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Disease-modifying drugs can reduce disability progression in relapsing multiple sclerosis

Maria Pia Amato,[1,2] Mattia Fonderico,[1] Emilio Portaccio,[3] Luisa Pastò,[1] Lorenzo Razzolini,[1] Elio Prestipino,[1] Angelo Bellinvia,[1] Laura Tudisco,[1] Roberto Fratangelo,[1] Giancarlo Comi,[4] Francesco Patti,[5] Giovanna De Luca,[6] Vincenzo Brescia Morra,[7] Eleonora Cocco,[8] Carlo Pozzilli,[9] Patrizia Sola,[10] Roberto Bergamaschi,[11] Giuseppe Salemi,[12] Matilde Inglese,[13,14] Enrico Millefiorini,[15] Simonetta Galgani,[16] Mauro Zaffaroni,[17] Angelo Ghezzi,[17] Marco Salvetti,[18,19] Giacomo Lus,[20] Ciro Florio,[21] Rocco Totaro,[22] Franco Granella,[23] Marika Vianello,[24] Maurizia Gatto,[25] Giancarlo Di Battista,[26] Umberto Aguglia,[27] Francesco Ottavio Logullo,[28] Marta Simone,[29] Giuseppe Lucisano,[30,31] Pietro Iaffaldano[31] and Maria Trojano[31] on behalf of the Italian Multiple Sclerosis Register Centers Group

An ever-expanding number of disease-modifying drugs for multiple sclerosis have become available in recent years, after demonstrating efficacy in clinical trials. In the real-world setting, however, disease-modifying drugs are prescribed in patient populations that differ from those included in pivotal studies, where extreme age patients are usually excluded or under-represented. In this multicentre, observational, retrospective Italian cohort study, we evaluated treatment exposure in three cohorts of patients with relapsing-remitting multiple sclerosis defined by age at onset: paediatric-onset ($\leqslant$18 years), adult-onset (18–49 years) and late-onset multiple sclerosis ($\geqslant$50 years). We included patients with a relapsing-remitting phenotype, $\geqslant$5 years follow-up, $\geqslant$3 Expanded Disability Status Scale (EDSS) evaluations and a first neurological evaluation within 3 years from the first demyelinating event. Multivariate Cox regression models (adjusted hazard ratio with 95% confidence intervals) were used to assess the risk of reaching a first 12-month confirmed disability worsening and the risk of reaching a sustained EDSS of 4.0. The effect of disease-modifying drugs was assessed as quartiles of time exposure. We found that disease-modifying drugs reduced the risk of 12-month confirmed disability worsening, with a progressive risk reduction in different quartiles of exposure in paediatric-onset and adult-onset patients [adjusted hazard ratios in non-exposed versus exposed >62% of the follow-up time: 8.0 (3.5–17.9) for paediatric-onset and 6.3 (4.9–8.0) for adult-onset, $P < 0.0001$] showing a trend in late-onset patients [adjusted hazard ratio = 1.9 (0.9–4.1), $P = 0.07$]. These results were confirmed for a sustained EDSS score of 4.0. We also found that relapses were a risk factor for 12-month confirmed disability worsening in all three cohorts, and female sex exerted a protective role in the late-onset cohort. This study provides evidence that sustained exposure to disease-modifying drugs decreases the risk of disability accumulation, seemingly in a dose-dependent manner. It confirms that the effectiveness of disease-modifying drugs is lower in late-onset patients, although still detectable.

1 Department NEUROFARBA, University of Florence, Florence, Italy
2 IRCCS Fondazione Don Carlo Gnocchi, Florence, Italy
3 SOC Neurologia, Ospedale San Giovanni di Dio, AUSL Toscana Centro1, Florence, Italy
4 San Raffaele Hospital - INSPE; Vita-Salute San Raffaele University, Milan, Italy
5 Dipartimento di Scienze Mediche e Chirurgiche e Tecnologie Avanzate, GF Ingrassia, Sez. Neuroscienze, Centro Sclerosi Multipla, University of Catania, Catania, Sicily, Italy
6 Centro Sclerosi Multipla, Clinica Neurologica, Policlinico SS Annunziata, Università 'G. d'Annunzio', Chieti-Pescara, Italy

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7 Department of Neuroscience, Reproductive and Odontostomatological Sciences, Federico II University, Napoli, Italy
8 Centro Sclerosi Multipla, ASSL Cagliari (ATS Sardegna); Dipartimento di Scienze Mediche e Sanità Pubblica, University of Cagliari, Cagliari, Italy
9 Multiple Sclerosis Center, S. Andrea Hospital, Dept. of Human Neuroscience, Sapienza University, Rome, Italy
10 Centro Malattie Demielinizzanti - Dipartimento di Neuroscienze, Azienda Ospedaliero-Universitaria/OCSAE, UO Neurologia, University of Modena and Reggio Emilia, Modena, Italy
11 IRCCS Mondino Foundation, Pavia, Italy
12 Department of Biomedicine, Neuroscience and Advanced Diagnostics, University of Palermo, Palermo, Sicily, Italy
13 Department of Neurosciences, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health (DINOGMI), University of Genoa, Genoa, Italy
14 Ospedale Policlinico San Martino, IRCCS, Genoa, Italy
15 Multiple Sclerosis Center, Policlinico Umberto I, Sapienza University, Rome, Italy
16 multiple sclerosis Centre, Department of Neurosciences, S. Camillo - Forlanini Hospital, Rome, Italy
17 ASST della Valle Olona, Multiple Sclerosis Center, S. Antonio Abate Hospital of Gallarate, Gallarate, Italy
18 Department of Neuroscience, Mental Health and Sensory Organs, Faculty of Medicine and Psychology, Centre for Experimental Neurological Therapies, S. Andrea Hospital/Sapienza University, Rome, Italy
19 IRCCS Istituto Neurologico Mediterraneo (INM) Neuromed, Rome, Italy
20 Università della Campania Luigi Vanvitelli, Naples, Italy
21 Multiple Sclerosis Center, Cardarelli Hospital, Naples, Italy
22 Demyelinating Diseases Center, Department of Neurology, San Salvatore Hospital, L'Aquila, Italy
23 Unit of Neurosciences, Department of Medicine and Surgery, University of Parma, Italy
24 Centro Sclerosi Multipla - Ospedale Regionale 'Ca' Foncello', Neurology Unit, Treviso, Italy
25 Ospedale Generale Regionale 'F. Miulli', Neurology Unit, Acquaviva delle Fonti (BA), Italy
26 Centro Sclerosi Multipla, ASL Roma 1, PO S. Filippo Neri, Rome, Italy
27 Department of Medical and Surgical Sciences, Magna Graecia University of Catanzaro, Neurology Unit, Catanzaro, Italy
28 Centro Sclerosi Multipla—UOC Neurologia—Ospedale di Macerata, Macerata, Italy
29 Child Neuropsychiatric Unit, Department of Biomedical Sciences and Human Oncology, University 'Aldo Moro' of Bari, Policlinico Piazza G. Cesare, 11, 70121, Bari, Italy
30 Center for Outcomes Research and Clinical Epidemiology, Pescara, Italy
31 Department of Basic Medical Sciences, Neurosciences and Sense Organs, University of Bari 'Aldo Moro' Policlinico, Bari, Italy

