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Article type : Original Article

Anti-inflammatory disease modifying treatment and disability progression in primary progressive multiple sclerosis: a cohort study

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Running title: Disease modifying treatment in PPMS

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Key words: Multiple sclerosis, primary progressive, immunomodulation, observational study, clinical outcomes

Potential conflicts of interest are listed in the Supplement.

Abstract

Background: Treatment options in primary progressive multiple sclerosis (PPMS) are scarce and, with the exception of ocrelizumab, anti-inflammatory agents failed to show efficacy in ameliorating disability progression.

Objective: To investigate a potential effect of anti-inflammatory disease modifying treatment on disability outcomes in PPMS.

Methods: Using MSBase, a large, international, observational database, we identified patients with PPMS who were either never treated or treated with a disease modifying agent. Propensity score-matching was used to select subpopulations with comparable baseline characteristics. Expanded Disability Status Scale (EDSS) outcomes were compared with an intention-to-treat and an as-treated approach in paired, pairwise-censored analyses.

Results: Of the 1284 included patients, 533 were matched (treated, n=195; untreated n=338). Median on-study pairwise-censored follow-up was 3.4 years (quartiles 1.2-5.5). No difference in the hazard of experiencing 3-month confirmed EDSS progression events was observed between the groups (HR [hazard ratio] 1.0, 95% CI [confidence interval] 0.6-1.7, p=0.87). We did not find significant differences in the hazards of confirmed EDSS improvement (HR 1.0, 95%CI 0.6-1.6, p=0.91) or reaching a confirmed EDSS step (HR 1.1, 95%CI 0.7-1.6, p=0.69).

Conclusion: Our pooled analysis of disease modifying agents suggests that these therapies have no substantial effect on short- to medium-term disability outcomes in PPMS.

Introduction

Primary progressive multiple sclerosis (PPMS) accounts for 10-15% of the overall population with multiple sclerosis.[1-3] The course of this disease is characterized by gradual worsening from symptom onset, although relapses may occur.[1] While substantial progress has been made in the development of effective treatments for relapsing-remitting multiple sclerosis (RRMS) in the past decades, similar success has not been achieved in PPMS.[4, 5] A number

of phase 3 trials did not show a beneficial effect of immunomodulatory treatment in patients with PPMS.[6-8] Recently, however, a randomized controlled trial of ocrelizumab demonstrated lower rates of clinical and magnetic resonance imaging (MRI) progression when compared to placebo.[9] In the absence of licensed therapeutic options, disease modifying drugs (DMT) available for the treatment of RRMS have been used off-label in PPMS at the discretion of patient and physician, despite the weight of evidence not supporting this practice.

High quality observational cohort studies collect longitudinal information that is representative of real-world clinical practice.[10, 11] This is of particular importance as clinical trials in progressive multiple sclerosis may suffer from limited generalizability due to strict inclusion and exclusion criteria.[12] We have previously demonstrated the utility of MSBase, a large, international, observational cohort study of patients with MS, in the analysis of treatment outcomes in RRMS as well as secondary progressive MS, using propensity score-matching to mitigate treatment indication bias.[13-15] The aim of the present study was to investigate the effect of anti-inflammatory disease modifying treatment on disability outcomes in patients with PPMS.

Methods

Standard Protocol Approvals, Registrations, and Patient Consents

The MSBase cohort study (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 centers (or exemptions granted, according to local laws and regulations). Written informed consent was obtained from enrolled patients as required, in accordance with the Declaration of Helsinki.

Database and study population

Longitudinal data were obtained from 72 MSBase centers in 24 countries in August 2018. The inclusion criteria were a diagnosis of PPMS[16, 17], no exposure to immunomodulatory treatment before the first recorded visit, no hematopoietic stem cell transplantation, no participation in randomized controlled trials, available minimum dataset (consisting of patient sex, year of birth, year of the first clinical presentation, multiple sclerosis course, treating center), and at least three clinical visits with recorded Expanded Disability Status Scale (EDSS) scores, with the second and the last visits at least three months apart. The data quality assessment was conducted using a series of procedures to identify any invalid or inconsistent

entries, as described elsewhere.[18] The analyzed data were recorded as part of clinical practice, mostly at tertiary multiple sclerosis centers. The usual data entry practice was data entry at the time of clinical visits. The MSBase protocol stipulates a required annual update of the minimum dataset, but patients with less frequent visits were not excluded from the analysis. Categorized results of brain MRI were reported by treating neurologists. The data entry portal was either the iMed patient record system or the MSBase online data entry system.

