BRAIN
ORIGINAL ARTICLE

Progression is independent of relapse activity in early multiple sclerosis: a real-life cohort study

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Disability accrual in multiple sclerosis may occur as relapse-associated worsening or progression independent of relapse activity. The role of progression independent of relapse activity in early multiple sclerosis is yet to be established. The objective of this multicentre, observational, retrospective cohort study was to investigate the contribution of relapse-associated worsening and progression independent of relapse activity to confirmed disability accumulation in patients with clinically isolated syndrome and early relapsing-remitting multiple sclerosis, assessed within one year from onset and with follow-up ≥5 years ($n = 5169$). Data were extracted from the Italian Multiple Sclerosis Register. Confirmed disability accumulation was defined by an increase in Expanded Disability Status Scale score confirmed at 6 months, and classified per temporal association with relapses. Factors associated with progression independent of relapse activity and relapse-associated worsening were assessed using multivariable Cox regression models. Over a follow-up period of 11.5 ± 5.5 years, progression independent of relapse activity occurred in 1427 (27.6%) and relapse-associated worsening in 922 (17.8%) patients. Progression independent of relapse activity was associated with older age at baseline [hazard ratio (HR) = 1.19; 95% confidence interval (CI) 1.13–1.25, $P < 0.001$], having a relapsing–remitting course at baseline (HR = 1.44; 95% CI 1.28–1.61, $P < 0.001$), longer disease duration at baseline (HR = 1.56; 95% CI 1.28–1.90, $P < 0.001$), lower Expanded Disability Status Scale at baseline (HR = 0.92; 95% CI 0.88–0.96, $P < 0.001$) and lower number of relapses before the event (HR = 0.76; 95% CI 0.73–0.80, $P < 0.001$). Relapse-associated worsening was associated with younger age at baseline (HR = 0.87; 95% CI 0.81–0.93, $P < 0.001$), having a relapsing–remitting course at baseline (HR = 1.55; 95% CI 1.35–1.79, $P < 0.001$), lower Expanded Disability Status Scale at baseline (HR = 0.94; 95% CI 0.89–0.99, $P = 0.017$) and a higher number of relapses before the event (HR = 1.04; 95% CI 1.01–1.07, $P < 0.001$). Longer exposure to disease-modifying drugs was associated with a lower risk of both progression independent of relapse activity and relapse-associated worsening ($P < 0.001$). This study provides evidence that in an early relapsing-onset multiple sclerosis cohort, progression independent of relapse activity was an important contributor to confirmed disability accumulation. Our findings indicate that insidious progression appears even in the earliest phases of the disease, suggesting that inflammation and neurodegeneration can represent a single disease continuum, in which age is one of the main determinants of disease phenomenology.

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Received October 16, 2021. Revised February 12, 2022. Accepted March 04, 2022. Advance access publication March 24, 2022

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Keywords: relapsing multiple sclerosis; progression independent of relapse activity; relapse-associated worsening

Abbreviations: CDA = confirmed disability accrual; CIS = clinically isolated syndrome; DMT = disease-modifying therapies; EDSS = Expanded Disability Status Scale; PIRA = progression independent of relapse activity; PP = primary progressive; RAW = relapse-associated worsening; RR = relapsing–remitting; SP = secondary progressive

Introduction

Most patients with multiple sclerosis (~85%) experience an initial relapsing–remitting (RR) phase, in which discrete acute attacks can produce temporary or permanent disability accumulation (relapse-associated worsening, RAW).[1] On the other hand, after conversion to secondary-progressive (SP) multiple sclerosis or in patients with primary progressive (PP) multiple sclerosis, relentless accumulation of permanent disability usually occurs independently of relapses (progression independent of relapse activity, PIRA).[1] However, it remains uncertain whether the clinical distinction in RR, SP and PP multiple sclerosis serves to identify potentially different physiopathological mechanisms. Recent observations have challenged the phenotypical dualism between relapsing and progressive forms of multiple sclerosis.[2–4] In relapsing multiple sclerosis patients, the introduction of disease-modifying therapies (DMT), in particular of highly effective agents, can markedly reduce or suppress relapse activity, uncovering a 'silent' progression since the earliest phases of the disease. Indeed, in contemporary cohorts based on randomized clinical trials[3,4] and a single-centre data set at the University of California, San Francisco,[2] RAW and PIRA were both detectable in the relapsing phase of multiple sclerosis. In

one study, in particular, 80–90% of overall disability accumulation occurred independently of relapses.[4]

In the present multicentre study based on the Italian Multiple Sclerosis register, we investigated the relative contribution of RAW and PIRA to confirmed disability accumulation and conversion to SP multiple sclerosis in a real-world cohort of patients with clinically isolated syndrome (CIS) or early RR multiple sclerosis.

Materials and methods

Patients

Anonymized clinical records of patients with a first demyelinating event were extracted from the Italian Multiple Sclerosis Register[5] in July 2020. The Italian Multiple Sclerosis Register was approved by the Policlinico of Bari Ethics Committee and by the local ethics committees in all participating centres. Written informed consent was obtained from all enrolled patients in accordance with the Declaration of Helsinki. The minimum data set required for this study also comprised the main demographic characteristics, the date of disease onset, clinical course, follow-up visit dates, Expanded Disability Status Scale (EDSS)[6] scores recorded at each visit, the date of all relapses, start and end dates of all DMTs and DMT type. Quality assurance through online certification of EDSS competency is required at each participating site. Inclusion criteria were: patients with a first neurological evaluation within 1 year from the first demyelinating event; CIS or RR course at the first neurological evaluation; a minimum of three visits with EDSS evaluation; a minimum of 5 years follow-up. We excluded patients with a PP and SP course at the first neurological evaluation and those enrolled in randomized controlled trials. The baseline was defined as the first neurological evaluation with EDSS scoring. If the first evaluation occurred within 30 days from a relapse, baseline was defined as the following assessment with EDSS scoring performed outside of a relapse and within the first year from disease onset. When re-baseline was not possible, patients were excluded. Multiple sclerosis duration was calculated from the first demyelinating event. The follow-up time was defined as the time between the first and last available EDSS entry.