Correspondence to: Mattia Fonderico
Department NEUROFARBA, University of Florence, Florence, Italy
E-mail: mattia.fonderico1991@gmail.com

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Abbreviations: AOMS = adult-onset multiple sclerosis; CDW = confirmed disability worsening; DMT = disease-modifying therapy; EDSS = Expanded Disability Status Scale; LOMS = late-onset multiple sclerosis; POMS = paediatric-onset multiple sclerosis; RCT = randomized clinical trial; RRMS = relapsing-remitting multiple sclerosis

Introduction

Multiple sclerosis is an inflammatory demyelinating disease of the CNS that is characterized by inflammation, demyelination, and degenerative changes. Most individuals are diagnosed with multiple sclerosis at age 20–40 years (Finlayson, 2004). Paediatric-onset multiple sclerosis (POMS), before the age of 18, represents 3–10% of the whole multiple sclerosis population (Iaffaldano *et al.*, 2017), while late-onset multiple sclerosis (LOMS), after the age of 50, now accounts for 3–5% of all multiple sclerosis diagnosis (Vaughn *et al.*, 2019). Age at onset plays an important prognostic role, not fully understood, and may impact disease course and treatment response. Clinic (Tutuncu *et al.*, 2013) and population (Confavreux and Vukusic, 2006*a*; Kremenchutzky *et al.*, 2006) based studies suggested that the onset of the progressive phase and time to Expanded Disability Status Scale (EDSS) milestones is an age-dependent phenomenon, independent of the initial course of multiple sclerosis. Nevertheless, predicting disability accumulation only on chronological age would be an oversimplification. In both POMS and adult-onset multiple sclerosis (AOMS), the strongest predictor for reaching the EDSS milestones is age at clinical onset: the earlier the onset of disease, the younger the age at which the main disability milestones are reached (Confavreux and Vukusic, 2006*b*; Renoux *et al.*, 2007). Moreover, considering disease progression solely as an age-dependent phenomenon would hide the high variability in progression rate observed among individuals with multiple sclerosis (Tremlett *et al.*, 2006).

Additionally, age at onset influences the response to disease-modifying therapy (DMT). A recent meta-analysis of the main randomized clinical trials (RCTs) demonstrated that the efficacy of DMTs on disability worsening has an inverse correlation with increasing age (Weideman *et al.*, 2017). These clinical results seem to be in line with the

progressive weakening of both adaptive and innate immune system called immunosenescence (Musella *et al.*, 2018). This model, however, was based on RCTs that generally excluded patients younger than 18 or older than 50 years. As the prevalence of LOMS is increasing (Vaughn *et al.*, 2019), data regarding DMT effectiveness in this group of patients are warranted. This is even more relevant due to comorbidity and possibly higher risks of treatment-related adverse events in this age group (Schweitzer *et al.*, 2019). As for the paediatric counterpart, clinical trials in POMS subjects are extremely limited, also due to ethical considerations on the use of placebo owing to highly active disease in this population (Waubant *et al.*, 2019). Although most of the DMTs are not licensed for POMS, their off-label prescription is increasing in this subpopulation (Iaffaldano *et al.*, 2017). Therefore, benefit to risk balance and treatment decision-making in these extreme age populations present unique age- and disease-related challenges.

As a sizeable proportion of paediatric and older patients are treated in the real-world setting, registry-based cohort studies represent a major source of data to elucidate the above issues.

The research question, addressed in this multicentre study based on the Italian multiple sclerosis register, was whether and how treatment response differ in three cohorts of patients with relapsing-remitting multiple sclerosis (RRMS) defined by age at onset: POMS ($\leqslant$18 years), AOMS (18–49 years) and LOMS ($\geqslant$50 years).

Patients and methods

Ethics statement

The Italian iMedWeb network 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, or in the case of POMS from their parents, in accordance with the Declaration of Helsinki.

Study design

We conducted a multicentre, observational, retrospective cohort study based on prospectively acquired clinical data. The aim was to evaluate how the effectiveness of DMTs can vary in three subgroups of RRMS patients defined by their age at onset. Anonymized clinical records of patients with a first demyelinating event were extracted from the Italian multiple sclerosis register (Trojano *et al.*, 2019) in November 2018. Inclusion criteria were: patients with a first neurological evaluation within 3 years from the first demyelinating event; a minimum of three visits with EDSS evaluation; a minimum of 5 years follow-up. We excluded patients with a primary progressive course and those enrolled in RCTs. 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.

