

Comparative effectiveness of anti-CD20 therapies and S1P receptor modulators in late-onset multiple sclerosis: real-world evidence from the MSBase registry

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Abstract

Background: Late-onset multiple sclerosis (LOMS), defined by symptom onset after age 50, is increasingly recognised as a distinct clinical entity. Evidence comparing disease-modifying therapies (DMTs) in this subgroup remains limited.

Objectives: To compare clinical outcomes of anti-CD20 monoclonal antibodies and sphingosine-1-phosphate receptor modulators (S1PRMs) in LOMS.

Design: Multicentre, observational cohort study based on real-world data from an international multiple sclerosis registry.

Methods: We analysed data from the MSBase registry, including relapsing–remitting LOMS patients treated with anti-CD20 therapies (ocrelizumab, ofatumumab, rituximab) or S1PRMs (fingolimod, ozanimod, siponimod, ponesimod) for ≥ 6 months. Primary outcomes were annualised relapse rate (ARR), Expanded Disability Status Scale (EDSS) change, confirmed disability worsening (CDW), progression independent of relapse activity (PIRA), and PIRA without MRI activity (PIRMA). Analyses used inverse probability of treatment weighting (IPTW). Causal forest and best linear projector (BLP) models explored effect modification.

Results: After weighting, 347 patients (median age 53.7 years; 69% female; median follow-up 6.9 years) were included. No significant differences were found for ARR, EDSS change, CDW, PIRA, or PIRMA. Exploratory analyses suggested greater anti-CD20 benefit in patients with earlier onset (≤ 55 years), shorter disease duration (≤ 2 years from diagnosis), and lower disability (EDSS < 3).

Conclusions: In this real-world LOMS cohort, no statistically significant differences were observed between anti-CD20 and S1PRM therapies. Exploratory analyses suggested anti-CD20 may be associated with better outcomes in selected subgroups; these findings are hypothesis-generating.

Trial Registration: Not applicable.

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Plain language summary

How two main treatments for late-onset multiple sclerosis compare in real life

Multiple sclerosis (MS) is a disease where the immune system attacks the brain and spinal cord. When MS begins after the age of 50, it is called late-onset multiple sclerosis (LOMS). This form of MS can progress faster and respond differently to treatment compared to cases that start earlier in life. In this study, we compared two important groups of modern MS treatments: - Anti-CD20 therapies, which target specific immune cells, and - S1P receptor modulators, which prevent immune cells from reaching the brain. We analysed real-world data from an international MS registry called MSBase, including people with relapsing LOMS who had used one of these therapies for at least six months. We looked at how often relapses occurred, how disability changed over time, and whether disability increased independently of relapses. The results showed that, overall, both treatment types worked similarly in preventing relapses and disability worsening. However, in some patients—especially those younger than 55, with early disease and lower disability—anti-CD20 therapies appeared to have a small advantage. These findings suggest that both therapies are effective for most people with late-onset MS, but that starting anti-CD20 treatment early may be beneficial for selected patients. This information can help doctors personalise treatment plans for older adults living with MS.

Keywords: anti-CD20, causal forest, disability progression, late-onset multiple sclerosis, real-world evidence, S1P receptor modulators

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Introduction

Late-onset multiple sclerosis (LOMS), defined by symptom onset after the age of 50, has long been considered uncommon, representing only 4%–6% of diagnoses in earlier cohorts.^{1–3} More recently, population-based registries have reported increasing recognition of LOMS, now accounting for up to 10%–12% of new MS cases.^{4–6} This trend reflects a demographic shift in ageing populations, as well as improved diagnostic accuracy through broader access to MRI, updated diagnostic criteria, and greater awareness of atypical presentations in older adults.^{7,8} National data from Denmark, Sweden and the UK confirm this increase and highlight important clinical distinctions: LOMS patients are more likely to present with progressive phenotypes, motor onset and faster disability accumulation compared with younger-onset cases.^{4–6,9,10}

Biological mechanisms also differentiate LOMS. Age-related immune remodelling, reduced lymphocyte repertoire diversity, and microglial activation contribute to a pro-inflammatory and

neurodegenerative milieu that limits recovery.^{11–16} Neuropathological studies report a predominance of chronic active lesions and relatively fewer gadolinium-enhancing lesions, consistent with a disease course that is less inflammatory and more insidiously progressive than in younger patients.¹⁷

These features have direct therapeutic implications. Although the expansion of high-efficacy disease-modifying therapies (DMTs) has transformed MS management, their benefit appears attenuated in older patients, with both age at onset and age at treatment initiation influencing responsiveness.^{18–20} At the same time, comorbidities and immunosenescence increase the risk of treatment-related complications, making safety a critical concern in this population.²¹

