25 (1.06-1.48)	0.009
Age at baseline (per year)	1.01 (1.00-1.03)	0.13	1.01 (1.00-1.03)	0.03	0.99 (0.98-1.00)	0.13
Disease duration at baseline (per year)	1.00 (0.89-1.13)	0.97	0.94 (0.85-1.03)	0.19	0.97 (0.90-1.04)	0.34
Annualised Relapse Rate						
- Pre-baseline (per relapse/year)	0.87 (0.70-1.08)	0.21	0.85 (0.69-1.05)	0.14	0.74 (0.62-0.88)	<0.001
- During epoch (per relapse/year)	3.01 (2.40-3.76)	<0.001	2.68 (2.28-3.16)	<0.001	1.84 (1.56-2.17)	<0.001
Rate of pre-baseline therapy initiation (per initiation/year)	1.39 (0.78-2.51)	0.27	1.17 (0.74-1.88)	0.50	0.95 (0.67-1.35)	0.77
Proportion of time on lower-efficacy therapies						
- Pre-baseline (per 25% increase)	1.00 (0.90-1.11)	1.00	0.96 (0.89-1.04)	0.31	1.06 (1.00-1.13)	0.07
- During epoch (per 25% increase)	0.99 (0.90-1.09)	0.84	1.00 (0.92-1.08)	0.96	1.00 (0.95-1.06)	0.98
Proportion of time on higher-efficacy therapies						
- Pre-baseline (per 25% increase)	0.74 (0.32-1.71)	0.48	1.44 (1.11-1.87)	0.006	1.06 (0.88-1.28)	0.52
- During epoch (per 25% increase)	0.80 (0.65-0.99)	0.04	0.82 (0.71-0.94)	0.006	0.89 (0.80-0.98)	0.02

Results of sensitivity analysis for each epoch. Unless stated otherwise, Cox proportional hazard models were utilised.

CI: confidence interval; HR: hazard ratio.

Table S4:
Sensitivity model 2 – patients with a baseline EDSS equal to or greater than the initial EDSS step for each epoch

	Study Epoch					
	EDSS 3-6		EDSS 4-6		EDSS 6-6.5	
	WAF (95% CI)	P-value	WAF (95% CI)	P-value	WAF (95% CI)	P-value
Sex (Male)	1.30 (1.03-1.63)	0.02	1.43 (1.10-1.88)	0.009	1.21 (0.88-1.65)	0.23
Age at baseline (per year)	1.01 (1.00-1.02)	0.17	1.01 (1.00-1.03)	0.08	0.97 (0.96-0.99)	0.003
Disease duration at baseline (per year)	1.02 (0.92-1.13)	0.71	0.92 (0.82-1.04)	0.20	0.92 (0.81-1.04)	0.18
Annualised Relapse Rate						
- Pre-baseline (per relapse/year)	1.13 (0.94-1.35)	0.21	1.16 (0.92-1.47)	0.20	0.77 (0.55-1.08)	0.12
- During epoch (per relapse/year)	1.47 (1.39-1.57)	<0.001	1.49 (1.35-1.64)	<0.001	0.84 (0.61-1.15)	0.27
Rate of pre-baseline therapy initiation (per initiation/year)	1.24 (0.74-2.05)	0.41	2.82 (1.58-5.03)	<0.001	1.59 (0.83-3.06)	0.17
Proportion of time on lower-efficacy therapies						
- Pre-baseline (per 25% increase)	0.98 (0.90-1.07)	0.68	0.95 (0.86-1.06)	0.36	0.99 (0.88-1.11)	0.85
- During epoch (per 25% increase)	0.90 (0.84-0.97)	0.009	0.84 (0.77-0.92)	<0.001	0.98 (0.88-1.08)	0.63
Proportion of time on higher-efficacy therapies						
- Pre-baseline (per 25% increase)	1.23 (0.82-1.86)	0.32	1.73 (1.23-2.43)	0.002	1.19 (0.85-1.67)	0.30
- During epoch (per 25% increase)	0.67 (0.57-0.79)	<0.001	0.53 (0.45-0.64)	<0.001	0.73 (0.61-0.87)	<0.001

Results of sensitivity analysis for each epoch. Weibull accelerated failure time models were utilised for all of the above. This sensitivity analysis included the following number of patients from the MSBase cohort: EDSS 3-6 epoch: 2,533; EDSS 4-6 epoch: 2,576; EDSS 6-6.5 epoch: 1,649.

CI: confidence interval; WAF: Weibull acceleration factor.

Table S5:
Sensitivity model 3 – results adjusted for patients' country of residence

	Study Epoch					
	EDSS 3-6[a]		EDSS 4-6		EDSS 6-6.5[a]	
	WAF (95% CI)	P-value	HR (95% CI)	P-value	WAF (95% CI)	P-value
Sex (Male)	1.06 (0.99-1.13)	0.09	1.33 (1.11-1.59)	0.002	1.20 (1.13-1.26)	<0.001
Age at baseline (per year)	1.01 (0.99-1.02)	0.41	1.01 (1.00-1.02)	0.04	0.99 (0.98-1.00)	0.003
Disease duration at baseline (per year)	1.00 (0.94-1.05)	0.87	0.91 (0.86 – 0.96)	0.001	0.96 (0.90-1.03)	0.27
Annualised Relapse Rate						
- Pre-baseline (per relapse/year)	0.98 (0.87-1.10)	0.71	0.93 (0.63-1.36)	0.70	0.79 (0.69-0.90)	<0.001
- During epoch (per relapse/year)	1.96 (1.76-2.18)	<0.001	2.41 (1.54-3.77)	<0.001	1.58 (1.44-1.74)	<0.001
Rate of pre-baseline therapy initiation (per initiation/year)	0.92 (0.57-1.49)	0.74	1.10 (0.86-1.40)	0.46	0.93 (0.73-1.17)	0.52
Proportion of time on lower-efficacy therapies						
- Pre-baseline (per 25% increase)	1.02 (0.93-1.12)	0.67	0.97 (0.91-1.04)	0.44	1.04 (0.98-1.10)	0.18
- During epoch (per 25% increase)	0.99 (0.96-1.02)	0.42	1.00 (0.94-1.06)	0.89	1.02 (0.96-1.07)	0.57
Proportion of time on higher-efficacy therapies						
- Pre-baseline (per 25% increase)	0.87 (0.56-1.35)	0.53	1.59 (1.22-2.07)	<0.001	1.10 (0.93-1.30)	0.25
- During epoch (per 25% increase)	0.80 (0.65-0.98)	0.03	0.79 (0.70-0.90)	<0.001	0.91 (0.85-0.97)	0.006

Results of sensitivity analysis for each epoch. Unless stated otherwise, Cox proportional hazard models were utilised.

[a]Weibull accelerated failure time models were utilised for these epochs.

CI: confidence interval; WAF: Weibull acceleration factor; HR: hazard ratio.

Full disclosures:

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