The Italian multiple sclerosis register protocol requires, for all patients registered, a minimum baseline dataset (Trojano *et al.*, 2019). The minimum dataset required for this study also comprised clinical course, follow-up visit dates, EDSS scores recorded at each visit, date of all relapses, start and end dates of all DMT commencements and DMT type. Quality assurance through online certification of EDSS competency is required at each participating site.

RRMS patients meeting the eligibility criteria were divided into three subgroups according to their age at the first demyelinating event: POMS ($\leqslant$18 years), AOMS (19–49 years) and LOMS ($\geqslant$50 years).

We considered the following outcomes: 12-month confirmed disability worsening (CDW) and EDSS 4.0. As an exploratory outcome, we also considered the time to EDSS 6.0. A minimum of three visits per patient over a minimum period of 12 months, with complete EDSS assessment, was required to assess the first 12-month CDW.

CDW events were defined as $\geqslant$12-month confirmed increase of: $\geqslant$1.0 point for those with a baseline EDSS score between 1.0 and 5.5, inclusive; and $\geqslant$1.5 points for those with a baseline EDSS score of 0. Irreversible assignment of EDSS score 4.0 or 6.0 was defined as reaching of EDSS score 4.0 or 6.0 with all subsequent EDSS scores being either equal to these scores, or greater. EDSS recorded within 30 days from a clinical relapse were excluded to avoid artificial increase of EDSS score changes over time. The Italian MS Register protocol stipulates a required biannual update of the minimum dataset, but patients with less frequent visits were not excluded from the analyses. The baseline of the study was the first visit. For each subgroup, we evaluated as possible prognostic predictors sex, symptom at onset (multifocal/unifocal), number of relapses, number of EDSS evaluations and treatment exposure.

Statistical analysis

The baseline and follow-up characteristics were expressed as mean and standard deviation (SD) or frequency and percentage for continuous and categorical covariates, respectively. Categorical and continuous variables were compared by using χ^2 statistic and Kruskal-Wallis test, respectively. Non-parametric tests were most conservative.

Predictors of first 12-month CDW and EDSS 4.0 were assessed using multivariable Cox proportional hazard regressions. The date of the first visit with full EDSS evaluation was used as time origin of the model to mitigate a possible immortal time bias. In the absence of a worsening or reaching EDSS 4.0, data were censored at the latest EDSS available. Results of Cox regression models were expressed as hazard ratio (HR) and 95% confidence interval (CI) of reaching the outcomes. We performed different models for each subgroup of patient (POMS, AOMS and LOMS). The multivariable modelling analyses were adjusted for the following covariates: sex (female versus male), symptom at onset (multifocal versus unifocal), number of relapses, percentage of time spent before the outcome (in quartiles) and EDSS score at first visit. As the visit frequency was different across the three cohorts, we further adjusted all the multivariate models for the number of EDSS evaluations. For DMT exposure, we considered the total time a patient spent on treatment, including any switches and gaps in treatment. During the survival time, we did not consider gaps $\leqslant$3 months as a therapy interruption. As the percentage spent on DMT before the outcome was not normally distributed, a statistical stratification in

four groups, of equal size (quartiles), was used. The fourth quartile (Q4), including patients who were above the 75th percentile, was regarded as the reference class in the Cox models. In the present study, 'never treated' was the patient group that did not receive any DMT treatment before the first disability worsening or EDSS 4.0 attainment. The exposure time was censored at the reaching of the outcome or at the last visit if a worsening event had not yet occurred. A sensitivity analysis was carried out by including patients registered after 2000.

All statistical analyses were performed with R version 3.2.0 and *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

Baseline and follow-up characteristics

The data extraction was completed in November 2018. We had access to 55 669 register patients from 77 Italian centres. By applying inclusion and exclusion criteria, we identified 646 POMS, 8473 AOMS and 382 LOMS patients at the first demyelinating event (Fig. 1). The baseline and follow-up characteristics of the three cohorts are described in Tables 1 and 2.

There was a comparable female prevalence in all three groups. Spinal cord symptoms at onset were more frequent in LOMS ($P < 0.001$), whereas optic neuritis was more represented in the two younger cohorts. LOMS patients had, on average, a higher mean EDSS baseline score compared with the other two cohorts ($P < 0.001$).

As for the first treatment (Table 1), we distinguished between moderately effective DMTs (IFNβ1a, IFNβ1b, glatiramer, dimethyl fumarate, teriflunomide and azathioprine) and highly effective DMTs (monoclonal antibodies, mitoxantrone, cladribine and fingolimod) (Rotstein and Montalban, 2019).

The vast majority of patients in the three groups received a moderately effective DMT as first treatment. Compared with the other two groups, a higher proportion of LOMS subjects (21.8%) were never exposed to a DMT (Table 1).

The mean follow-up time was ~12 years for POMS, 11 years for AOMS and 9 years for LOMS patients ($P < 0.0001$). Mean disease duration was longer in POMS (13 years) compared with AOMS (12 years) and LOMS (10 years). The first EDSS evaluation was made, on average, within 13 months from disease onset in all the three cohorts ($P = 0.28$). The mean number of EDSS evaluations was higher in the two younger cohorts ($P < 0.0001$); moreover, LOMS patients exhibited lower annualized EDSS evaluations compared with the two younger cohorts ($P = 0.005$).

All three cohorts received the first DMT, on average, within 3 years from symptom onset, without any significant difference ($P = 0.568$). LOMS patients spent a lower percentage of follow-up time under a DMT than the other two cohorts (5.8 versus 6.8 and 7.2 years of AOMS and POMS patients, respectively $P = 0.003$). During the follow-up period, the mean number of relapses was higher in POMS (6.8) and AOMS (5.3) compared with LOMS (3.7) subjects, $P < 0.0001$.

The frequency of switch from moderate to highly effective DMTs was significantly higher in the POMS and AOMS compared with the LOMS cohort, $P < 0.0001$ (Table 2).

In terms of outcome, the LOMS cohort experienced a higher rate of 12-month CDW and accrual of EDSS 4.0 than the two younger cohorts ($P < 0.0001$), although the number of EDSS evaluations was lower (Table 2).