Confirmed disability accrual (CDA) was defined as ≥24-week confirmed disability increase from study baseline, measured by EDSS (increase ≥1.5 points if baseline EDSS = 0; increase ≥1.0 point if baseline EDSS ≥ 1.0 and ≤5.5; increase ≥0.5 point if baseline EDSS ≥ 6.0). The date of CDA was assigned at the first EDSS score at which an increase occurred. RAW events were defined as a subset of CDA events. In these, the initial disability increase from study baseline occurred ≤90 days after or ≤30 days before the onset of a relapse. Otherwise, PIRA was defined as a CDA event occurring >90 days after and >30 days before the onset of a relapse.

In a subgroup of patients with an MRI assessment ≤90 days before or ≤30 days after the CDA, progression independent of relapse and radiological activity (true PIRA) was defined as a CDA event occurring >90 days after and >30 days before the onset of a relapse and the presence of disease activity at the MRI evaluation (T_1 gadolinium-enhancing lesions and/or T_2 new/enlarging lesions). Otherwise, CDA events occurring ≤90 days after or ≤30 days before the onset of a relapse and/or the presence of disease activity at the MRI evaluation were defined as relapse and/or radiological activity associated worsening (true RAW).

A relapse was defined as the occurrence of new symptoms or the exacerbation of existing symptoms that persisted for 24 h or more in the absence of concurrent illness or fever and that occurred 30 days or more after a previous relapse.[7]

Transition to SP was defined according to the following definitions: (i) The neurologist definition, based on the subjective decision made by the neurologists according to the Lublin criteria for SP.[8,9] For this definition, the date of SP conversion assigned by the neurologists was used. (ii) A data-driven algorithm based on a previous published definition[10] with some modifications: a PIRA event with a minimum EDSS score of 4.0 at the time of conversion to SP multiple sclerosis and at the end of follow-up (final EDSS ≥ 4.0). For this definition, the date of PIRA event was assigned to SP conversion.

For DMT exposure, the proportion of time during which patients received DMT was defined by the recorded starting and ending dates. The total time a patient spent on treatment was calculated including any switches and gaps in treatment. We did not consider gaps <3 months as a therapy interruption. For DMT in which extended treatment effects are recognized, the estimated treatment effect duration was used to calculate the proportion of time that patients received therapy (6 months for mitoxantrone, rituximab, ocrelizumab; 5 years for alemtuzumab and autologous haematopoietic stem-cell transplantation; 2 months for natalizumab; 12 months for cladribine).[11]

The following sensitivity analyses were carried out: (i) by including patients with the first neurological evaluation on or after 1 January 2000; and (ii) CDA events were reclassified considering a time window of 365 days instead of 90 days as previously specified.

Statistical analysis

The baseline and follow-up characteristics were expressed as mean and SD or frequency and percentage for continuous and categorical covariates, respectively. Categorical and continuous variables were compared by using chi^2 statistic, Mann–Whitney and Kruskal–Wallis tests, as appropriate.

Factors associated with of first 24-week CDA (PIRA or RAW) and transition to SP were assessed using multivariable Cox proportional hazard regressions. The proportional hazard assumption was assessed through graphical inspection of residuals and scaled Schoenfeld residuals test. In case of assumption violation, interaction terms between the covariates and time were added to the model.[12] The date of the first visit with full EDSS evaluation was used as time origin of the model. In the absence of outcome occurrence, data were censored at the latest EDSS available. The exposure time was censored at the reaching of the outcome or at the last visit. Results of Cox regression models were expressed as hazard ratio (HR) and 95% confidence interval (CI) of reaching the outcomes. The multivariable modelling analyses on the first 24-week CDA (PIRA and RAW) were adjusted for the following covariates: sex (female versus male), symptom at onset (multifocal versus unifocal), age at first visit (≤20, 21–30, 31–40, 41–50, 51–60, ≥61 years), disease duration at first visit, disease course (RR versus CIS) and EDSS score at first visit, number of relapses before the event, percentage of time spent on DMT before the event, number of EDSS evaluations before the event. The risk of first RAW and first PIRA event in DMT-treated and -untreated patients was assessed through Kaplan–Meier survival curves.

The role of CDA type (PIRA or RAW) on the risk of SP transition according to the two different definitions was assessed in patients with one or more CDA events during the follow-up. The survival models on the risk of SP were adjusted for the following covariates: sex (female versus male), symptom at onset (multifocal versus

unifocal), age at first visit (≤20, 21–30, 31–40, 41–50, 51–60, ≥61 years), disease duration at first visit, disease course (RR versus CIS) and EDSS score at first visit, number of relapses before SP transition, percentage of time spent on DMT before SP transition, proportion of PIRA events (number of PIRA events/number of CDA events) before SP transition.

All statistical analyses were performed with SPSS version 25.0 and R version 4.1.2. *P*-value <0.05 was considered statistically significant.

Data availability

Anonymized data, not published in the article, will be shared on reasonable request from a qualified investigator.