To date, data are scant and the few available studies have examined treatment efficacy in LOMS by grouping DMTs into broad categories, essentially according to their level of efficacy (e.g., LET), without directly comparing agents that differ in both mechanism of action and molecular

size, factors that may influence their ability to cross the blood–brain barrier. In this study, we directly evaluate two therapeutic strategies frequently used in clinical practice—anti-CD20 monoclonal antibodies and sphingosine-1-phosphate receptor modulators (S1PRMs). By analysing relapse outcomes, disability progression and safety outcomes in a real-world LOMS cohort, we aim to provide clinically relevant evidence to guide treatment decisions in this increasingly prevalent subgroup.

Methods

Study population

Demographic and clinical data were collected from patients with LOMS, defined as symptom onset after age 50, enrolled in MSBase, a large international observational registry of patients with multiple sclerosis. Prior to cohort selection, standardised quality-control procedures were applied, as routinely implemented in MSBase studies. Automated scripts were used to assess data accuracy (error rates), data density across key domains (follow-up, demographics, clinical visits, relapses, paraclinical data, therapies) and generalizability, in accordance with previously published MSBase methodology.²²

Patients were included if they had a diagnosis of relapsing–remitting MS (RRMS) established according to the McDonald criteria valid at the time of diagnosis, and if symptom onset occurred between January 1, 2000 and April 30, 2025. Additional inclusion criteria were the availability of a complete baseline EDSS assessment, at least two recorded EDSS evaluations, and treatment with DMTs belonging to either the anti-CD20 class (ocrelizumab, ofatumumab, or rituximab) or the S1PRMs (fingolimod, ozanimod, siponimod or ponesimod), for at least 6 months.

Demographic variables analysed included age at symptom onset, age at diagnosis, sex and disease duration. Clinical variables comprised the type of first clinical manifestation (classified as optic, supratentorial, brainstem or spinal), EDSS score at baseline, the annualised relapse rate (ARR) during the year preceding the initiation of anti-CD20 or S1PRM therapy, and the number of previous DMTs. To account for potential

confounding in cumulative probability models, visit frequency (visits per year) and MRI monitoring (MRIs per year) were also included.

This study was designed, conducted and reported in accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines,²³ with a completed checklist and a structured overview of the statistical models (including covariate adjustment and effect measures) provided in the Supplemental Material (Tables S1–S2).

Outcomes and definitions

The primary outcomes considered in this study were the ARR, longitudinal changes in the EDSS, the reaching of EDSS milestones 4.0 and 6.0, confirmed disability worsening (CDW), progression independent of relapse activity (PIRA), and progression independent of relapse activity with no MRI activity (PIRMA).

ARR was defined as the number of relapses divided by patient-years of follow-up.²⁴ A relapse was defined as the onset of new, or worsening of existing, neurological symptoms lasting at least 24 h, not attributable to fever or infection, and separated by at least 30 days from a previous relapse.²⁵

Longitudinal EDSS changes were assessed by evaluating the trajectory of EDSS scores across the follow-up period, based on all available assessments.²⁶ Reaching EDSS milestones was defined as the first EDSS score of at least 4.0 or 6.0, sustained for 6 months, provided that the baseline EDSS was below the respective threshold.⁴

CDW was defined as a sustained increase in EDSS confirmed at 6 months. Specifically, CDW was defined as an increase of ≥ 1.5 points if the baseline EDSS was 0.0, ≥ 1.0 point if the baseline EDSS was between 1.0 and 5.5, or ≥ 0.5 point if the baseline EDSS was > 5.5 .²⁷

PIRA was defined as a 6-month confirmed CDW event occurring in the absence of a clinical relapse within 30 days before or 90 days after the worsening event.²⁸ PIRMA was defined as a PIRA event occurring more than 30 days before or more than 90 days after a clinical relapse, in the absence of

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any new or enlarging T2-hyperintense lesions and/or gadolinium-enhancing lesions on brain MRI within the 12 months preceding the event.²⁹

Safety outcomes included severe infections and malignancies. Severe infections were defined as infections that were life-threatening, opportunistic, required intravenous or prolonged antimicrobial therapy, or showed a severe or prolonged clinical course. Infection events were considered treatment-associated if occurring during DMT exposure or within 6 months after treatment discontinuation. Malignancies were defined as any newly diagnosed neoplastic disease and were considered treatment-associated if occurring during DMT exposure or within 24 months after treatment discontinuation.

