

Association of Inflammation and Disability Accrual in Patients With Progressive-Onset Multiple Sclerosis

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 Supplemental content

IMPORTANCE The role of inflammatory disease activity as a determinant of disability in progressive-onset multiple sclerosis (MS) remains contested.

OBJECTIVE To examine the association of superimposed relapses in progressive-onset MS on disease outcomes.

DESIGN, SETTING, AND PARTICIPANTS Observational cohort study from MSBase, a prospectively collected, international database. Data were collected between January 1995 and February 2017. Analyses began in February 2017. From 44 449 patients at time of extraction, 1419 eligible patients (31.9%) were identified for analysis. Inclusion criteria consisted of primary progressive MS (PPMS) or progressive-relapsing MS (PRMS), adult-onset disease, and minimum data set (including ≥ 3 visits with disability recorded, ≥ 3 months between second and last visit). Data were analyzed using multivariable regression models (Andersen-Gill) with mixed effects. Two sensitivity analyses to exclude both relapse-related disability progression and bout-onset progressive MS were performed.

EXPOSURES Grouped according to presence or absence of relapse, defined as an acute episode of clinical worsening. Quantifiable disability change or correlation on imaging was not required to confirm relapse.

MAIN OUTCOMES AND MEASURES Cumulative hazard of disability progression.

RESULTS Patients with PRMS were younger than those with PPMS (mean [SD] age, 46 [15] vs 51 [10] years, Cohen $d=0.40$) and demonstrated a mean lower Expanded Disability Status Scale score (mean [SD] score, 4.0 [3] vs 4.5 [2.5], Cohen $d=0.28$) at inclusion. The ratio of men to women was similar in the PRMS and PPMS groups (252:301 vs 394:472). The overall mean (SD) age was 48 (11) years for men and 50 (10) years for women. Likelihood of confirmed disability progression was lower in patients with superimposed relapses (hazard ratio [HR], 0.83; 95% CI, 0.74-0.94; $P=.003$). Proportion of follow-up time spent on disease-modifying therapy significantly reduced the hazard of confirmed disability progression in the cohort with relapse (HR, 0.96; 95% CI, 0.94-0.99; $P=.01$) but not in those without relapse (HR, 1.02; 95% CI, 0.99-1.05; $P=.26$). When accounting for relapse-related progression, the association of disease-modifying therapy in the cohort with superimposed relapse was no longer observed (HR, 1.10; 95% CI, 0.96-1.24; $P=.16$).

CONCLUSIONS AND RELEVANCE In progressive-onset MS, superimposed relapses are associated with a lower risk of confirmed disability progression. This is most likely attributed to the association of disease-modifying therapy with the prevention of relapse-related disability accrual in patients with superimposed relapse. These findings suggest that inflammatory relapses are an important and modifiable determinant of disability accrual in progressive-onset disease.

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Multiple sclerosis (MS) represents a disease with a high burden of morbidity and substantial impact on quality of life.^{1,2} Primary progressive MS (PPMS) accounts for 10% to 20% of MS and is characterized by a gradual decline in neurological function from the onset of symptoms.²⁻⁶ A subset of patients with progressive-onset MS will also experience episodes of distinct clinical relapse, representing the previously described progressive-relapsing phenotype of MS (PRMS).^{7,8}

In 2014, Lublin et al⁷ proposed a reclassification of progressive-onset MS phenotypes in which PPMS and PRMS are categorized as a single phenotype under the umbrella of PPMS. This single phenotype can be further described by disease activity, defined as the presence or absence of either superimposed clinical relapses or new activity (gadolinium-enhancing or T2 lesions) on magnetic resonance imaging.

Progressive-onset MS with and without superimposed relapse is associated with a reduced time to irreversible disability milestones; however, there is limited research to date identifying factors that contribute to this disability accrual.^{9,10} In particular, likely owing to the low prevalence of PRMS, the role of episodic inflammation in disability accumulation remains contested.¹¹⁻¹⁶

While previous landmark cohort studies did not identify any association of superimposed relapse with disability outcomes in progressive-onset MS, findings of more recent research indicates that a subset of patients with a more rapidly deteriorating course may exist.¹¹⁻¹⁶ Moreover, results of recent randomized clinical trials provide further support for the notion of a subset of patients with progressive-onset MS characterized by a greater degree of ongoing inflammatory activity.^{17,18} The implications of characterizing this subset of patients with progressive-onset MS include (1) identification of a subgroup of patients that may benefit from preexisting therapy, (2) recognition of inflammatory relapse as a disability modifier in design of future therapeutic trials, and (3) a better pathophysiological understanding of the interaction between relapse and progression, the 2 core phenomena of MS.¹⁹ Hence, characterizing the clinical features of progressive-onset MS with and without relapse represents an area of unmet need.

Our study used MSBase, a large international, observational cohort, to examine the association of superimposed relapses on disability accumulation in progressive-onset MS.²⁰ We first described the clinical characteristics of patients with progressive-onset with relapse vs those without. Following this, we evaluated the association between superimposed relapses and disability outcomes. Finally, we investigated the interaction between disease activity and disease-modifying therapy (DMT) in progressive-onset MS.