Results

Data extraction was completed in July 2020. We had access to 49 741 register patients from 77 Italian multiple sclerosis centres. By applying inclusion and exclusion criteria, we identified 5169 patients (Fig. 1). Characteristics of the study sample are depicted in Table 1. Over a follow-up period of 11.5 ± 5.5 years, CDA occurred in 2349 (45.4%) patients. Patients with CDA had lower EDSS at baseline (1.5/1.6 versus 1.8), longer follow-up duration (12.7/13.7 versus 10.1 years) and were less frequently treated with DMT during the follow-up period before the event (15.3/22.8% versus 86.7%; Table 1). As for the first DMT, 2712 (93.2%) patients received platform therapies (interferons, glatiramer acetate, teriflunomide, dimethyl fumarate) while 199 (6.8%) received highly effective treatments (natalizumab, fingolimod, cladribine, alemtuzumab, mitoxantrone, rituximab, ocrelizumab). CDA patients had higher EDSS score at the end of the follow-up (3.7 versus 1.4; Table 1).

Factors associated with first RAW and PIRA event

PIRA ($n = 1427$) accounted for 60.7% of first CDA and were already detectable in the first years of follow-up, becoming more frequent than RAW since the second year (Fig. 2). On the whole, 682 out of 1427 (47.8%) first PIRA and 570 out of 922 (61.8%) first RAW events occurred during the first 5 years of follow-up.

In the multivariable analysis, RAW was associated with younger age at baseline (HR = 0.87; 95% CI 0.81–0.93, $P < 0.001$), having a RR course at baseline (HR = 1.55; 95% CI 1.35–1.79, $P < 0.001$), lower EDSS at baseline (HR = 0.94; 95% CI 0.89–0.99, $P = 0.017$), higher number of relapses before the event (HR = 1.04; 95% CI 1.01–1.07, $P < 0.001$) and shorter exposure to DMT before the event (HR = 0.16; 95% CI 0.12–0.20, $P < 0.001$; Table 2). The survival curve for the risk of RAW in treated and untreated patients is reported in Fig. 3A.

On the other hand, in the multivariable analysis, PIRA was associated with older age at baseline (HR = 1.19; 95% CI 1.13–1.25, $P < 0.001$), having a RR course at baseline (HR = 1.44; 95% CI 1.28–1.61, $P < 0.001$), longer disease duration at baseline (HR = 1.56; 95% CI 1.28–1.90, $P < 0.001$), lower EDSS at baseline (HR = 0.92; 95% CI 0.88–0.96, $P < 0.001$), lower number of relapses before the event (HR = 0.76; 95% CI 0.73–0.80, $P < 0.001$) and shorter exposure to DMT before the event (HR = 0.18; 95% CI 0.15–0.22, $P < 0.001$; Table 3). The survival curve for the risk of PIRA in treated and untreated patients is reported in Fig. 3B.

A subgroup of 359 of 2349 (15.3%) CDA patients had an MRI assessment close to the event. Spinal cord MRI was available in 217 cases (60.4%). According to clinical definition, 187 RAW (52.1%) and 172 PIRA (47.9%) occurred. Taking into account MRI activity, true PIRA decreased to 84 (23.4%), while the remaining 275 (76.6%) CDA events were reclassified as true RAW. Factors associated with true RAW and true PIRA were comparable to those of RAW and PIRA (Supplementary Tables 1 and 2). In particular, true RAW was associated with having an RR course at baseline (HR = 1.73; 95% CI 1.33–2.26, $P < 0.001$), lower EDSS at baseline (HR = 0.75; 95% CI 0.67–0.84, $P < 0.001$), higher number of relapses before the event (HR = 1.15; 95% CI 1.08–1.23, $P < 0.001$) and shorter exposure to DMT before the event (HR = 0.07; 95% CI 0.05–0.11, $P < 0.001$; Supplementary Table 1). True PIRA was associated older age at baseline (HR = 1.45; 95% CI 1.16–1.80, $P < 0.001$), having an RR course at baseline (HR = 2.20; 95% CI 1.33–3.65, $P = 0.002$), longer disease duration at baseline (HR = 2.48; 95% CI 1.10–5.60, $P = 0.029$) and shorter exposure to DMT before the event (HR = 0.10; 95% CI 0.06–0.19, $P < 0.001$; Supplementary Table 2).

PIRA, RAW and risk of secondary progressive multiple sclerosis

Over the follow-up period, 322 (6.2%) patients transitioned to SP multiple sclerosis according to the neurologist definition (14.1% of RAW and 12.9% of PIRA subjects), while 840 (16.3%) patients fulfilled the algorithmic definition of SP multiple sclerosis (27.0% of RAW and 41.4% of PIRA subjects; Table 1).

Focusing on patients with one or more CDA, SP course according to both definitions was associated with older age at baseline (HR = 1.28–1.31; 95% CI 1.15–1.49, $P < 0.001$), higher EDSS at baseline (HR = 1.38–1.48; 95% CI 1.26–1.55, $P < 0.001$) and lower number of relapses before transition (HR = 0.91; 95% CI 0.85–0.96, $P \leq 0.001$). SP multiple sclerosis according to the neurologist definition was associated with a lower proportion of PIRA events before transition (HR = 0.47; 95% CI 0.34–0.64, $P < 0.001$) and lower exposure to DMT before transition (HR = 0.25; 95% CI 0.18–0.35, $P < 0.001$). On the other hand, a higher proportion of PIRA events before transition was associated with a higher risk of SP multiple sclerosis according to the algorithmic definition (HR = 3.35; 95% CI 2.67–4.22, $P < 0.001$; Table 4).

Sensitivity analyses

The sensitivity analyses performed (i) by including patients with the first neurological evaluation on or after 1 January 2000; and (ii) reclassifying CDA events considering a time window of 365 days instead of 90 days confirmed the results of primary models (Supplementary Tables 3–10).