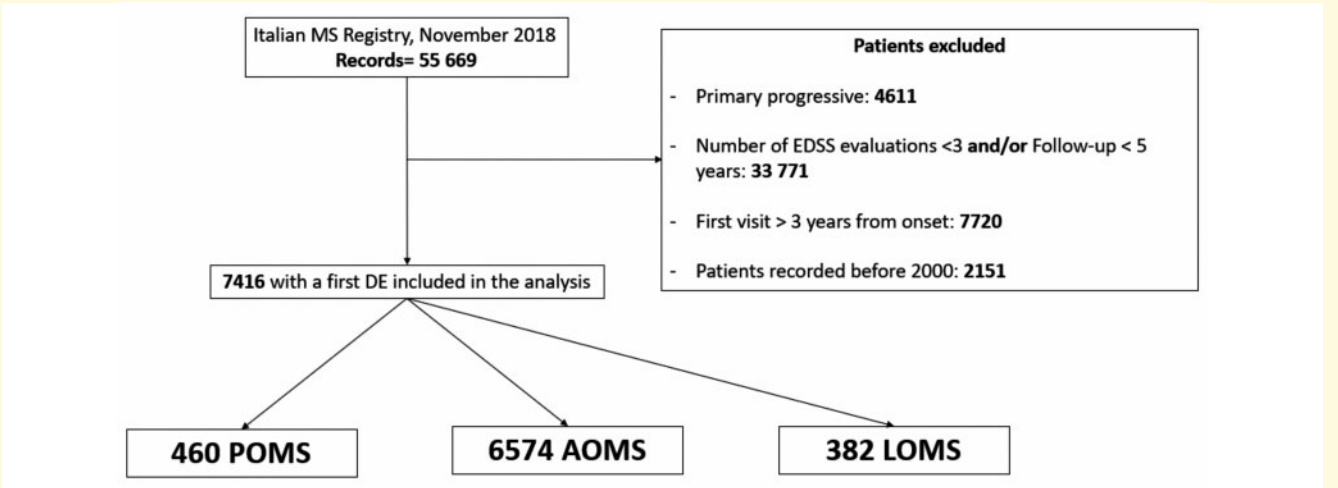

Figure 1 Flow-chart showing patients selection. DE = demyelinating event.

Table 1 Baseline characteristics of the three cohorts defined by age at onset

Total, *n* = 9567	Paediatric-onset *n* = 646	Adult-onset *n* = 8473	Late-onset *n* = 448	*P*-value
Age at onset, mean ± SD	15.48 ± 2.43	31.21 ± 7.91	54.29 ± 9.20	<0.0001
Sex, female *n* (%)	448 (69.35)	5704 (67.32)	299 (66.74)	0.541
CIS topography *n* (%)				
Optic neuritis	156 (24.15)	1818 (21.48)	67 (15.02)	<0.0001
Brainstem symptoms	140 (21.67)	1646 (19.44)	90 (20.18)	
Spinal symptoms	82 (12.69)	1659 (19.60)	113 (25.34)	
Supratentorial symptoms	170 (26.32)	2167 (25.60)	124 (27.80)	
Combination of symptoms	98 (15.17)	1175 (13.88)	52 (11.66)	
First EDSS score, mean ± SD	1.52 ± 1.12	1.68 ± 1.21	2.39 ± 1.51	<0.0001
Treatment *n* (%)				
First DMT, moderate efficacy	583 (90.25)	7378 (87.01)	336 (75.0)	0.167
First DMT, high efficacy	34 (5.26)	336 (4.36)	14 (4.00)	
Never treated	29 (4.48)	759 (8.96)	98 (21.8)	
Percentage of follow-up spent on DMT	43.52 ± 27.04	39.99 ± 27.47	36.52 ± 27.71	0.003
Time to first DMT, days	959.46 ± 1341.97	880.46 ± 1132.51	835.28 ± 919.36	0.568

Moderate efficacy DMTs comprise IFNβ1a, IFNβ1b, glatiramer, dimethyl fumarate, teriflunomide and azathioprine. High efficacy DMTs comprise monoclonal antibodies, mitoxantrone, cladribine and fingolimod.
CIS = clinically isolated syndrome.

Table 2 Follow-up characteristics of the three cohorts defined by age at onset

Total *n* = 9567	Paediatric-onset MS *n* = 646	Adult-onset MS *n* = 8473	Late-onset MS *n* = 448	*P*-value
Follow-up, years, mean ± SD	12.18 ± 6.09	11.30 ± 5.79	9.47 ± 3.60	<0.0001
Disease duration, years, mean ± SD	13.18 ± 5.81	12.27 ± 5.85	10.03 ± 9.83	<0.0001
Time to first EDSS evaluation, months, mean ± SD	13.01 ± 10.33	12.46 ± 10.12	13.02 ± 10.35	0.28
Number of EDSS evaluations per patient, mean ± SD	21.73 ± 13.30	19.72 ± 13.24	15.81 ± 10.07	<0.0001
Mean annualized EDSS evaluation, mean ± SD	1.94 ± 1.08	1.87 ± 1.12	1.76 ± 1.00	0.005
Time to first DMT, days, mean ± SD	959.46 ± 1341.97	880.46 ± 1132.51	835.28 ± 919.36	0.5685
Time spent on DMT, years	7.18 ± 4.14	6.81 ± 4.77	5.83 ± 3.79	<0.0001
Quartiles of time spent on DMT, *n* (%) (*n* = 6353)				
Q1 (1–19.6%)	115 (22.07)	1416 (25.17)	58 (28.16)	0.099
Q2 (19.7–40.4%)	113 (21.69)	1420 (25.24)	55 (26.70)	
Q3 (40.5–65.5%)	149 (28.60)	1393 (24.76)	46 (22.33)	
Q4 (>65.5%)	144 (27.64)	1397 (24.83)	47 (22.82)	
Number of relapses, mean ± SD	6.80 ± 5.08	5.26 ± 3.94	3.72 ± 2.39	<0.0001
Mean annualized assessment rate of relapses	0.59 ± 0.37	0.50 ± 0.34	0.42 ± 0.27	<0.0001
Patients who changed from moderate to high efficacy DMT, *n* (%)	253 (38.57)	1819 (21.47)	42 (9.37)	<0.0001
Outcome, *n* (%)				
12 months CDW	128 (19.81)	2078 (24.52)	150 (33.48)	<0.0001
EDSS 4.0[a]	67 (10.81)	1496 (18.66)	130 (34.57)	<0.0001