Methods

Ethics

The MSBase registry²⁰ (registered with WHO ICTRP, anzctr.org.au identifier: [ACTRN12605000455662](https://www.anzctr.org.au/Trial/Registration/TrialRegistration.aspx?ACTRN12605000455662)) was approved by the Melbourne Health Human Research Ethics Committee and the

Key Points

Question What is the role of inflammatory relapses in disability accumulation for patients with progressive-onset multiple sclerosis?

Findings In this longitudinal, prospective cohort study of 1419 patients with progressive-onset multiple sclerosis, superimposed relapse was associated with a reduced likelihood of confirmed disability progression. Time spent on disease-modifying therapy reduced the likelihood of progression in progressive-onset patients with relapse but not in those without relapse.

Meaning Disease-modifying therapy may prevent relapse-related disability accrual in patients with progressive-onset multiple sclerosis.

local ethics committees of participating centers (or exemptions were granted in accordance with local laws and regulations). If required, enrolled patients provided written informed consent.

Participants

Data from 44 449 patients from 117 centers in 36 countries were extracted from the MSBase registry in February 2017. The study followed the complete-case analysis principle. The inclusion criteria consisted of the diagnosis of definite PPMS or PRMS (according to 2005 or 2010 revised McDonald criteria^{21,22}), adult-onset disease, 3 or more visits with Expanded Disability Status Scale (EDSS) score recorded, more than 3 months between second and last visit, and availability of the minimum data set. The minimum data set requirements included date of birth, sex, MS course, and center; only patient data from centers contributing 10 or more patient records were included.

Data entry into MSBase registry was near real time and was achieved through the iMed clinical record system or the MSBase online data entry portal. Data were collected between January 1995 and February 2017, and analyses began in February 2017. Data recorded in local databases before the launch of MSBase were merged into MSBase in 2004 or later.²⁰ Data quality was assessed prior to screening for inclusion and statistical analysis as per standard MSBase procedures (eTable 1 in the [Supplement](#)).²³

Lublin et al⁷ have defined PPMS as with or without relapses, which replaced the previous diagnoses of PRMS and PPMS, respectively. For simplicity, we will use PRMS and PPMS as diagnostic categories throughout the remainder of the article and progressive-onset MS when describing both groups. Patients were categorized into the PRMS group based on the diagnosis of PRMS and/or progressive-onset MS with a recorded relapse in the data set; otherwise they were categorized as PPMS.

Study Design and Outcomes

On-study follow-up was defined as the time between first and last eligible visit, where the eligibility of the latter was defined by the presence of 1 further confirmatory visit 3 or more months later. Only visits from January 1, 1995, with EDSS score recorded were included.

Disability was measured using the EDSS, with neurostatus certification required at each participating center to improve the reliability of clinical disability assessment.²⁴ Relapse was defined as the 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.²⁵ MSBase protocol does not require quantifiable disability change or correlation on imaging to confirm relapse. Progression was defined as an increase in EDSS score by 1 step (1.5 steps if baseline EDSS score was 0, and 0.5 steps if baseline EDSS score was >5.5).

The primary outcome was a confirmed disability progression event, defined as increase in EDSS score by 1.5 steps if baseline EDSS score was 0, 1 step if baseline EDSS score was 1 to 5.5, and 0.5 steps if baseline EDSS score was 6 or greater. As multiple progression events were allowed per patient, periods of EDSS score progression were measured from each base visit, defined as the date of inclusion and 1 day after subsequent confirmed progression events. Expanded Disability Status Scale score was confirmed at a minimum of 3 months and sustained for the remainder of follow-up.²⁶ While EDSS scores irrespective of their association with relapse were eligible to establish disability progression, only EDSS scores recorded more than 30 days from onset of relapse could be used to confirm disability progression. Patients who did not reach end points were censored at the final eligible visit.

Statistical Analysis

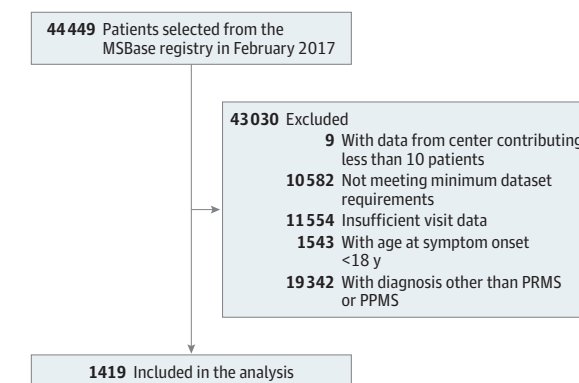
Mean with 95% CIs or median with quartiles (first quartile to third quartile) were used to describe data distributions. Cohen *d* was calculated to determine effect size across PRMS vs PPMS groups.