Discussion

Accumulation of disability in multiple sclerosis can occur as RAW, in which disability increases in relation to an overt inflammatory manifestation (relapse), and as PIRA, in which 'silent' disability accrual takes place in the absence of clinically evident inflammatory activity. RAW has been historically considered as the main epiphenomenon of RR multiple sclerosis and earliest phases of the disease, while PIRA is regarded as the feature of more advanced stages (SP multiple sclerosis) and PP multiple sclerosis. However, recent studies have challenged the current clinical distinction of relapsing and progressive forms, showing that in active relapsing multiple sclerosis a vast proportion of disability accrual can occur independently of relapses.[2–4]

In the present multicentre, observational, retrospective cohort study based on prospectively acquired clinical data, PIRA accounted for approximately two-thirds of disability worsening

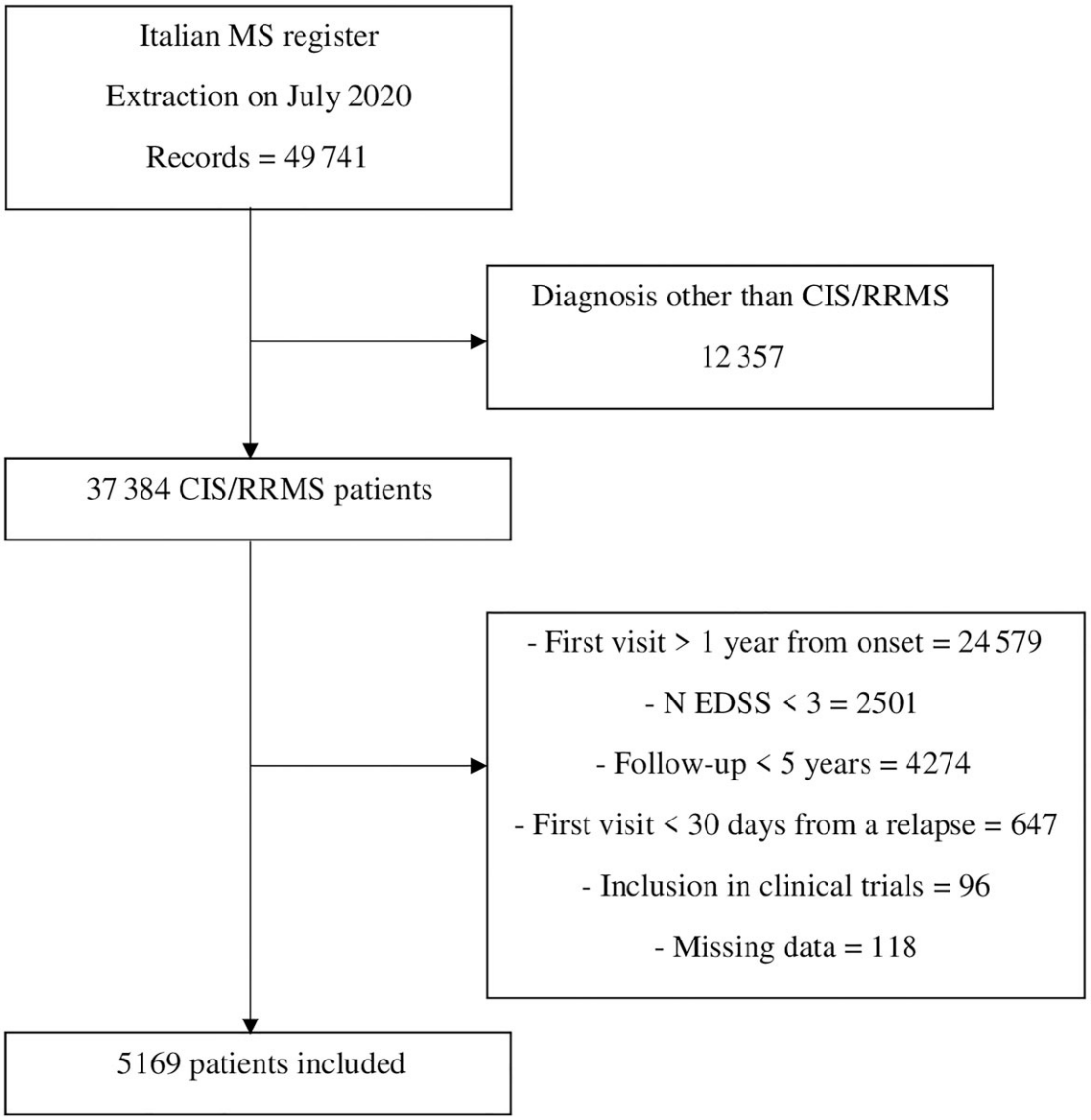

Figure 1 Study population flow chart. MS = multiple sclerosis.

events. Notably, all patients were diagnosed with CIS or RR multiple sclerosis and had the first EDSS evaluation within 1 year from onset. On the one hand, this could limit the generalizability of our findings, as the majority of people with multiple sclerosis actually attend the clinic >1 year after onset. Indeed, patients included in the present study were younger (31.8 ± 9.9 versus 37.7 ± 10.5 years, $P < 0.001$) and less disabled (EDSS score 1.7 ± 1.2 versus 2.3 ± 1.5, $P < 0.001$) than CIS and RR multiple sclerosis subjects with a first visit performed >1 year form disease onset. On the other hand, however, our cohort is ideal to establish a proof-of-principle about the role of PIRA in the first years of the disease. Therefore, our data clearly demonstrate that underlying disease progression is already relevant in the earliest phases of multiple sclerosis, suggesting that the disease could be considered as a continuum in which relapse-dependent and -independent disability worsening takes place since onset. The key determinant is the way by which CDA occurs appears to be age, with RAW events being more frequent in younger patients and PIRA predominant in older patients.