Moderate efficacy DMTs comprise IFNβ1a, IFNβ1b, glatiramer, dimethyl fumarate, teriflunomide and azathioprine. High efficacy DMTs comprise monoclonal antibodies, mitoxantrone, cladribine and fingolimod.
[a]For the outcome EDSS 4.0 the patients with a first EDSS ⩾ 4 were excluded.

Treatment effect on 12-month confirmed disability worsening and EDSS 4.0

Table 3 shows the results of the adjusted multivariate Cox regression model for the outcome 12-month CDW, whereas Table 4 shows the results for the outcome EDSS 4.0. To mitigate for possible secular trend bias, the same models were run as sensitivity analyses by including only patients registered after 2000 (Tables 5 and 6). The results were adjusted for sex, type of onset (unifocal versus multifocal), number of relapses and of EDSS evaluations and, for the EDSS 4.0 outcome, for baseline EDSS score. We evaluated the treatment effect with a time-dependent approach considering the total time a patient spent on treatment, including any switches and gaps. We further divided exposure time into quartiles. The fourth quartile (Q4) was the quartile of patients who were above the 75th percentile and has been

Table 3 Multivariate Cox model for the first 12-month confirmed disability worsening in the overall sample (*n* = 9567)

Overall sample, *n* = 9567		Paediatric-onset MS *n* = 646	Adult-onset MS *n* = 8473	Late-onset MS *n* = 448
Number of events, *n* (%)		128 (19.8%)	2078 (24.5%)	150 (33.4)
Variable	**Reference class**	**aHR (95%CI)**	**aHR (95%CI)**	**aHR (95%CI)**
Sex, female	Male	1.15 (0.78–1.70)	1.04 (0.95–1.14)	0.74 (0.53–1.04)
Symptom at onset, multifocal	Unifocal	1.06 (0.67–1.68)	0.87 (0.78–0.98)*	1.13 (0.69–1.85)
Number of relapses	–	1.17 (1.14–1.20)**	1.17 (1.17–1.18)**	1.40 (1.32–1.48)**
Number of EDSS evaluations	–	0.97 (0.95–0.98)**	0.98 (0.98–0.99)**	0.98 (0.96–1.00)*
DMT exposure[a]	Q4[b]			
Never treated		7.98 (3.55–17.95)**	6.27 (4.92–7.98)**	1.95 (0.94–4.06)
Q1		3.69 (1.61–8.48)*	4.46 (3.47–5.73)**	1.10 (0.47–2.54)
Q2		3.59 (1.53–8.44)*	3.07 (2.37–3.97)**	1.40 (0.61–3.25)
Q3		2.94 (1.22–7.06)*	2.30 (1.76–3.02)**	0.85 (0.32–2.28)

aHR = adjusted hazard ratio; MS = multiple sclerosis.
[a]For DMT exposure, we considered the total time a patient spent on treatment, including any switches and/or gaps.
[b]We divided exposure time into quartiles. The fourth quartile (Q4) is the quartile of patients who were above the 75th percentile and has been regarded as the reference class in the Cox models. 'Never treated' were the patients who did not receive any DMT before the first 12 months disability worsening or EDSS 4.0. The exposure time was censored at the reaching of the outcome or most recent visit if a worsening event had not yet occurred.
*P-value < 0.05; **P-value < 0.001.

Table 4 Multivariate Cox model for the risk of reaching EDSS 4 in the overall sample (*n* = 9012)

Overall sample (*n* = 9012)		Paediatric-onset MS *n* = 620	Adult-onset MS *n* = 8016	Late-onset MS *n* = 374
Number of events, *n* (%)		67 (10.81)	1496 (18.66)	130 (34.57)
Variable	**Reference class**	**aHR (95% CI)**	**aHR (95% CI)**	**aHR (95% CI)**
Sex, female	Male	0.91 (0.53–1.59)	0.97 (0.87–1.08)	0.42 (0.29–0.60)**
Symptom at onset, multifocal	Unifocal	0.92 (0.49–1.71)	1.03 (0.90–1.19)	1.52 (0.87–2.64)
First EDSS	–	1.48 (1.12–1.97)*	1.76 (1.66–1.86)**	1.89 (1.55–2.29)**
Number of relapses	–	1.15 (1.12–1.18)**	1.17 (1.16–1.17)**	1.49 (1.39–1.59)**
Number of EDSS evaluations	–	0.99 (0.97–1.01)	1.00 (1.00–1.01)*	1.00 (0.99–1.02)
DMT exposure[a]	Q4[b]			
Never treated		7.06 (2.05–24.34)*	10.34 (7.42–14.40)**	9.36 (1.30–67.67)*
Q1		4.76 (1.35–16.76)*	6.67 (4.74–9.38)**	9.21 (1.22–69.51)*
Q2		3.86 (1.07–13.97)*	4.44 (3.13–6.30)**	3.80 (0.48–29.81)
Q3		3.17 (0.87–11.58)	3.44 (2.39–4.95)**	2.95 (0.35–24.64)

aHR = adjusted hazard ratio; MS = multiple sclerosis.
[a]For DMT exposure, we considered the total time a patient spent on treatment, including any switches and/or gaps.
[b]We divided exposure time into quartiles. The fourth quartile (Q4) is the quartile of patients who were above the 75th percentile and has been regarded as the reference class in the Cox models. 'Never treated' were the patients who did not receive any DMT before the first 12-month disability worsening or EDSS 4.0. The exposure time was censored at the reaching of the outcome or most recent visit if a worsening event had not yet occurred.
*P-value < 0.05; **P-value < 0.001.

regarded as the reference class in the Cox models. In the present study, patients who did not receive any DMT before reaching the two clinical outcomes represented the 'never treated' class. The exposure time was censored at the reaching of the outcome or the last visit if a worsening event had not occurred yet.