Study design

Applying an ‘intention-to-treat’ design, included patients were allocated to the treatment group if they were receiving immunomodulatory treatment during the observational period. Patients who were never treated with immunomodulatory or immunosuppressive agents were allocated to the untreated group. The study baseline was defined as the first recorded visit with an EDSS assessment for the untreated patients and the start of immunomodulatory treatment for the treated patients. The two groups were matched at baseline and disability and relapse outcomes were compared between the matched groups. MS duration was calculated from the time of first symptoms as estimated by the treating physician. The prospective on-study follow-up was defined as the time between the first and the last available EDSS entry. Six sensitivity analyses were carried out: 1) repeating the primary analysis with modified endpoints: disability progression confirmed at 6 months, time to confirmed EDSS steps ≥ 4 and 6; 2) only including patients younger than 45 years at baseline; 3) only including patients treated with a highly-effective DMT (alemtuzumab, rituximab, ocrelizumab, natalizumab, mitoxantrone or fingolimod) in the treatment group; 4) comparing patients on highly-effective DMT with those on platform therapy (interferon beta or glatiramer acetate); 5) only including patients with relapses; and 6) only including patients with a treatment persistence of ≥ 2 years. We also performed an ‘as-treated’ analysis for which the study baseline was determined as the first recorded visit, irrespective of the patients’ treatment status. In this analysis, exposure to DMT was modeled as a time-dependent variable in order to avoid immortal time bias: For the epoch between the first visit and start of treatment, the treatment variable was forced to “untreated”.

Study endpoints

Disability was scored by accredited scorers (Neurostatus certification was required at each center) using the EDSS.[19] Confirmed disability progression was defined as an EDSS

increase of 1 point (1.5 points if the baseline EDSS step was 0, and 0.5 points if baseline EDSS was ≥ 6) sustained for ≥ 3 months. Confirmed disability improvement was defined as decrease of EDSS by 1 point (0.5 points if baseline EDSS was ≥ 6.5) sustained for ≥ 3 months.[20] The endpoints of EDSS ≥ 4 , 6 or 7 were reached at the time a patient progressed to the respective EDSS step with confirmation over the next ≥ 3 months. A relapse was defined as occurrence of new symptoms or exacerbation of existing symptoms persisting for at least 24 hours, in the absence of concurrent illness or fever, and occurring at least 30 days after a previous relapse. Individual ARR was calculated as the annualized number of recorded relapses between baseline and a censoring event.

Matching and statistical analysis

Matching and statistical analysis was conducted by J.L. using R (v3.4.2) with the MatchIt and survival extension packages.[21-23] Patients were matched on their propensity for receiving vs. not receiving DMT. The propensity score was based on a multivariable logistic regression model with treatment allocation as the outcome variable and the demographic and clinical variables available to treating neurologists at baseline as the independent variables. These comprised sex, age, baseline EDSS, Multiple Sclerosis Severity Scale at baseline,[24] number of relapses in the year prior to baseline, and center. To adjust for residual imbalance between the treated and untreated groups, the observed post-baseline ARR was used as an additional independent variable for the final model. Patients were then matched in a variable (1:1 to 1:3) ratio with exact matching on disease duration (in three-year epochs) by nearest neighbour matching within a caliper of 0.1 standard deviations of the propensity score, without replacement. The common on-treatment follow-up was determined as the shorter of the two individual follow-up periods for each matched patient pair (pairwise censoring), in order to control attrition bias.[10, 11] In the 'as-treated' analysis, pairwise censoring occurred either at discontinuation of treatment in the treated group or end of follow-up in the untreated group. We designed all subsequent analyses as paired models adjusted for visit density and with weighting for the variable matching ratio. The maximum cumulative weight for each matched patient was 1. The cumulative hazards of the confirmed disability progression, disability improvement events, or relapses were evaluated by marginal proportional hazards models for recurrent events with robust estimation of variance, the cluster term indicating the matched pairs.[25] For confirmed EDSS step ≥ 4 , 6 and 7, we applied marginal proportional hazards models for time to single event. Patients with a baseline EDSS of ≥ 4 (6 or 7, respectively) were excluded from these analyses. Proportionality of hazards was assessed by the

Schoenfeld's global test. Observed differences were considered significant if $p \leq 0.05$. When no significant differences were observed, we quantified analytical power as the minimum effect magnitude detectable within the available cohort at $1 - \beta = 0.8$ using 200 simulations.