The influence of age on multiple sclerosis course has been consistently reported since the early epidemiological studies.[13] In the natural history cohorts, age at assignment of disability landmarks was not substantially influenced by the type of the initial course of multiple sclerosis (be it RR or progressive) and mean age at onset of the progressive phase was similar between PP multiple sclerosis and SP multiple sclerosis patients.[14,15] These observations induced a unitary hypothesis,[15] proposing multiple sclerosis as one-stage disorder in which acute focal recurrent inflammation and diffuse chronic progressive neurodegeneration are tightly intermingled since the outset of the disease. Several studies demonstrated the converse relationship between age and number of attacks,[16–18] with a florid inflammatory activity reported in younger patients and a gradual relapse decrease in frequency with age.

At the neuropathological and immunological levels, the role of age could be explained, at least in part, by immunosenescence[19] and inflamm-aging[20] processes. In younger subjects,

Table 1 Characteristics of the study sample

	First CDA				
	Total $n = 5169$	RAW $n = 922$	PIRA $n = 1427$	No CDA $n = 2820$	P
Age at baseline, year, mean ± SD	31.8 ± 9.9	30.3 ± 9.8	34.0 ± 10.1	31.1 ± 9.6	**RAW versus no CDA 0.033** **PIRA versus no CDA <0.001** **RAW versus PIRA <0.001**
Sex, female *n* (%)	3503 (67.8)	645 (70.0)	956 (67.0)	1902 (67.4)	0.280
Disease course at baseline, *n* (%)					0.575
CIS	2082 (40.3)	373 (40.5)	590 (41.3)	1119 (39.7)	
RR	3087 (59.7)	549 (59.5)	837 (58.7)	1701 (60.3)	
Disease duration at baseline, year, mean ± SD	0.42 ± 0.27	0.42 ± 0.27	0.44 ± 0.28	0.41 ± 0.27	RAW versus no CDA 0.417 **PIRA versus no CDA <0.001** RAW versus PIRA 0.313
EDSS at baseline, mean ± SD	1.7 ± 1.2	1.5 ± 1.1	1.6 ± 1.3	1.8 ± 1.2	**RAW versus no CDA <0.001** **PIRA versus no CDA <0.001** RAW versus PIRA 0.621
Onset topography, *n* (%)					0.082
Unifocal	4402 (85.2)	774 (83.9)	1198 (84.0)	2430 (86.2)	
Multifocal	767 (14.8)	148 (16.1)	229 (16.0)	390 (13.8)	
Follow-up duration, year, mean ± SD	11.5 ± 5.5	13.7 ± 6.5	12.7 ± 5.9	10.1 ± 4.5	**RAW versus no CDA <0.001** **PIRA versus no CDA <0.001** **RAW versus PIRA 0.001**
Number of visits during follow-up, mean ± SD	15.4 ± 12.5	9.2 ± 8.8	11.1 ± 10.3	19.6 ± 13.0	**RAW versus no CDA <0.001** **PIRA versus no CDA <0.001** **RAW versus PIRA <0.001**
DMT during follow-up, *n* (%)	2911 (56.3)	141 (15.3)	326 (22.8)	2444 (86.7)	**<0.001**
Percentage of follow-up spent on DMT, mean ± SD	46.4 ± 44.7	13.5 ± 33.0	18.8 ± 36.9	71.1 ± 35.6	**RAW versus no CDA <0.001** **PIRA versus no CDA <0.001** **RAW versus PIRA 0.018**
Final EDSS, mean ± SD	2.5 ± 2.0	3.7 ± 2.2	3.7 ± 2.0	1.4 ± 1.0	**RAW versus no CDA <0.001** **PIRA versus no CDA <0.001** RAW versus PIRA 0.999
SP at follow-up, *n* (%)	322 (6.2)	130 (14.1)	184 (12.9)	8 (0.3)	**<0.001**
Algorithmic definition SP at follow-up, *n* (%)	840 (16.3)	249 (27.0)	591 (41.4)	0 (0.0)	**<0.001**

Significant *P*-values are highlighted in bold.

immunological responses are mainly driven by the adaptive system, which strongly characterizes active lesions of relapsing multiple sclerosis. With advancing age, immunosenescence decreases the activity and efficacy of the adaptive system, while a 'chronic' inflammatory status, mainly sustained by the innate immune system, tends to emerge. In this scenario, 'silent' neurodegeneration and disease progression can occur. Interestingly, activation of microglia in the perilesional normal-appearing white matter as detected by translocator protein–PET imaging has been linked to later PIRA over 4-year follow-up period.[21] Moreover, smouldering lesions, in which the slowly expanding edge is mainly populated by activated microglia, are considered as markers of the progressive phase.[22] Therefore, it would be of interest to assess whether the presence of smouldering lesions is associated with higher risk of PIRA.

A higher number of relapses was associated with RAW events, while PIRA was related to lower relapse rate before CDA. This finding is not surprising, as a more 'inflammatory' clinical phenotype is more likely to determine RAW, while a lower number of relapses reveals underlying 'silent' progression, as shown in recent observations.[2,4] For instance, in the pooled analysis of two randomized clinical trials on ocrelizumab in RR multiple sclerosis, the suppression of relapse activity by both interferon β-1a and ocrelizumab uncovered the presence of relentless progression even in a phase of the disease in which relapses usually dominate.[4]

Other factors associated with CDA, in particular the RR disease course and lower EDSS score at baseline, were shared by both RAW and PIRA and were consistent with well-acknowledged predictors of disability worsening in early multiple sclerosis.[23]

Importantly, a longer exposure to DMT was associated with a lower risk of any CDA, independent of the phenotype. The efficacy of DMT on PIRA, in particular the superiority of ocrelizumab over interferon β-1a, has already been reported in the pooled analysis of OPERA-1 and OPERA-2 trials.[4] While the prevention of RAW is a straightforward outcome of inflammatory and relapse activity suppression, the effectiveness of DMT on PIRA also indicates that 'silent' progression could be, at least in part, sustained by an inflammatory component. It has to be noted that our study is purely clinically grounded, and we cannot exclude that acute inflammatory activity on MRI have contributed to PIRA. Indeed, in the subgroup of patients in which MRI assessment close to CDA was available, the proportion of true PIRA was reduced to 23.4% of observed CDA. However, even in this analysis, DMT was effective in reducing the risk of true PIRA, suggesting that disability worsening was still attributable to an ongoing inflammatory activity.