Multivariable models with mixed effects adjusted for annualized visit rate were fitted to analyze the association of superimposed relapse on the cumulative hazard of confirmed disability progression events (Andersen-Gill). In addition to MS group (PRMS or PPMS), sex, frequency of visits with EDSS scores, and proportion of follow-up on both DMT and immunosuppression were modeled as covariates. Age and EDSS scores were additionally modeled as time-dependent covariates, measured at each base visit. To account for center-specific bias (including any differences in the years of patient inclusion) and within-patient dependence, we modeled center and patient identification as random effects. Proportional hazards assumption was assessed with Schoenfeld residuals and any violations corrected by introducing an interaction term with a time variable.

To identify any differential association of DMT with confirmed disability progression between groups, we subsequently introduced an interaction term between proportion of follow-up receiving DMT (per 10% follow-up time receiving DMT) and MS group to each model. Finally, to further characterize this potential interaction, we stratified each model according to MS group.

Two sensitivity analyses were performed to (1) exclude the role of relapse-related disability progression by excluding visits preceded by relapse within 12 months and (2) exclude bout-

Figure 1. CONSORT Flowchart of Patient Eligibility



Patients excluded owing to incomplete minimum data set had at least 1 of the following information missing: date of birth, sex, center, multiple sclerosis (MS) course, or MS diagnosis date. Patients excluded owing to insufficient visit data had fewer than 3 visits with Expanded Disability Status Scale score recorded or less than 3 months between second and last visit. PPMS indicates primary progressive MS; PRMS, progressive-relapsing MS.

onset progressive MS by selecting only patients with recorded relapses 30 days or more from symptom onset.

All statistical analyses were performed using R, version 3.3.2 (R Foundation for Statistical Computing). Mixed-effects models were fitted using the *coxme* package. Models were selected according to model validity, clinical relevance, and goodness of fit determined by the Akaike Information Criterion. All hypotheses were tested at a 2-tailed .05 level of significance.

Results

Patient Demographics

Prior to inclusion, progressive-onset disease represented 6.4% of patients with recorded MS course in the MSBase registry. Of the patients enrolled in the MSBase registry at time of data extraction, 1419 patients from 83 centers across 28 countries were eligible for analysis after the inclusion criteria were applied (Figure 1 and eTable 2 in the Supplement). Data were captured between January 1995 and February 2017, with 1219 patients (86%) with the first visit recorded after 2000 (eFigure in the Supplement). Median prospective follow-up period was 5.0 (quartiles, 2.3-9.0) years per patient.

Patient, treatment, and relapse characteristics in the PRMS vs PPMS groups are summarized in Table 1. Patients with PRMS were younger at disease onset (mean [SD] age, 39 [11] vs 43 [10] years; Cohen *d* = 0.38) and date of inclusion (mean [SD] age, 46 [15] vs 51 [10] years; Cohen *d* = 0.40), and demonstrated a lower EDSS at inclusion (mean [SD] score, 4.0 [3] vs 4.5 [2.5]; Cohen *d* = 0.28) compared with those in the PPMS group. The male-female ratio in the PRMS group was 1:1.19 compared with 1:1.20 in the PPMS group. Of the patients who received treatment, interferon-beta was most common in both the PRMS and PPMS groups (186 [73%] and 99 [56%] patients, respectively).

Of the 553 patients in the PRMS group, 320 (58%) experienced a total of 864 recorded relapses during follow-up. The

Table 1. Patient and Relapse Characteristics

Characteristic	No. (%)		Cohen <i>d</i>
	PRMS Group	PPMS Group	
Patients	553 (39)	866 (61)	NA
Men	252 (46)	394 (45)	NA
Age at symptom onset, mean (SD), y	39 (11)	43 (10)	0.38
Age at inclusion, mean (SD), y	46 (15)	51 (10)	0.40
Duration from symptom onset to inclusion, median (IQR), y	5.4 (8.7)	5.8 (8.2)	0.06 ^a
EDSS score at inclusion, median (IQR)	4.0 (3.0)	4.5 (2.5)	0.28 ^a
Follow-up time from inclusion to last eligible visit, median (IQR), y	5.8 (6.9)	4.5 (6.3)	0.29 ^a
Proportion of follow-up on treatment, %			
0	299 (54)	688 (79.5)	NA
0-50	119 (22)	96 (11)	NA
50-100	135 (24)	82 (9.5)	NA
Proportion of patients treated with disease-modifying therapy receiving specific treatment	254	178	NA
Low efficacy ^b			
Interferon beta	186 (73)	99 (56)	NA
Glatiramer acetate	50 (20)	23 (13)	NA
Teriflunomide	3 (1)	2 (1)	NA
Medium efficacy ^b			
Fingolimod	31 (12)	28 (16)	NA
Cladribine	NA	1 (0.6)	NA
Dimethyl fumarate	4 (2)	4 (2)	NA
High efficacy ^b			
Natalizumab	24 (9)	15 (8)	NA
Alemtuzumab	1 (0.4)	NA	NA
Rituximab	1 (0.4)	4 (2)	NA
Ocrelizumab	NA	2 (1)	NA
Mitoxantrone	33 (13)	30 (17)	NA
ASCT	1 (0.4)	NA	NA
Proportion of patients treated with immunosuppressant receiving specific treatment	190	134	NA
Azathioprine	113 (59)	70 (52)	NA
Methotrexate	79 (42)	61 (46)	NA
Cyclophosphamide	31 (16)	21 (16)	NA
Mycophenolate mofetil	2 (1)	NA	NA
Proportion of patients with oligoclonal bands in CSF			
Positive	223 (40)	328 (38)	NA
Negative	25 (5)	47 (5)	NA
Not recorded	305 (55)	491 (57)	NA
Annualized visit rate, median (IQR), visits/y of follow-up	1.7 (1.4)	1.6 (1.4)	0.03 ^a
Patients with relapse recorded following inclusion	320 (58)	NA	NA
Patients with bout-onset progressive MS	117 (21)	0	NA
No. of relapses during follow-up, median (IQR)	1 (2)	NA	NA
Relapse phenotype (n = 864) ^c			
Pyramidal	505 (58)	NA	NA
Sensory	206 (24)	NA	NA
Cerebellar	113 (13)	NA	NA
Brainstem	92 (11)	NA	NA
Bowel/bladder	73 (8)	NA	NA
Visual	52 (6)	NA	NA
Neuropsychology	25 (3)	NA	NA
Annualized relapse rate from symptom onset, median (IQR), relapses/y ^d	0.15 (0.18)	NA	NA