Results

A total of 1284 patients with PPMS were included in the analysis (Figure 1). Of the included patients, 533 were matched (treated, $n=195$; untreated $n=338$). Median on-study pairwise-censored follow-up was 3.4 years (quartiles 1.2-5.5). Several demographic factors and markers of disease severity differed markedly between the unmatched patient groups (Table 1).

The logistic model used to calculate the propensity scores confirmed that treated patients were younger compared to untreated patients and had more relapses (Supplementary Table). The matching procedure retained 195 (55%) treated and 338 (36%) untreated patients, and substantially improved the overall match, as indicated by the decrease from 1.4 to 0.02 (by 98%) in the mean difference in propensity scores (Supplementary Figure). This was also reflected by the improved match in the individual determinants of treatment allocation, including age, disease duration and number of relapses in the year before baseline (Table 1). The median treatment persistence was 1.8 years (0.9-3.1) and the mean proportion of time on treatment was 70% (standard deviation 35%).

The results of the primary analysis are shown in Figure 2. We did not observe any difference in the cumulative hazard of confirmed disability progression events (HR [hazard ratio] 1.0, 95% CI [confidence interval] 0.6-1.7, $p=0.87$) between the treated and the untreated groups. The proportion of patients with at least one progression event after 4 years was 16% (95% CI 11-22%) in the treated, and 11% (95% CI 6-16%) in the untreated group. In the unmatched cohort, the proportion of patients with at least one progression event after 4 years was 12% (95% CI 8-16%). The cumulative hazards of confirmed disability improvement (HR 1.0, 95% CI 0.6-1.6, $p=0.91$) did not differ between the two groups, and there was no difference in the risk of reaching confirmed EDSS ≥ 7 (HR 1.1, 95% CI 0.7-1.6, $p=0.69$). The matching process effectively adjusted the analysis for a potential effect of post-baseline relapses, as demonstrated by the lack of difference in relapse activity between the matched groups (HR 0.8, 95% CI 0.5-1.1, $p=0.20$). In participants for whom sufficient post-baseline MRI data was available (35% in the treated and 29% in the untreated group), the proportion of patients who showed new or gadolinium-enhancing lesions at any time during the follow-up was 7% in the treated and 4% in the untreated group (Table 2).

The sensitivity analyses confirmed the results of the primary analysis (Table 3).

Similarly, the 'as-treated' analysis did not find any evidence of an effect of disease modifying treatment on the cumulative hazard of disability progression (HR 0.8, 95% CI 0.6-1.3, $p=0.44$). However, the treated patients had a higher probability of confirmed disability improvement compared to the untreated patients (HR 1.8, 95% CI 1.1-3.1, $p=0.02$). The groups were no different in the hazard of post-baseline relapses (HR 1.0, 95% CI 0.5-1.8, $p=0.91$).

The primary analysis was sufficiently powered to detect minimum differences of 50% in the hazard of disability progression, 44% in the probability of disability improvement, 44% in the hazard of EDSS \geq 7 and 50% in the hazard of relapses.

Discussion

In this observational, propensity score-matched study in MSBase, we found no effect of the available immunotherapies, used off-label to treat primary progressive MS, on short- to medium-term disability outcomes.

The first large randomized controlled trial undertaken in patients with PPMS was the study of glatiramer acetate vs. placebo.[6] In this trial, 943 patients with a mean age of 50.4 years (standard deviation [SD] 8.3), a disease duration of 10.9 (SD 7.5) years and a mean EDSS step of 4.9 (SD 1.2) at baseline, were followed-up for 96 weeks, and the trial did not find a treatment effect of glatiramer acetate. The study of fingolimod in PPMS (INFORMS) examined the effect of fingolimod vs. placebo in 823 patients with PPMS.[8] While age (mean 48.5, SD 8.4 years) and disability at baseline (median EDSS 4.5, range 2.0-6.5) were comparable with the previous study, disease duration was shorter (mean 5.8, SD 2.4 years), and the on-study follow-up was considerably longer (3 and 5 years). No effect of fingolimod on a composite endpoint of EDSS progression, Timed-25-Foot-Walk Test and Nine-Hole Peg Test was found.