Female sex was a protective factor for LOMS patients decreasing the risk of reaching EDSS 4.0 of 58% [adjusted HR (aHR) = 0.42, 95% CI 0.29–0.60, $P < 0.001$]. Sensitivity analyses confirmed the same protective role with a similar magnitude.

A higher number of relapses was associated with an increased risk of both 12-month CDW and EDSS 4.0 in all the three cohorts (Tables 3 and 4). These results were also confirmed in the sensitivity analyses, with an adjusted HR for 12-month-CDW and EDSS 4.0 ranging from 1.15 to 2.11 (Tables 5 and 6).

As for type of onset (multifocal versus unifocal), a multifocal onset showed a weak protective effect for a first 12-month CDW in AOMS (aHR = 0.87, 95% CI = 0.78–0.98, $P < 0.005$) but did not significantly influence the risk of reaching the EDSS 4.

The most significant predictive factor of 12-month CDW was DMT treatment, which was especially evident in the two younger cohorts. In POMS and AOMS, increasing the DMT exposure resulted in a stepwise reduction of ~2 points

Table 5 Multivariate Cox model for the first 12-month confirmed disability worsening performed in patients with disease onset after 2000 (*n* = 7416)

Overall sample (*n* = 7416)		Paediatric-onset MS *n* = 460	Adult-onset MS *n* = 6574	Late-onset MS *n* = 382
Number of events, *n* (%)		52 (11.30)	1205 (18.33)	115 (30.10)
Variable	**Reference class**	**aHR (95%CI)**	**aHR (95%CI)**	**aHR (95%CI)**
Sex, female	Male	0.64 (0.33–1.25)	1.02 (0.90–1.15)	0.74 (0.51–1.09)
Symptom at onset, multifocal	Unifocal	1.06 (0.44–2.55)	0.95 (0.81–1.11)	1.54 (0.86–2.77)
Number of EDSS evaluations	–	0.95 (0.93–0.98)*	0.97 (0.97–0.98)**	0.99 (0.97–1.01)
Number of relapses	–	1.41 (1.33–1.49)**	1.37 (1.36–1.39)**	1.40 (1.31–1.49)**
DMT exposure[a]	Q4[b]			
Never treated		9.71 (2.72–34.61)**	6.96 (5.14–9.43)**	1.82 (0.83–3.99)
Q1		6.88 (1.92–24.72)*	4.21 (3.07–5.76)**	0.81 (0.32–2.03)
Q2		2.25 (0.60–8.50)	4.17 (3.03–5.73)**	1.61 (0.68–3.86)
Q3		2.34 (0.61–8.93)	2.45 (1.75–3.43)**	0.43 (0.11–1.66)

aHR = adjusted hazard ratio; MS = multiple sclerosis.
[a]For DMT exposure, we considered the total time a patient spent on treatment, including any switches and/or gaps.
[b]We divided exposure time into quartiles. The fourth quartile (Q4) is the quartile of patients who were above the 75th percentile and has been regarded as the reference class in the Cox models. 'Never treated' were the patients who did not receive any DMT before the first 12-month disability worsening or EDSS 4.0. The exposure time was censored at the reaching of the outcome or most recent visit if a worsening event had not yet occurred.
*P-value < 0.05; **P-value < 0.001.

Table 6 Multivariate Cox model for the risk of reaching EDSS 4.0 in patients with disease onset after 2000 (*n* = 7006)

Overall sample (*n* = 7006)		Paediatric-onset MS *n* = 444	Adult-onset MS *n* = 6234	Late-onset MS *n* = 328
Number of events, *n* (%)		25 (5.63)	857 (13.75)	104 (31.71)
Variable	**Reference class**	**aHR (95%CI)**	**aHR (95%CI)**	**aHR (95%CI)**
Sex, female	Male	0.82 (0.30–2.24)	0.80 (0.69–0.92)*	0.44 (0.29–0.67)**
Symptom at onset, multifocal	Unifocal	0.74 (0.20–2.72)	0.83 (0.69–0.99)*	2.04 (1.07–3.90)*
Number of EDSS evaluations	–	0.96 (0.91–1.01)	1.01 (1.01–1.02)**	1.01 (0.99–1.03)
Number of relapses	–	1.60 (1.42–1.80)**	1.31 (1.29–1.32)**	1.48 (1.38–1.59)**
First EDSS	–	2.16 (1.24–3.78)*	1.91 (1.76–2.06)**	1.87 (1.51–2.32)**
DMT exposure[a]	Q4[b]			
Never treated		30.39 (5.14–179.76)**	8.97 (6.13–13.11)**	7.75 (1.07–56.38)*
Q1		7.19 (1.17–44.14)*	6.69 (4.54–9.87)**	8.04 (1.07–60.42)*
Q2		6.46 (1.11–37.44)*	3.96 (2.65–5.92)**	3.38 (0.42–27.50)
Q3		2.98 (0.45–19.83)	1.33 (0.85–2.08)**	2.73 (0.33–22.91)

aHR = adjusted hazard ratio; MS = multiple sclerosis.
[a]For DMT exposure, we considered the total time a patient spent on treatment, including any switches and/or gaps.
[b]We divided exposure time into quartiles. The fourth quartile (Q4) is the quartile of patients who were above the 75th percentile and has been regarded as the reference class in the Cox models. 'Never treated' were the patients who did not receive any DMT before the first 12-month disability worsening or EDSS 4.0. The exposure time was censored at the reaching of the outcome or most recent visit if a worsening event had not yet occurred.
*P-value < 0.05; **P-value < 0.001.

in the rate of 12-month CDW. In the same cohorts, adjusting for baseline EDSS and number of EDSS evaluations, we found similar results considering the risk of reaching EDSS 4.0. Furthermore, the sensitivity models confirmed that the protective role of treatment in POMS and AOMS is related to the cumulative time spent under treatment, seemingly in a time-dependent manner.