It has been argued that the same underlying process that causes silent progression could be responsible for SP multiple sclerosis when the march of clinical worsening is more evident.[2] Indeed, patients with PIRA were characterized by accelerated brain atrophy over time,[2] and PIRA has been proposed as a criterion to mark, on

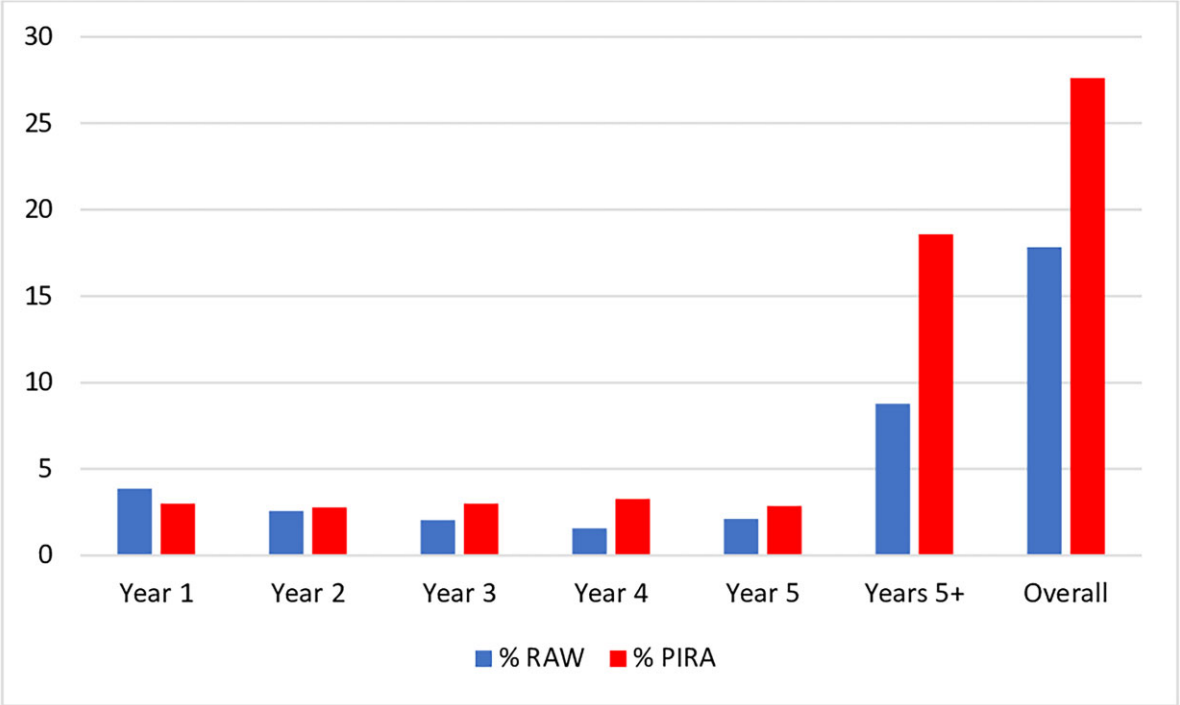

Figure 2 Percentage of RAW and PIRA events over the follow-up period.

Table 2 Factors associated with first RAW event

	HR	95% CI	P
Sex (female versus male)	1.13	0.98–1.30	0.091
Onset topography (multifocal versus unifocal)	0.97	0.81–1.16	0.733
Age at baseline	0.87	0.81–0.93	<0.001
Disease course at baseline (RR versus CIS)	1.55	1.35–1.79	<0.001
Disease duration at baseline	1.12	0.87–1.44	0.384
EDSS at baseline	0.94	0.89–0.99	0.017
Percentage of time spent on DMT before the event	0.16	0.12–0.20	<0.001
Number of relapses before the event[a]	1.04	1.01–1.07	0.004
Number of EDSS evaluations before the event[a]	0.86	0.85–0.88	<0.001

[a]Adjusted for an interaction term with time.

clinical grounds, the putative onset of the progressive phase in relapsing multiple sclerosis subjects.[4] However, in our study, the occurrence of PIRA and, therefore, the potential onset of progression in the earliest phases of the disease appeared to be undetected or misclassified by the clinicians. The neurologist definition identified only 322 (6.2%) SP patients, while the more objective definition, derived from that proposed by Lorscheider and colleagues,[10] identified 840 (16.3%) SP cases. Moreover, unexpectedly, in multivariable models, SP course according to the neurologist definition was mostly driven by RAW events, while a higher proportion of PIRA was associated with a higher risk of SP according to the algorithmic definition. These differences could be explained, at least in part, by the selection of patients having the first visit within 1 year from disease onset. It is possible that, in the first years of the disease, neurologists may be prone to misclassification and feel hesitant to irreversibly assign an SP course, significantly narrowing the availability of effective and approved DMT options.