In the trial of rituximab in patients with primary progressive multiple sclerosis (OLYMPUS), 439 patients with similar age (mean 49.9, SD 8.9 years), disease duration (mean 9.1, SD 6.6 years) and disability (median EDSS step 5.0, range 2.0-6.5) received rituximab or placebo.[7] The trial duration was also 96 weeks and, similarly, its result did not favor rituximab over placebo. Interestingly, subgroup analyses suggested a beneficial effect of B-cell depletion in younger PPMS patients (<51 years of age) with active MRI lesions. A recent study examined the effect of ocrelizumab vs. placebo in a population of patients with PPMS similar to the responders to treatment in the OLYMPUS trial. This study followed 732 patients over 216

weeks. Patients were younger (mean age 44.4-44.7 years) and had a relatively shorter disease duration (mean 6.1-6.7 years) than in the previous studies, but disability levels were comparable (median EDSS step 4.5, range 2.5-7.0). Of note, 25-28% of the included patients had gadolinium-enhancing lesions on their baseline MRI. The trial was the first to show efficacy of an active comparator, ocrelizumab, on 12-week confirmed disability progression in patients with PPMS.[9]

With the mean age at inclusion of 48 years, disease duration of 7 years and median EDSS of 4.5, the core characteristics of our study population closely resembled the INFORMS study. We did not observe any effect of pooled immunomodulatory agents on disability progression, disability improvement and time to EDSS step 7, which corresponds to becoming wheelchair-bound, in the intention-to-treat analysis. While the 'intention-to-treat' analysis evaluated overall cumulative effect of exposure to therapy, including delayed disability outcomes, the 'as-treated' analysis evaluated immediate outcomes during treatment exposure, not influenced by potential confounding during the untreated epochs. Interestingly, in the 'as-treated' analyses, patients were more likely to experience confirmed disability improvement when treated with an immunomodulatory drug. As this analysis was effectively matched on ARR during follow-up, this result cannot be attributed to an imbalance in relapse activity and subsequent recovery from a temporary deficit between the groups. While this may represent a placebo effect in a cohort treated in un-blinded fashion, it may also reflect true decline in previously accrued disability, which can be observed in some therapies shortly after treatment initiation.[13, 14, 26]

It is of note that the proportion of patients with at least one confirmed progression event was rather low in our cohort (12% in the entire unmatched cohort and 11% in the matched untreated group after four years, respectively). The previous randomized trials reported substantially higher progression rates in their placebo groups ranging from 39% in the OLYMPUS to 59% in the INFORMS trial over 2 years.[6-9] To an extent, this can be explained by the observational study design and a lower intensity of follow-up assessments. Another contributing factor may be the over-representation of patients with a more progressive disease phenotype in clinical trials, which raises concerns about their generalizability, as the included patients are only representative of a subset of PPMS patients.[12]

Our study largely reflects the outcomes of treatment with injectable immunomodulatory therapies in PPMS, as only about one third of the treated patients received more potent immunotherapies. The low number of patients exposed to individual drugs did not allow us to

analyze single drug exposure versus no treatment. Therefore, it is possible that one or more of these drugs, when studied separately in sufficiently large samples, could prove beneficial for disability outcomes in PPMS.

The limitation of our primary disability outcome reflects the limitations of the EDSS. The EDSS relies heavily on lower limb function and its sensitivity to cognitive changes and upper limb function in more advanced MS is relatively low.[27] In addition, the EDSS is burdened with a relatively low intra- and inter-rater reliability. [28, 29] We aimed to mitigate this variability through the requirement of Neurostatus certification.

Due to the relative lack of MRI data, we could not match patients on MRI activity or analyze potential subgroup effects in patients with radiologically active disease. In patients for whom sufficient MRI data was available, a larger proportion of treated patients showed new or contrast-enhancing lesions in the year before baseline. Even though a difference in MRI activity between the groups remained during follow-up, indicating residual bias in terms of a higher inflammatory activity in the treatment group, it became less pronounced after patients commenced immunotherapy.