Abbreviations: ASCT, autologous stem cell transplant; CSF, cerebrospinal fluid; EDSS, Expanded Disability Status Scale; IQR, interquartile range; MS, multiple sclerosis; NA, not applicable; PPMS, primary progressive multiple sclerosis; PRMS, progressive-relapsing multiple sclerosis.

^a Cohen *d* formula adjusted for median where median (IQR) reported.

^b The number of patients treated with each disease-modifying therapy includes patients treated with multiple therapies during prospective follow-up and therefore does not sum to 100%.

^c The number of relapses with the specific phenotypes includes both monosymptomatic and polysymptomatic relapses and therefore does not sum to 100%.

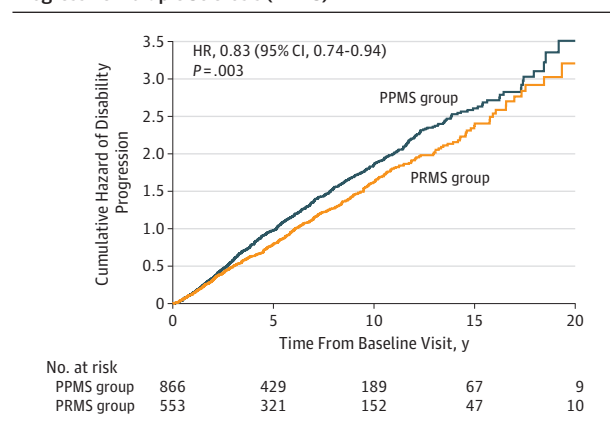
^d Number of relapses per year from symptom onset to final visit.

majority (505 of 864 [58%]) of relapses involved the pyramidal tract. The median annualized relapse rate from symptom onset to end of follow-up was 0.15 (quartiles, 0.08-0.26) relapses per year.

Primary Analysis

The preliminary univariable analysis unadjusted for confounding covariates revealed a lower risk of disability progression in patients with PRMS compared with PPMS (hazard ratio [HR],

Figure 2. Cumulative Hazard of Confirmed Disability Progression in Progressive-Relapsing Multiple Sclerosis (PRMS) vs Primary Progressive Multiple Sclerosis (PPMS)



Multivariable Andersen-Gill model adjusted for multiple potential confounders of disease outcomes. More than 1 progressive event per patient was allowed. HR indicates hazard ratio.

0.86; 95% CI: 0.78-0.96; $P = .005$). When adjusting for potential confounders of disease outcomes, a lower likelihood of confirmed disability progression in PRMS was maintained (HR, 0.83; 95% CI, 0.74-0.94; $P = .003$). The adjusted cumulative hazard of confirmed disability progression events in the PRMS and PPMS groups is visualized in **Figure 2**.

To further investigate the association between DMT and disease course, we incorporated an interaction term between the proportion of time receiving DMT and MS group into the multivariable model. The association between exposure to DMT (per 10% follow-up time spent receiving DMT) and likelihood of confirmed disability progression was dependent on allocation to PRMS or PPMS group (HR, 0.93; 95% CI, 0.90-0.97; $P < .001$).