In our opinion, these findings are in line with the hypothesis of multiple sclerosis as a single disease entity, in which RAW and PIRA can coexist since disease onset, both contributing to the accumulation of irreversible disability and the transition to the progressive phase. The exhaustion of compensatory mechanisms and age-related neurodegeneration are likely to play a role in the onset of the formerly described 'amnesic phenomen',[24] i.e. the self-perpetuating accumulation of disability after a threshold of irreversible disability has been reached, irrespective (amnesic) of the prior clinical history of the disease. Of note, in our sample, beyond the CDA event, older age at baseline, and a higher baseline EDSS score were the main prognostic factors associated with a higher risk of transition to SP multiple sclerosis. These results are in agreement with those from previous studies on predictors of the onset of the progression phase following relapsing multiple sclerosis.[25–30]

In the interpretation of the study findings, a few limitations should be taken into account. The analysis of factors associated with disability worsening was limited to the first CDA event and on the EDSS score alone. In a previous observation, PIRA was largely driven by other disability measures, such as the Timed 25-Foot Walk Test and the 9-Hole Peg Test[4]; therefore, an underestimation of PIRA events in our sample cannot be excluded. However, this issue did not likely affect the main study finding, that is, the occurrence of PIRA in a relevant proportion of multiple sclerosis patients even in the earliest phases of the disease. On the other hand, we cannot exclude that unnoticed (milder) relapses or MRI inflammatory activity may have contributed to PIRA events. Indeed, in the subgroup of subjects in which MRI assessment was available, the proportion of PIRA was reduced. Nevertheless, also in this subsample true PIRA events were still

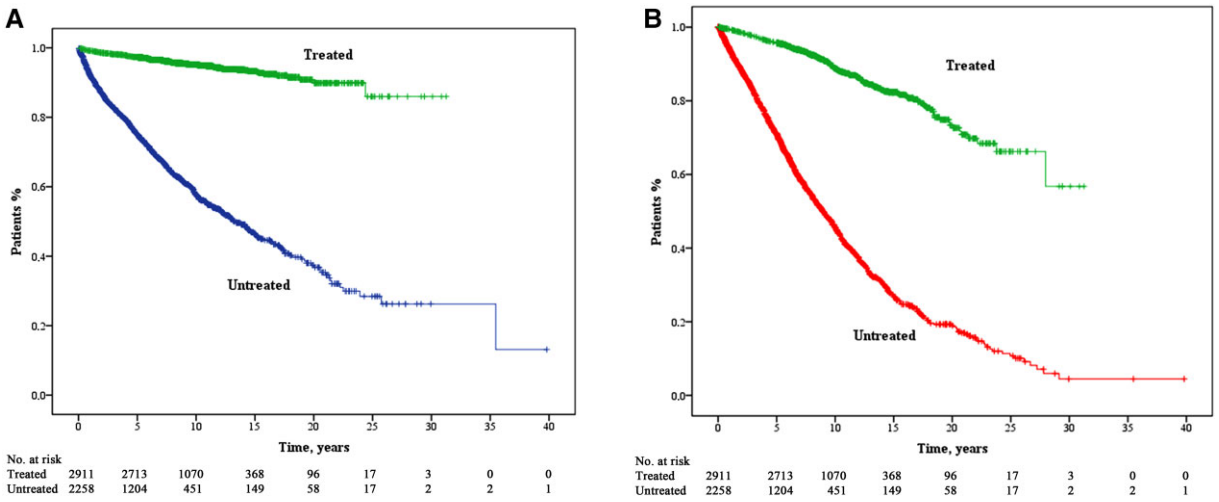

Figure 3 Risk of first RAW (A) and first PIRA (B) in DMT-treated and -untreated patients (Kaplan–Meier survival curves, log rank $P < 0.001$).

Table 3 Factors associated with first PIRA event

	HR	95% CI	P
Sex (female versus male)	0.99	0.89–1.11	0.857
Onset topography (multifocal versus unifocal)	1.02	0.89–1.18	0.763
Age at baseline	1.19	1.13–1.25	<0.001
Disease course at baseline (RR versus CIS)	1.44	1.28–1.61	<0.001
Disease duration at baseline	1.56	1.28–1.90	<0.001
EDSS at baseline	0.92	0.88–0.96	<0.001
Percentage of time spent on DMT before the event	0.18	0.15–0.22	<0.001
Number of relapses before the event[a]	0.76	0.73–0.80	<0.001
Number of EDSS evaluations before the event[a]	0.91	0.90–0.92	<0.001

[a]Adjusted for an interaction term with time.

Table 4 Factors associated with SP in patients with one or more CDA event

	Neurologist definition SP			Algorithmic definition SP		
	HR	95% CI	P	HR	95% CI	P
Sex (female versus male)	0.84	0.64–1.09	0.191	0.95	0.82–1.09	0.434
Onset topography (multifocal versus unifocal)	1.65	1.22–2.23	0.001	1.04	0.87–1.24	0.707
Age at baseline	1.31	1.15–1.49	<0.001	1.28	1.19–1.37	<0.001
Disease course at baseline (RR versus CIS)	1.12	0.84–1.49	0.457	1.04	0.89–1.21	0.631
Disease duration at baseline	0.88	0.53–1.45	0.617	1.09	0.84–1.42	0.504
EDSS at baseline	1.38	1.26–1.52	<0.001	1.48	1.42–1.55	<0.001
Percentage of time spent on DMT before the event	0.25	0.18–0.35	<0.001	0.97	0.79–1.17	0.721
Number of relapses before the event[a]	0.91	0.85–0.96	0.001	0.91	0.88–0.94	<0.001
Percentage of PIRA events	0.47	0.34–0.64	<0.001	3.35	2.67–4.22	<0.001

[a]Adjusted for an interaction term with time.

detectable and the main findings of multivariable survival analyses were comparable to those obtained in the whole sample. Finally, although DMT exposure was defined as the proportion of time during which patients received treatments, an immortal time bias cannot be completely ruled out, particularly for events that naturally take longer to occur.