To mitigate the known treatment indication bias, we employed propensity score matching. Unlike randomization, propensity score matching does not eliminate unknown confounders. However, this is unlikely to have a substantial effect on our overall conclusions, as sensitivity analyses with varying inclusion criteria confirmed the results of the primary analysis. The study used strict matching criteria, including exact matching on disease duration and two disability metrics. Pairwise censoring was applied to control for attrition bias. We also adjusted for reporting bias by taking into account the frequency of follow-up visits.

Cumulative follow-up and generalizability were maximized by inclusion of a broad spectrum of patients with only minimum follow-up requirements that were necessary to assess confirmed disability outcomes. While we cannot rule out that a small treatment effect was present, our study was powered sufficiently to demonstrate effects of moderate magnitude or greater.

In conclusion, our study shows that anti-inflammatory drugs currently used off-label in patients with PPMS in real-world practice did not reduce the rate of disability accumulation. However, ocrelizumab has recently been shown to reduce accumulation of disability in PPMS, at least to a modest degree and over the short-to medium-term.[9] Therefore, separate evaluations of the efficacy of more aggressive anti-inflammatory drugs in PPMS, and especially B-cell depleting therapies, are needed.

Acknowledgements

The MSBase Study co-investigators are listed in the Supplementary Material.

Funding

Funding for this study is described in the Supplementary Material.

References

References are listed in the Supplementary Material.

Table captions

Table 1: Baseline characteristics

EDSS = Expanded Disability Status Scale, MSSS = Multiple Sclerosis Severity Score, SD = standard deviation

^aCohen's d

^bFor matched patients, follow-up after pairwise censoring is given

^cMore than one treatment per patient is possible

Table 2: MRI outcomes

DMT = disease modifying treatment

^aProportion of all patients in a group

^bProportion of patients with available MRI

Table 3: Sensitivity analyses

Results from marginal proportional hazards models for recurrent events.

HR = hazard ratio, CI = confidence interval, CDP= confirmed disability progression, DMT = disease modifying treatment, EDSS = Expanded Disability Status Scale

^aAlemtuzumab, rituximab, ocrelizumab, natalizumab, mitoxantrone or fingolimod

^bInterferon-beta or glatiramer acetate

Figure legends

Figure 1: CONSORT flowchart of patient disposition

PPMS = Primary progressive multiple sclerosis, EDSS = Expanded Disability Status Scale,
RCT = randomized controlled trial

Figure 2: Disability outcomes, propensity score matched comparison

A) Cumulative hazard of confirmed disability progression, B) Cumulative hazard of disability improvement, C) Proportion of patients not reaching a confirmed Expanded Disability Status step of ≥ 7 .

DMT = disease modifying treatment. HR = hazard ratio. 95%CI=95% confidence interval.

Table 1: Baseline characteristics

Characteristics	Unmatched			Matched		
	Treated	Untreated	d ^a	Treated	Untreated	d ^a
Patients, No. (% female)	354 (53%)	930 (55%)		195 (52%)	338 (53%)	
Age, years, mean \pm SD	45.4 (10.4)	52.9 (10.2)	0.74	47.2 (9.8)	48.7 (10.4)	0.15
Disease duration, years, mean \pm SD	7.8 (6.8)	9.2 (8.1)	0.19	6.7 (5.8)	6.7 (6.1)	0.003
Disability, EDSS, mean \pm SD	4.7 (1.6)	4.8 (1.9)	0.06	4.6 (1.7)	4.5 (1.9)	0.06
MSSS, mean \pm SD	7.0 (2.2)	6.9 (2.2)	0.04	7.3 (2.1)	7.2 (2.2)	0.05
Relapses 12 months before baseline, mean \pm SD	0.31 (0.62)	0.04 (0.19)	0.73	0.14 (0.36)	0.09 (0.29)	0.17
Patients relapsing 12 months before baseline, n (%)	87 (25%)	33 (4%)		26 (13%)	28 (8%)	
Post-baseline follow-up ^b , years, Median (quartiles)	6.5 (3.5-10.6)	6.1 (3.3-10.2)		3.4 (1.2-5.5)	3.4 (1.2-5.5)	
On study visit density per year, mean (SD)	2.0 (2.0)	1.3 (0.6)	0.62	1.9 (1.2)	1.9 (1.)	0.02
Treatment at baseline, n (%)						
Interferon beta	191 (53%)			94 (48%)		
Glatiramer acetate	55 (16%)			26 (13%)		
Teriflunomide	3 (<1%)			2 (1%)		
Fingolimod	30 (8%)			19 (10%)		
Natalizumab	14 (4%)			13 (7%)		
Rituximab	4 (<1%)			1 (<1%)		
Alemtuzumab	1 (<1%)			1 (<1%)		
Mitoxantrone	56 (16%)			39 (20%)		
Treatments during entire follow-up ^c , n						
Interferon beta	225			112		
Glatiramer acetate	89			37		