Outcomes of the stratified models are outlined in **Table 2**. In the PRMS cohort ($n = 553$), we observed a 4% relative decrease in the hazard of confirmed disability progression events for each 10% increment in persistence receiving DMT (HR, 0.96; 95% CI, 0.94-0.99; $P = .01$). This association was not seen in the PPMS cohort ($n = 866$; HR, 1.02; 95% CI, 0.99-1.05; $P = .26$). In addition, we observed that male sex (PRMS group: HR, 1.19; 95% CI, 1.00-1.40; $P = .04$; PPMS group: HR, 1.22; 95% CI, 1.07-1.39; $P = .003$) and EDSS score at each base visit (PRMS group: HR, 1.09; 95% CI, 1.04-1.14; $P < .001$; PPMS group: HR, 1.04; 95% CI, 1.00-1.08; $P = .03$) increased the likelihood of confirmed disability progression within PRMS and PPMS groups. We did not observe any association between age (PRMS group: HR, 1.00; 95% CI, 0.99-1.00; $P = .40$; PPMS group: HR, 1.00; 95% CI, 0.99-1.00; $P = .14$) or proportion of follow-up receiving immunosuppression (PRMS group: HR, 1.00; 95% CI, 0.98-1.03; $P = .77$; PPMS group: HR, 1.00; 95% CI, 0.96-1.03; $P = .82$) and likelihood of confirmed disability progression.

Sensitivity Analyses

The first sensitivity analysis, which excluded relapse-related disability progression, identified 1356 patients from the original cohort. When accounting for relapse-related progression,

Table 2. Multivariable Analyses of the Cumulative Hazard of Confirmed Disability Progression Stratified by Group^a

Covariate	HR (95% CI)	
	PRMS Group	PPMS Group
Percentage of follow-up receiving disease-modifying therapy (per 10% increment of time receiving therapy)	0.96 (0.94-0.99) ^b	1.02 (0.99-1.05)
Percentage of follow-up receiving immunosuppression (per 10% increment of time receiving therapy) ^c	1.00 (0.98-1.03)	1.00 (0.96-1.03)
Men	1.19 (1.00-1.40) ^b	1.22 (1.07-1.39) ^b
Age at baseline visit, y	1.00 (0.99-1.00)	1.00 (0.99-1.00)
EDSS score at baseline visit	1.09 (1.04-1.14) ^{b,d}	1.04 (1.00-1.08) ^{b,d}
Annualized visit rate, visit/y	1.10 (1.07-1.14) ^b	1.26 (1.19-1.33) ^b

Abbreviations: EDSS, Expanded Disability Status Scale; HR, hazard ratio; PPMS, primary progressive multiple sclerosis; PRMS, progressive-relapsing multiple sclerosis.

^a HR (95% CI) from stratified Andersen-Gill analyses (stratified by group). Center and patient identification modeled as random effects. Percentage of follow-up receiving disease-modifying therapy and percentage of follow-up receiving immunosuppression presented as HR per 10% increments in proportion of follow-up receiving therapy.

^b $P < .05$.

^c Pooled immunosuppressants included azathioprine, methotrexate, cyclophosphamide, and mycophenolate mofetil.

^d Proportional hazards assumption was violated for this covariate.

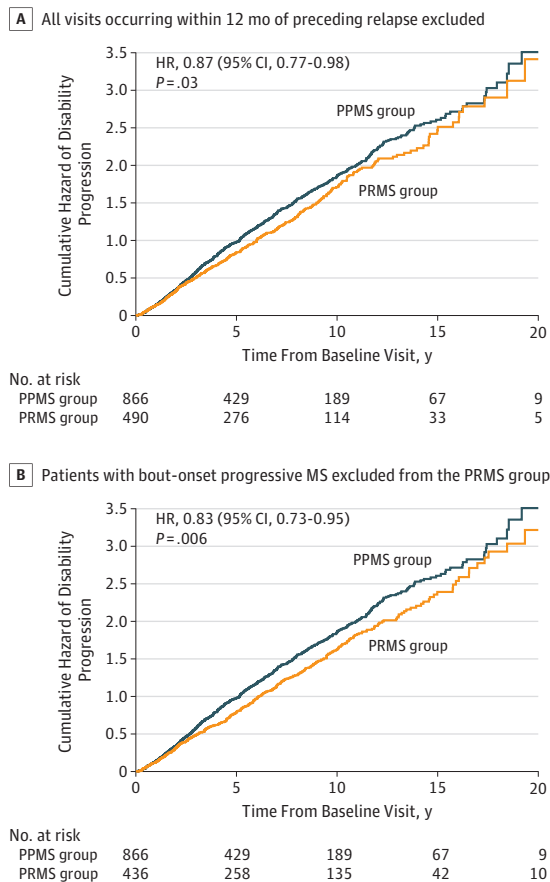
a reduced likelihood of confirmed disability progression in patients with PRMS vs those with PPMS was maintained (HR, 0.87; 95% CI, 0.77-0.98; $P = .03$) (**Figure 3A**). However, when stratified according to MS group (PRMS or PPMS), results of this sensitivity analysis revealed no association between proportion of follow-up time on DMT and cumulative hazard of disability progression in PRMS (HR, 1.10; 95% CI, 0.96-1.24; $P = .16$).

The second sensitivity analysis identified 436 patients with relapses that occurred later than the first 30 days of symptom onset. A reduced likelihood of disability progression in the PRMS group was maintained after excluding bout-onset progressive MS (HR, 0.83; 95% CI, 0.73-0.95; $P = .006$) (**Figure 3B**).