Statistical analysis

To minimise confounding from non-random treatment allocation, we applied inverse probability of treatment weighting (IPTW) using propensity scores estimated from baseline demographic and clinical variables, including age at onset and at diagnosis, disease duration, sex, baseline EDSS, annualised relapse rate in the year prior to treatment initiation, first symptom localisation, number of previous DMTs, follow-up time, and surveillance intensity (visits and brain MRI per year). Stabilised weights were used. To account for residual imbalance and potential non-linear relationships between baseline covariates and treatment assignment, spline terms were introduced for covariates showing residual imbalance after weighting: standardised mean differences (SMD) > 0.10. This flexible specification helps to reduce model misspecification and improve covariate balance in IPTW analyses.³⁰ All outcomes were analysed in the weighted population.

ARR was assessed with negative binomial regression (incidence rate ratio, IRR). Longitudinal EDSS change was evaluated using ANCOVA (adjusted mean difference). Time to EDSS 4.0 and 6.0 was analysed with Cox proportional hazards models (hazard ratios, HR). Recurrent disability outcomes (CDW, PIRA, PIRMA) were modelled with Andersen–Gill extensions of the Cox model (HR).

Sensitivity analyses were performed in treatment-naïve patients to avoid confounding from prior therapy exposure, and in sex-stratified subgroups

given the potential influence of biological and clinical differences between men and women on treatment response. Additional sensitivity analyses were conducted by restricting follow-up to a common 2-year period to address potential survival bias due to differential follow-up duration between treatment groups.

Furthermore, we applied a causal forest for the same disability outcomes (CDW, PIRA, PIRMA) to capture potential non-linear associations that conventional proportional hazards models may not detect. The forest was fitted on the unweighted study population, in accordance with methodological recommendations, over a fixed 5-year time horizon, and included the same baseline covariates as the IPTW models. To further explore effect modification, we applied a best linear projector (BLP) to the estimated conditional effects, evaluating predefined subgroups by age at onset, sex, clinical onset phenotype, disease duration, baseline EDSS and prior treatment exposure.

All analyses were performed in R software (version 2024.12.1 + 563), and a two-sided *p*-value < 0.05 was considered statistically significant.

Results

Of the 117,419 people with multiple sclerosis recorded in the MSBase registry, 447 were included in the analysis. The study population flow diagram is presented in Figure 1.

The median age at onset was 53.7 years (IQR 51.6–57.7), and the median age at diagnosis was 55.6 years (IQR 53.0–59.3). Median disease duration was 2.5 years (IQR 0.9–5.6). A total of 109 patients (24%) were treatment-naïve, and the median follow-up time was 6.9 years (IQR 4.2–10.2). The cohort included 307 women (68.7%). The median baseline EDSS was 3.5 (IQR 2.5–5.0), and the median number of previous DMTs was 2 (IQR 1–5).

Of the 447 eligible patients, 100 (22.4%) with missing baseline covariates were excluded prior to weighting, leaving 347 patients for the IPTW analyses. Complete baseline characteristics of both the weighted and unweighted cohorts are summarised in Table 1.

Residual imbalance was mainly observed for continuous variables with potentially non-linear

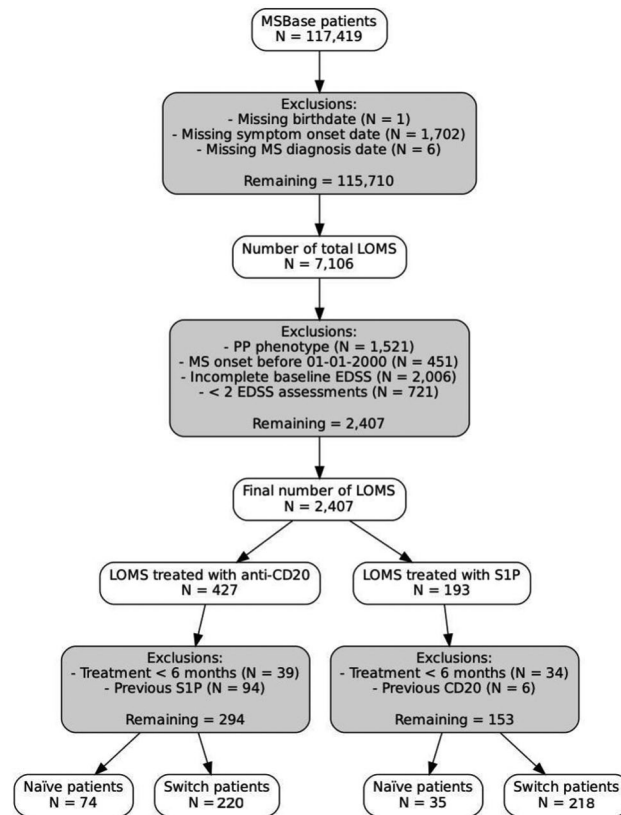


Figure 1. Study population flow diagram. Selection of late-onset multiple sclerosis (LOMS) patients from the MSBase registry and stratification by treatment group (anti-CD20 vs S1PRMs).