Teriflunomide	7		4	
Dimethyl fumarate	5		2	
Fingolimod	52		29	
Natalizumab	32		17	
Alemtuzumab	3		2	
Rituximab	12		5	
Ocrelizumab	8		6	
Mitoxantrone	84		53	
Prior or subsequent immunosuppressive treatment, n (%)	140 (40%)		70 (36%)	

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Table 2: MRI outcomes

Patients with new T2 and/or contrast enhancing T1-lesions, n (%)	1 year pre-baseline		On-study	
	DMT	Control	DMT	Control
Missing information	149 (78%) ^a	273 (81%) ^a	125 (65%) ^a	241 (71%) ^a
Yes	6 (3%) ^a (13%) ^b	5 (1%) ^a (8%) ^b	5 (3%) ^a (7%) ^b	4 (1%) ^a (4%) ^b
No	40 (21%) ^a (87%) ^b	60 (18%) ^a (92%) ^b	65 (33%) ^a (93%) ^b	93 (28%) ^a (96%) ^b

Table 3: Sensitivity analyses

1) Primary analysis with modified endpoints (DMT, n=195; Control, n=338)		
	HR (95%CI)	p-value
6-months CDP	0.9 (0.7-1.2)	0.41
EDSS \geq 4	0.8 (0.6-1.1)	0.20
EDSS \geq 6	1.0 (0.7-1.4)	0.87
2) Only patients younger than 45 years at baseline (DMT, n=69; Control, n=94)		
Disability progression	0.9 (0.5-1.8)	0.84
EDSS \geq 7	1.1 (0.5-2.2)	0.86
Disability improvement	2.1 (0.8-5.4)	0.09
Incidence of relapses	1.0 (0.5-2.3)	0.84
3) Only patients treated with a highly-active DMT^a (DMT, n= 103; Control, n=207)		
Disability progression	0.8 (0.4-1.5)	0.43
EDSS \geq 7	1.5 (0.9-3.0)	0.22
Disability improvement	0.9 (0.5-1.8)	0.76
Incidence of relapses	1.0 (0.5-1.9)	0.89
4) Highly-active vs platform DMT^b (highly-active, n= 69; platform, n=109)		
Disability progression	0.8 (0.3-2.0)	0.68
EDSS \geq 7	1.1 (0.5-2.6)	0.76
Disability improvement	0.7 (0.3-1.8)	0.47
Incidence of relapses	0.8 (0.4-1.3)	0.34
5) Only patients with relapses (DMT, n= 35; Control, n=47)		
Disability progression	0.7 (0.2-2.3)	0.65
EDSS \geq 7	0.6 (0.2-2.2)	0.44
Disability reduction	0.5 (0.1-1.7)	0.25
Incidence of relapses	1.0 (0.6-1.6)	0.95
6) Treatment persistence \geq 2 years (DMT, n=123; Control, n=262)		
Disability progression	1.1 (0.6-1.8)	0.76
EDSS \geq 7	1.1 (0.7-1.9)	0.61
Disability reduction	1.0 (0.6-1.7)	0.88
Incidence of relapses	0.7 (0.4-1.7)	0.14

MSBase registry, August 2018
n=60,900

Excluded patients:

Erroneous or incomplete data: 165
Diagnosis other than PPMS: 57,206

Primary progressive multiple sclerosis
n=3,529

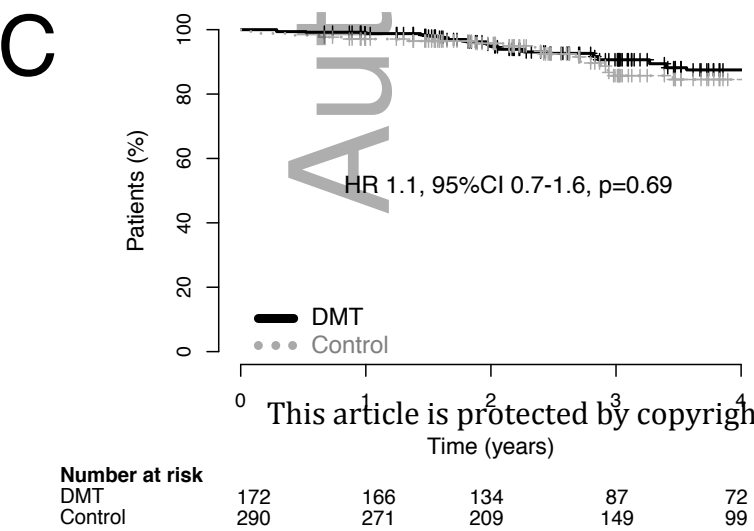
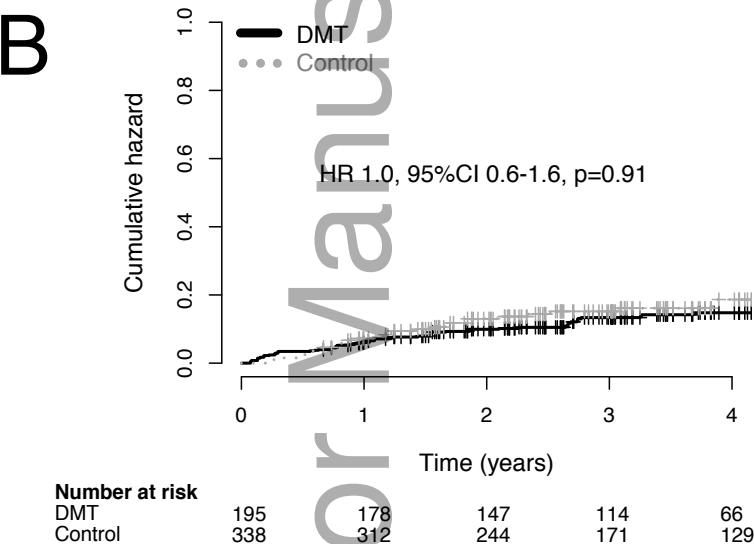
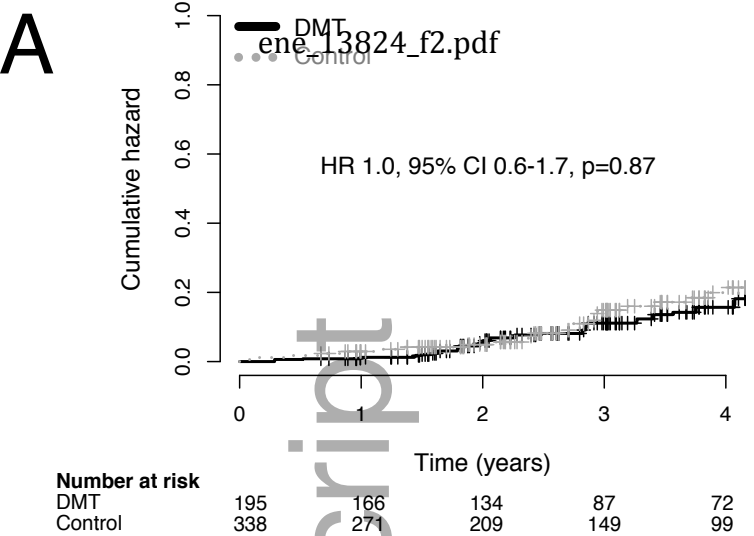
Start of treatment before first recorded visit: 578
Less than 3 EDSS scores at least 3 months apart: 1118
Inclusion in RCT or treatment with immunosuppressive drugs: 549

Included in the analysis
n=1,284

DMT
n=354

Untreated
n=930

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