Discussion

In this study of 1419 patients from the international, observational MSBase cohort, we have demonstrated that the presence of superimposed relapse in progressive-onset MS is associated with a reduced progression of disability. Interestingly, we have shown that DMT reduces the likelihood of progression in progressive-onset MS with relapse but not in progressive-onset MS without relapse. The sensitivity analysis excluding disability progression events that were preceded by relapses showed that the association of DMT with disability progression is mediated through controlling relapse-related disability worsening. This suggests that relapses in progressive-onset MS, as a clinical correlate of episodic inflammatory activity, represent a positive prognostic marker and provide an opportunity to improve disease outcomes through prevention of relapse-related disability accrual.

Figure 3. Cumulative Hazard of Confirmed Disability Progression in Progressive-Relapsing Multiple Sclerosis (PRMS) vs Primary Progressive Multiple Sclerosis (PPMS) (Sensitivity Analyses)



A, Exclusion of all visits that occurred within 12 months of preceding relapse was performed to exclude relapse-associated disability progression. B, Exclusion of bout-onset progressive multiple sclerosis (MS) was performed to identify the effect of ongoing relapses on disability progression in PPMS.

To date and to our knowledge, there are limited epidemiologic data describing the characteristics of progressive-onset MS with superimposed relapse vs without. The ratio of men to women in our study (1:1.19 in PRMS and 1:1.20 in PPMS) was consistent with previous studies describing the clinical characteristics of PPMS and those comparing PRMS with PPMS.^{5,10-12,27,28} Where previous research has identified no difference in age at onset between patients with vs without relapse, we demonstrated that patients with PRMS were younger at disease onset compared with those with PPMS.¹² This may be attributed to a reduced time to diagnosis due to the bout onset of the disease in a proportion of patients with PRMS.

Additionally, few studies have described the relapse characteristics of patients with PRMS, to our knowledge.^{12,13} Tullman et al¹³ described a mean (SD) annualized relapse rate of 0.6 (0.8) in a cohort of 16 patients with PRMS. Our median annualized relapse rate of 0.15 (quartiles 0.08 to 0.26) is likely a conservative estimate, as it includes time from symptom on-

set prior to inclusion date. Consistent with previous findings, the domain most commonly affected by relapses was the motor system.^{12,13}

The role of superimposed relapse in disability accumulation in progressive-onset MS remains contested.¹¹⁻¹⁶ Several recent studies have identified superimposed relapse as an independent determinant of disability accrual.^{13,15,16} Conversely, other studies have identified no influence of superimposed relapse on the accumulation of disability in progressive-onset MS phenotypes.^{11,12,14} Our study established a negative association between superimposed relapses in progressive-onset MS and the likelihood of confirmed disability progression, which can be attributed to an association of treatment in the PRMS but not the PPMS group. Additionally, the findings of our first sensitivity analysis suggest that, in the absence of treatment effect, patients with PRMS continue to have a reduced likelihood of disability progression compared with those with PPMS. These findings may indicate a difference in the underlying natural history of PRMS vs PPMS when accounting for relapse-related progression.

A substantially greater proportion of patients with PRMS received DMT compared with PPMS (46% vs 21%). The relatively high proportion of patients with progressive-onset MS receiving DMT likely represents individual practices in tertiary centers, which we have accounted for by incorporating center as a random effect in our mixed-effects model. Persistence receiving DMT reduced the likelihood of progression in patients with PRMS, an association that was not observed in those with PPMS. This observation is in keeping with the outcomes of the INFORMS trial, which did not find any effect of fingolimod on 3-month confirmed disability progression in PPMS over 3 years.²⁹ Our own observational study extended this result to other DMT in patients with PPMS without superimposed episodic inflammatory activity.³⁰ This finding is also consistent with previous findings that patients with episodic clinical worsening or inflammatory changes on magnetic resonance imaging are more likely to respond to DMT.^{17,18,31,32} Furthermore, when relapse-related disability progression was excluded in a sensitivity analysis, the association of DMT in PRMS was no longer observed. Given that clinical relapse is seen as a clinical correlate of acute inflammatory changes, this finding suggests that DMT in progressive-onset MS mitigates acute episodic inflammation-associated disability accrual.³³

We confirmed the results of previous studies documenting male sex as a negative prognostic factor in PPMS.^{9,34,35} Compared with the role of DMT, time receiving immunosuppression did not influence likelihood of disability progression. The finding that a higher EDSS score at baseline visit increases the risk of disability accrual in both patient cohorts may be inherent to the definition of progression, where a baseline EDSS score greater than 5.5 requires only a half-step increment. However, given that higher EDSS scores are relatively infrequent, this may also reflect the association of patients with a more severe disability trajectory as described by Signori et al.³¹

Studies of observational data are subject to multiple biases. We have mitigated the impact of detection bias by adjusting the analyses for the frequency of recorded EDSS scores, which is representative of the frequency of clinical appoint-

ments. We have accounted for confounding by sex and baseline EDSS score by incorporating these as covariates. The median duration between symptom onset and inclusion was similar for both PRMS and PPMS groups (Cohen $d = 0.06$). By modeling age as a time-dependent covariate from date of inclusion, we have concurrently adjusted for disease duration from inclusion. We have also controlled for center-specific management and within-patient dependence by incorporating center and patient identification as random effects within our models. Finally, we have shown that the reduced rate of disability progression remains present when excluding patients with bout-onset progressive MS.