As for the LOMS cohort, there was a trend towards a DMT treatment-related lower risk of 12-month CDW. We found that never treated, and the first quartile classes were at higher risk of EDSS 4.0 (Table 4). The sensitivity analyses performed on patients registered after 2000 confirmed the results of the primary model (Tables 5 and 6).

As an exploratory analysis, we investigated the risk of reaching EDSS 6.0. In the AOMS cohort, treatment exposure confirmed its protective role in all the four quartiles. In the LOMS cohort, never treated patients confirmed to be at higher risk of reaching this disability milestone. In the POMS cohort, where only 4.8% of the subjects reached EDSS 6.0, the results were not statistically significant (Supplementary Table 1).

Discussion

In recent years, various modern DMTs for multiple sclerosis have become available after demonstrating efficacy in

clinical trials. However, after evaluation and approval by regulatory agencies, in the real-world setting, these drugs are prescribed in patient populations that differ from those included in pivotal studies. Age can represent a key factor that could change the benefit-risk balance and the therapeutic choice, as it may associate with different efficacy and risk of adverse events of DMTs. Therapeutic decision-making can be particularly challenging in paediatric and older patients who are usually excluded from RCTs. As observational data from registry studies are, therefore, of critical relevance to address issues that are otherwise difficult or impossible to study (Trojano *et al.*, 2017). In this multicentre registry Italian study, we aimed to elucidate how different age at onset can influence the prognostic outcomes and effectiveness of DMTs in preventing disability worsening.

Our real-world data covered a mean follow-up period of ~10 years in nearly 9500 patients. Prior works suggested that a 12-month confirmation period of disability worsening is a robust outcome measure as it reliably captures irreversible disability accrual (Trojano *et al.*, 2018). Furthermore, EDSS 4.0 is a meaningful clinical milestone as it marks the patient reduced autonomy in ambulation. Moreover, the results of our exploratory analysis of EDSS 6.0 altogether were in line with those of the primary analysis. However, they did not reach the statistical significance in POMS patients, due to the low number of events in this cohort. It is likely that a longer follow-up period is needed to fully investigate harder disability milestones (Tremlett *et al.*, 2006; Scalfari *et al.*, 2013; Cree *et al.*, 2016).

In most of our patients the first treatment was represented by a moderately effective drug. However, during the follow-up period, the two younger cohorts, with more clinically active disease, exhibited a higher proportion of patients who switched to a highly effective drug.

Overall, our study showed that DMTs can reduce the risk of 12-month CDW and accrual of EDSS 4.0. These findings are consistent with previous observational studies performed with the use of immunomodulatory drugs (Kappos *et al.*, 2009; Jokubaitis *et al.*, 2016; Trojano *et al.*, 2018). In particular, in our AOMS cohort, we found that, in different quartiles of exposure, the risk reduction was related to the cumulative time spent under therapy. This adds evidence that the longer the exposure time, the more likely the protective role against a confirmed disability progression (Trojano *et al.*, 2009; Uitdehaag *et al.*, 2009, 2011; Jokubaitis *et al.*, 2015, 2016), which was also confirmed in sensitivity analyses. These findings are in line with those of Jokubaitis *et al.* (2015) who found a significant benefit on 12-month CDW in patients treated for >50% of the observation period, versus <50% of the time. Notably, we also found very similar results in our large POMS cohort (Alroughani and Boyko, 2018). An international consensus (Chitnis *et al.*, 2012) highlighted the importance for early initiation of DMTs in children and adolescents with multiple sclerosis. POMS patients have, on average, a higher relapse rate, shorter duration between relapses and subsequent accumulation of disability. Although progression may be slower than in adults, moderate-to-severe disability is reached at a younger age (Alroughani and Boyko, 2018). Moreover, although the recovery from relapses seems to be more efficient in POMS because of neuronal plasticity, cognitive impairment is observed in nearly one-third of patients (Amato *et al.*, 2014). To date, however, the only approved DMTs in paediatric multiple sclerosis (>10 years) are interferons, glatiramer and, more recently, fingolimod. The literature describing the effectiveness of DMTs in POMS is limited to observational studies with small sample size (Ghezzi *et al.*, 2016; Alroughani and Boyko, 2018; Waubant *et al.*, 2019). Paediatric clinical trials are challenging due to ethical concerns and difficulties in the recruitment, the study follow-up and site-specific issues (Waubant *et al.*, 2019). In this study, we found that POMS patients never exposed to DMTs during the observation period had the highest risk of experiencing a first CDW or reaching the EDSS 4.0. Despite the small sample, consistent findings also resulted from sensitivity analyses. Furthermore, also in this cohort, a prolonged DMT exposure was associated with a stepwise risk reduction. Further studies are necessary to assess the safety profile of a prolonged DMT exposure, to establish the role of DMT in cognitive impairment in this subset of patients and to evaluate the effectiveness of an escalation versus induction approach.