associations with treatment allocation (age at diagnosis, disease duration and follow-up time). To address this, spline terms were added for these covariates in the propensity score model, as recommended for inverse probability weighting analyses with continuous predictors. After refitting, covariate balance improved markedly (all $SMD < 0.10$), except for *disease duration* ($SMD = 0.12$), which remained slightly unbalanced and was therefore included as an adjustment covariate in the weighted outcome models. Graphical representations of covariate balance distributions further confirmed the quality of the weighting process (Figure S1).

Outcomes analysis in the weighted cohort

The mean ARR was 0.05 (95% CI 0.02–0.14) among patients treated with S1PRMs and 0.03 (95% CI 0.01–0.08) among those receiving anti-CD20 therapies. In the negative binomial regression model, S1PRM treatment was not associated with a significantly higher relapse rate compared

with anti-CD20 (IRR 1.62, 95% CI 0.85–3.07; $p = 0.14$).

Regarding disability outcomes, the adjusted mean difference in EDSS change between groups (S1PRM vs anti-CD20) was -0.15 (95% CI -0.37 to 0.06 ; $p = 0.16$), indicating no significant difference in disability progression. During follow-up, 20 patients reached EDSS 4.0 and 18 reached EDSS 6.0. In Cox regression models, S1PRM therapy was not associated with a significantly different risk of reaching EDSS 4.0 (HR 0.66, 95% CI 0.26–1.66; $p = 0.38$) or EDSS 6.0 (HR 0.52, 95% CI 0.19–1.41; $p = 0.19$). Kaplan–Meier curves showed no separation between groups, with overlapping confidence intervals throughout follow-up (Figures 2–3).

For CDW, 33 (15%) patients treated with anti-CD20 therapies and 25 (20%) treated with S1PRM experienced at least one event (median time to first event: 18.0 months in both groups). In the Andersen–Gill model, S1PRM treatment

Table 1. Baseline demographic and clinical characteristics of the study cohort.

Variables	Overall cohort	Anti-CD20	S1PRM	SMD unweighted	SMD weighted
Demographics					
Age at onset, median (IQR)	53.7 (51.6–57.7)	54.8 (51.8–58.1)	52.9 (51.4–56.2)	0.171	0.056
Age at diagnosis, median (IQR)	55.6 (53.0–59.3)	56.3 (53.2–59.4)	54.4 (53.2–59.4)	0.196	0.111
Disease duration, median (IQR)	2.5 (0.9–5.6)	1.9 (0.6–5.0)	3.8 (1.5–6.4)	0.159	0.119
Female sex, <i>n</i> (%)	307 (68.7)	196 (66.7)	111 (72.5)	0.074	0.014
First clinical symptom, <i>n</i> (%)					
Optic	77 (17.2)	54 (19.0)	23 (15.0)	0.040	0.022
Supratentorial	105 (23.5)	64 (21.8)	41 (26.8)	0.054	0.010
Brainstem	104 (23.3)	56 (19.0)	48 (31.4)	0.111	0.004
Spinal cord	139 (31.1)	98 (33.3)	41 (26.8)	0.064	0.006
Clinical characteristics					
EDSS at baseline, median (IQR)	3.5 (2.5–5.0)	3.5 (2.5–5.5)	3.0 (2.0–4.5)	0.320	0.017
ARR prior to treatment, median (IQR)	0 (0–1)	0 (0–1)	0 (0–1)	0.016	0.036
Previous DMTs, median (IQR)	2 (1–5)	2 (0–4)	3 (1–6)	0.040	0.017
Follow-up time, years, median (IQR)	6.9 (4.2–10.2)	5.8 (3.4–8.6)	9.1 (6.6–12.2)	0.651	0.102
Visits per year, median (IQR)	1.9 (1.4–2.7)	1.8 (1.4–2.7)	2.1 (1.3–3.1)	0.083	0.059
MRI per year, median (IQR)	0.5 (0–1.0)	0.6 (0–1.1)	0.5 (0–0.9)	0.058	0.037
ARR, Annualized Relapse Rate; DMTs, disease-modifying therapies; EDSS, Expanded Disability Status Scale; IPTW = inverse probability of treatment weighting; IQR, Interquartile Range; LOMS = late-onset multiple sclerosis; MRI = magnetic resonance imaging; S1PRM, Sphingosine-1-Phosphate Receptor Modulator(s); SMD, Standardized Mean Difference.					

was not associated with a significantly different risk compared with anti-CD20 (HR 1.12, 95% CI 0.66–1.90; $p=0.67$). The mean cumulative function (MCF) curves confirmed overlapping trajectories (Figure 4).