Limitations

The principal limitation of this study is inherent in the use of the EDSS as a clinical measure of disability. We have enhanced reliability of disability measurement by requiring neurostatus certification from involved centers.²⁴ The proportion of patients with progressive-onset MS in our cohort (6.4% prior to exclusion criteria) was lower than previously documented.²⁻⁶ This may represent a level of underreporting of progressive-onset MS by clinicians and thus may impact negatively on the generalizability of results. Furthermore, the MSBase observational plan does not require quantifiable disability change to confirm relapse. We have attempted to minimize erroneous report-

ing through standardized quality assurance procedures as described elsewhere.²³ Magnetic resonance imaging as a marker of inflammatory activity may provide further insight into the role of DMTs in progressive-onset MS; however, to date, we are limited by availability of imaging data in this cohort.

Conclusions

In patients with progressive-onset MS, superimposed relapses are associated with a lower risk of confirmed disability progression. This is most likely attributed to differences in natural disease course as well as the preventive association of DMT on relapse-related disability accrual in patients with progressive-onset disease and superimposed relapse. These findings provide further evidence for a progressive-onset MS phenotype with acute episodic inflammatory changes, thereby identifying patients who may respond to existing immunotherapies. Relapse, as a clinical correlate of acute episodic inflammation in progressive-onset MS, therefore constitutes a prognostic marker and a treatment target. Further research is needed to characterize the role of acute episodic inflammation in progressive-onset disease, in particular incorporating evidence of inflammatory magnetic resonance imaging activity as a predictor of disease course.