In the LOMS cohort, DMTs did not significantly influence the time to the first 12-month CDW, but we found that they significantly reduced the risk of reaching EDSS 4.0. RCTs of DMTs for RRMS were not designed to assess efficacy in ageing patients. Pivotal clinical trials specifically excluded individuals aged >50 years [glatiramer acetate (Johnson *et al.*, 1995), IFNβ1b (Paty and Li, 1993), natalizumab (Polman *et al.*, 2006), alemtuzumab (Panitch *et al.*, 2008)] and aged >55 years [IFNβ1a (Jacobs *et al.*, 2000), dimethyl fumarate (Gold *et al.*, 2012), fingolimod (Kappos *et al.*, 2010), teriflunomide (O'Connor *et al.*, 2011), rituximab (Hauser *et al.*, 2008), ocrelizumab (Hauser *et al.*, 2017) and ozanimod (Comi *et al.*, 2019)]. Moreover, a recent meta-analysis of 38 RCTs found that, after age 53, there is no predicted benefit of immunomodulatory therapy (Weideman *et al.*, 2017). This model, however, was based on the above-cited clinical trials, so that the analyses were underpowered in patients aged >50 years. Furthermore, the model was based on patients' mean outcomes, whereas the clinical choice has to deal with individual patient's outcome. It is, therefore, reasonable to hypothesize that among LOMS patients there can also be responders to DMTs. Indeed, the *post hoc* analyses of the CLARITY trial (cladribine tablets treating multiple sclerosis orally), where the upper age limit was 65 years (Giovannoni *et al.*, 2010), revealed that the medication was similarly effective in younger and older patients with RRMS using a cut-off of 40 years of age (Giovannoni *et al.*, 2011; Rammohan *et al.*, 2012). Similarly, in the CONCERTO trial on laquinimod, although the primary outcome was negative, the authors were able to find a subgroup of patients that responded to the drug, represented mainly by older females (Bovis *et al.*, 2019).

Overall, our findings confirmed previous works (Shirani *et al.*, 2015; Guillemin *et al.*, 2017, Weideman *et al.*, 2017; Vaughn *et al.*, 2019) and age-based subgroup analyses of RCTs (Devonshire *et al.*, 2012; Miller *et al.*, 2012) that suggested the existence of different impactful periods of intervention: higher impact in POMS and AOMS and progressively lower, although still detectable, impact in LOMS. At the same time, our results emphasize the importance of further research to clarify the existence of a hypothetical 'upper limit' of age for the response to DMTs; moreover, to characterize good responders among LOMS, in which benefits may overwhelm treatment-related risks. Long-term safety studies are warranted in this more vulnerable population.

Our study also highlighted the prognostic role of relapses and gender.

As expected, the mean number of relapses was higher in POMS than in AOMS and LOMS. Natural history studies in RRMS (Tremlett *et al.*, 2009; Scalfari *et al.*, 2010) found that only early relapses can significantly impact time to EDSS 6.0 and secondary progression. It has also been reported that the effect of relapses is modulated by age, as the impact seems to be higher in younger (<25 years at onset) than in older (>35 years) patients (Tremlett *et al.*, 2009). In our three cohorts, the total number of relapses predicted a higher risk of mid-term disability progression. Our study, however, was not specifically designed to explore the effect of relapses on disability, and we did not stratify early versus late relapses. Despite these limitations, we found that a higher number of relapses was associated with a greater risk of disability, also in the LOMS cohort. We can therefore hypothesize that, although neurodegenerative mechanisms may be prevalent in the later stages of the disease, the inflammatory process can persist and impact disability accrual also in older patients.

As for gender, our female:male ratio of 2.00 in LOMS was more elevated compared to previous studies (Polliack *et al.*, 2001; Tremlett and Devonshire, 2006) that did not control for phenotype at onset, while it was similar to that reported in another study (Bove *et al.*, 2012) considering phenotype at onset. Our study suggested that female sex can exert a protective role only in the LOMS cohort. This result was confirmed in sensitivity analyses. Previous studies assessing the effect of gender on disability worsening did not control for progressive compared with relapsing onset (Polliack *et al.*, 2001; Tremlett and Devonshire, 2006). The only study that specifically investigated the effect of gender in RR-LOMS found that time to EDSS 6.0 was delayed in AOMS female but not in LOMS female in a large cohort (Bove *et al.*, 2012). Different reasons can explain our conflicting results. First, we assessed the time to EDSS 4.0 after adjusting for baseline EDSS, relapses and treatment exposure. Second, the authors in the cited study did not explicitly report the number of events they registered. Finally, it was a monocentric study, and the presence of referral bias cannot be ruled out. The impact, if any, of menopause on multiple sclerosis course is controversial with some authors reporting no differences in disability progression before and after menopause (Ladeira *et al.*, 2019), while others suggest a possible worsening of multiple sclerosis disability (Bove *et al.*, 2016). At low levels, oestrogens seem to worsen the course of multiple sclerosis, while at higher levels they seem to have anti-inflammatory properties that are under investigation (Collongues *et al.*, 2018). As neither the age at menopause was systematically recorded in Italian multiple sclerosis registry nor the proportion of LOMS female under hormone replacement therapy, we are not able to assess the effect that menopause had in RR-LOMS females. Further investigations are warranted to shed some light in this field.

In interpreting our results, we have to take into account a few study limitations. As we included patients with a first evaluation within 3 years from symptom onset, immortal time bias can represent a concern. Indeed, we were not able to perform a reliable sensitivity analysis because of the limited sample of patients with a first visit within 1 year from disease onset. Furthermore, we included patients diagnosed with different diagnostic criteria, which may lead to a phenomenon known as the Will Rogers effect (Kalincik and Butzkueven, 2016; Trojano *et al.*, 2017). We tried to mitigate the inclusion of 'historical patients' by running sensitivity analyses of patients recorded in the registry after 2000. However, we were not able to further stratify patients according to their referring centre or region due to the under-representation of POMS and LOMS cohorts. Our patients were mostly treated with moderately effective DMTs, so that results cannot be directly extrapolated to patients treated with highly effective DMTs. Finally, due to the observational nature of the study, the presence of unknown confounders cannot be ruled out.

In conclusion, our real-world data add to available evidence on the critical role of age in the evaluation of the benefit-risk balance and provide some cues to treatment decision-making in younger and older patient populations under-represented in clinical trials.

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Competing interests

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 BMC Neurology. E.P. served on a scientific advisory board for Biogen and Merck Serono. He received honoraria from

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Supplementary material

Supplementary material is available at *Brain* online.

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