Despite these limitations, our data add to previous observations as they are based on a large real life, multicentric cohort of patients followed-up for a substantial period of time from the earliest stages of the disease and include SP multiple sclerosis as outcome and DMT effect in the analysis. The study findings are consistent with the view of multiple sclerosis as a single continuum, in which RAW and PIRA occur since the earliest phases of the disease, with age representing one of the main determinants of disease phenomenology. In the first years of the disease, although frequent, PIRA events and their potential relationship with the onset of progression appear to be neglected by the clinicians, leading to an underestimation or a delay in the identification of transition to SP multiple sclerosis. Furthermore, the study underscores the potential role of early DMT treatment in preventing the occurrence of any CDA,[31] both RAW and PIRA, and, in turn, in slowing down the transition to the progressive phase, overall reducing the burden of the disease in the long term.

Funding

No funding was received towards this work.

Competing interests

E.P. received compensation for travel grants, participation in advisory board and/or speaking activities from Biogen, Merck Serono, Sanofi, Teva and Novartis; and serves on the editorial board of *Frontiers in Neurology and Brain Sciences*. L.P. received research support from Novartis, Biogen and speaker honoraria from Teva. L.R. received research support from Novartis. R.T. received funding for travel or speaker honoraria from Alfa Wasserman, Bayer, Biogen, CLS Bering, Merck Serono, Novartis,

SanofiAventis, Roche and Teva. D.S. received honoraria as a consultant on scientific advisory boards by Bayer-Schering, Novartis and Sanofi-Aventis and compensation for travel from Novartis, Biogen, Sanofi Aventis, Teva and Merck. A.L. served as a Biogen, Merck, Mylan, Novartis, Roche, Sanofi/Genzyme and Teva Advisory Board Member. She received congress and travel/accommodation expense compensations or speaker honoraria from Biogen, Merck, Mylan, Novartis, Sanofi/Genzyme, Teva and Fondazione Italiana Sclerosi Multipla (FISM). Her institutions received research grants from Novartis. E.C. received research grants and honoraria as a speaker and member of advisory boards by: Almirall, Bayer, Biogen Idec, Merck Serono, Novartis, Sanofi Genzyme, Teva and Roche. F.P. received honoraria for speaking activities by Almirall, Bayer Schering, Biogen Idec, Merck Serono, Novartis, Roche, Sanof Genzyme and Teva; he also served as an advisory board member to the following companies: Bayer Schering, Biogen Idec, Merck Serono, Novartis, Roche, Sanof Genzyme and Teva; he was also funded by Pfizer and FISM for epidemiological studies; and received grants for congress participation from Almirall, Bayer Schering, Biogen Idec, Merck Serono, Novartis, Roche, Sanof Genzyme and Teva. P.C. received honoraria for speaking, consultation fees or travel to attend scientific events from Merck Serono, Biogen Idec, Novartis, Teva and Roche. He also received institutional research support from Merck-Serono, Novartis and Roche. G.T.M. received personal compensation from Serono, Biogen, Novartis, Roche and Teva for public speaking and advisory boards. V.B.M. received grants to attend scientifc congresses or speaker honoraria from Biogen, Merck-Serono, Novartis, Roche, Sanofi/Genzyme and Teva. G.S. received grants to attend scientific congresses or speaker honoraria from Biogen, Merck-Serono, Novartis, Roche, Sanofi/Genzyme and Teva. F.G. received grants to attend scientific congresses or speaker honoraria from Biogen, Merck-Serono, Novartis, Roche, Sanof/Genzyme and Teva. R.B. has served on scientific advisory boards for Biogen, Merck-Serono, Novartis and Sanofi-Genzyme; received research support from Almirall, Bayer, Biogen, Merck-Serono, Novartis and Sanofi-Genzyme; received support for travel and congress from Biogen, Roche, Merck-Serono, Sanofi-Genzyme and Teva; received honoraria for speaking engagement from Biogen, Merck-Serono, Novartis and Sanofi-Genzyme. U.A. received grants to attend scientific congresses or speaker honoraria from Biogen, Merck-Serono, Novartis, Roche, Sanof/Genzyme and Teva. P.I. received grants to attend scientific congresses or speaker honoraria from Biogen, Merck-Serono, Novartis, Roche, Sanof/Genzyme and Teva. M. Filippi is Editor-in-Chief of the *Journal of Neurology*; and received compensation for consulting services and/or speaking activities from Bayer, Biogen Idec, Merck Serono, Novartis, Roche, Sanofi Genzyme, Takeda, and Teva Pharmaceutical Industries; and still receives research support from Biogen Idec, Merck Serono, Novartis, Roche, Teva Pharmaceutical Industries, Italian Ministry of Health, Fondazione Italiana Sclerosi Multipla and ARiSLA (Fondazione Italiana di Ricerca per la SLA). M.T. received travel and/or speaker honoraria from Sanofi Aventis, Genzyme, Biogen Idec, Teva, Merck, Serono and Novartis; and reported receiving speaker honoraria and research grants to her institution from and serving on advisory boards of Biogen, Merck Serono and Novartis. M.P.A. served on scientific advisory boards for and has received speaker honoraria and research support from Biogen Idec, Merck Serono, Bayer Schering Pharma and Sanofi Aventis, and serves on the editorial board of *Multiple Sclerosis Journal* and *BMC Neurology*. All other authors report no competing interests.

Supplementary material

Supplementary material is available at *Brain* online.

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