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REFERENCES

- Giovannoni G, Butzkueven H, Dhib-Jalbut S, et al. Brain health: time matters in multiple sclerosis. *Mult Scler Relat Disord*. 2016;9(suppl 1):S5-S48. doi:10.1016/j.msard.2016.07.003
- Antel J, Antel S, Caramanos Z, Arnold DL, Kuhlmann T. Primary progressive multiple sclerosis: part of the MS disease spectrum or separate disease entity? *Acta Neuropathol*. 2012;123(5):627-638. doi:10.1007/s00401-012-0953-0
- Compston A, Coles A. Multiple sclerosis. *Lancet*. 2008;372(9648):1502-1517. doi:10.1016/S0140-6736(08)61620-7
- Miller DH, Leary SM. Primary-progressive multiple sclerosis. *Lancet Neurol*. 2007;6(10):903-912. doi:10.1016/S1474-4422(07)70243-0
- Rice CM, Cottrell D, Wilkins A, Scolding NJ. Primary progressive multiple sclerosis: progress and challenges. *J Neurol Neurosurg Psychiatry*. 2013;84(10):1100-1106. doi:10.1136/jnnp-2012-304140
- Correale J, Gaitán MI, Ysraeli MC, Fiol MP. Progressive multiple sclerosis: from pathogenic mechanisms to treatment. *Brain*. 2017;140(3):527-546.
- Lublin FD, Reingold SC, Cohen JA, et al. Defining the clinical course of multiple sclerosis: the 2013 revisions. *Neurology*. 2014;83(3):278-286. doi:10.1212/WNL.0000000000000560
- Vukusic S, Confavreux C. Primary and secondary progressive multiple sclerosis. *J Neurol Sci*. 2003;206(2):153-155. doi:10.1016/S0022-510X(02)00427-6
- Confavreux C, Vukusic S, Adeleine P. Early clinical predictors and progression of irreversible disability in multiple sclerosis: an amnesic process. *Brain*. 2003;126(Pt 4):770-782. doi:10.1093/brain/awg081
- Confavreux C, Vukusic S. Natural history of multiple sclerosis: a unifying concept. *Brain*. 2006;129(Pt 3):606-616. doi:10.1093/brain/awl007
- Confavreux C, Vukusic S, Moreau T, Adeleine P. Relapses and progression of disability in multiple sclerosis. *N Engl J Med*. 2000;343(20):1430-1438. doi:10.1056/NEJM200011163432001
- Andersson PB, Waubant E, Gee L, Goodkin DE. Multiple sclerosis that is progressive from the time of onset: clinical characteristics and progression of disability. *Arch Neurol*. 1999;56(9):1138-1142. doi:10.1001/archneur.56.9.1138
- Tullman MJ, Oshinsky RJ, Lublin FD, Cutter GR. Clinical characteristics of progressive relapsing multiple sclerosis. *Mult Scler*. 2004;10(4):451-454. doi:10.1191/1352458504ms1059oa
- Kremenchutzky M, Cottrell D, Rice G, et al. The natural history of multiple sclerosis: a geographically based study: 7: progressive-relapsing and relapsing-progressive multiple sclerosis: a re-evaluation. *Brain*. 1999;122(Pt 10):1941-1950. doi:10.1093/brain/122.10.1941
- Paz Soldán MM, Novotna M, Abou Zeid N, et al. Relapses and disability accumulation in progressive multiple sclerosis. *Neurology*. 2015;84(1):81-88. doi:10.1212/WNL.0000000000001094
- Fabian MT, Lublin FD, Wolinsky J, The PROMISE Trial Study Group. P07197: Evaluation of progressive relapsing MS patients in the PROMISE Trial. *Neurology*. 2011;76(suppl 4):A613.
- Montalban X, Hauser SL, Kappos L, et al; ORATORIO Clinical Investigators. Ocrelizumab versus placebo in primary progressive multiple sclerosis. *N Engl J Med*. 2017;376(3):209-220. doi:10.1056/NEJMoa1606468
- Hawker K, O'Connor P, Freedman MS, et al; OLYMPUS trial group. Rituximab in patients with primary progressive multiple sclerosis: results of a randomized double-blind placebo-controlled multicenter trial. *Ann Neurol*. 2009;66(4):460-471. doi:10.1002/ana.21867
- Lublin FD. Disease activity free status in MS. *Mult Scler Relat Disord*. 2012;1(1):6-7. doi:10.1016/j.msard.2011.08.001
- Butzkueven H, Chapman J, Cristiano E, et al. MSBase: an international, online registry and platform for collaborative outcomes research in multiple sclerosis. *Mult Scler*. 2006;12(6):769-774. doi:10.1177/1352458506070775
- Polman CH, Reingold SC, Edan G, et al. Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald Criteria". *Ann Neurol*. 2005;58(6):840-846. doi:10.1002/ana.20703
- Polman CH, Reingold SC, Banwell B, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. *Ann Neurol*. 2011;69(2):292-302. doi:10.1002/ana.22366
- Kalincik T, Kuhle J, Pucci E, et al; MSBase Scientific Leadership Group and MSBase Study Group. Data quality evaluation for observational multiple sclerosis registries. *Mult Scler*. 2017;23(5):647-655. doi:10.1177/1352458516662728
- D'Souza M, Yaldizli Ö, John R, et al. Neurostatus e-scoring improves consistency of expanded disability status scale assessments: a proof of concept study. *Mult Scler*. 2017;23(4):597-603. doi:10.1177/1352458516657439
- Schumacher GA, Beebe G, Kibler RF, et al. Problems of experimental trials of therapy in multiple sclerosis: report by the panel on the evaluation of experimental trials in multiple sclerosis. *Ann N Y Acad Sci*. 1965;122:552-568. doi:10.1111/j.1749-6632.1965.tb20235.x
- Kalincik T, Cutter G, Spelman T, et al. Defining reliable disability outcomes in multiple sclerosis. *Brain*. 2015;138(Pt 11):3287-3298. doi:10.1093/brain/awv258
- Weinshenker BG, Bass B, Rice GP, et al. The natural history of multiple sclerosis: a geographically based study: I: clinical course and disability. *Brain*. 1989;112(Pt 1):133-146. doi:10.1093/brain/112.1.133
- Trojano M, Liguori M, Bosco Zimatore G, et al. Age-related disability in multiple sclerosis. *Ann Neurol*. 2002;51(4):475-480. doi:10.1002/ana.10147
- Lublin F, Miller DH, Freedman MS, et al; INFORMS study investigators. Oral fingolimod in primary progressive multiple sclerosis (INFORMS): a phase 3, randomised, double-blind, placebo-controlled trial. *Lancet*. 2016;387(10023):1075-1084. doi:10.1016/S0140-6736(15)01314-8
- Lorscheider J, Jokubaitis VG, Spelman T, et al; MSBase Study Group. Anti-inflammatory disease-modifying treatment and short-term disability progression in SPMS. *Neurology*. 2017;89(10):1050-1059. doi:10.1212/WNL.0000000000004330
- Signori A, Izquierdo G, Lugaes A, et al. Long-term disability trajectories in primary progressive MS patients: a latent class growth analysis. *Mult Scler*. 2017;24(5):642-652. doi:10.1177/1352458517038000
- Wolinsky JS, Narayana PA, O'Connor P, et al; PROMISE Trial Study Group. Glatiramer acetate in primary progressive multiple sclerosis: results of a multinational, multicenter, double-blind, placebo-controlled trial. *Ann Neurol*. 2007;61(1):14-24. doi:10.1002/ana.21079
- Filippi M, Rocca MA, Barkhof F, et al; Attendees of the Correlation between Pathological MRI findings in MS workshop. Association between pathological and MRI findings in multiple sclerosis. *Lancet Neurol*. 2012;11(4):349-360. doi:10.1016/S1474-4422(12)70003-0
- Harding KE, Wardle M, Moore P, et al. Modelling the natural history of primary progressive multiple sclerosis. *J Neurol Neurosurg Psychiatry*. 2015;86(1):13-19. doi:10.1136/jnnp-2014-307791
- Khaleeli Z, Ciccarelli O, Manfredonia F, et al. Predicting progression in primary progressive multiple sclerosis: a 10-year multicenter study. *Ann Neurol*. 2008;63(6):790-793. doi:10.1002/ana.21375