For PIRA, 32 patients (15%) in the anti-CD20 group and 22 patients (18%) in the S1PRM group experienced at least one event (median time to first event: 19.4 months in both groups). S1PRM treatment was not associated with a significantly different risk compared with anti-CD20 (HR 1.09, 95% CI 0.63–1.88; $p=0.76$), and MCF curves were largely overlapping (Figure 5).

For PIRMA, 19 patients treated with anti-CD20 (8.6%) and 10 treated with S1PRM (7.9%) experienced at least one event (median time to first

event: 18.0 vs 26.7 months, respectively). S1PRM therapy was not associated with a significantly different risk compared with anti-CD20 (HR 0.94, 95% CI 0.46–1.89; $p=0.85$). MCF curves for PIRMA were also overlapping (Figure 6).

The distribution of recurrent events, including CDW, PIRA and PIRMA, is summarised in the Supplemental Material (Figure S2).

Sensitivity analysis for the risk of CDW, PIRA and PIRMA

In sensitivity analyses restricted to treatment-naïve patients, S1PRMs did not differ significantly from anti-CD20 therapies: CDW (HR 1.42, 95% CI 0.66–3.04; $p=0.37$), PIRA (HR 1.38, 95% CI 0.61–3.09; $p=0.44$) and PIRMA (HR 1.28, 95%

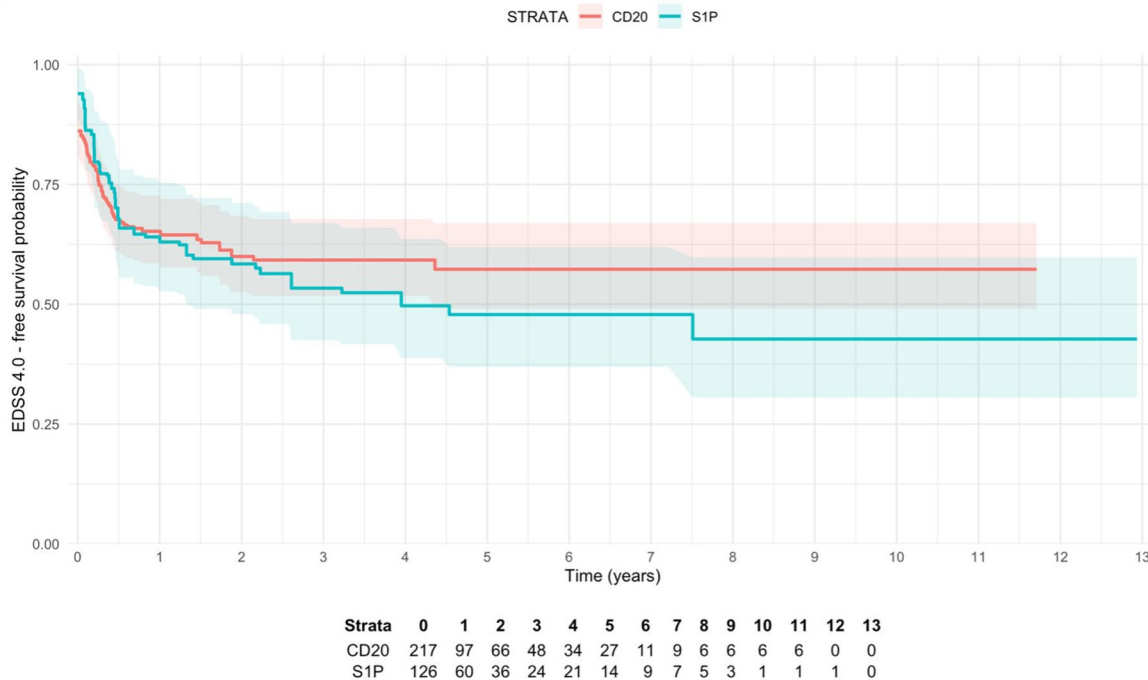


Figure 2. Kaplan–Meier curves for time to EDSS ≥ 4.0 . The probability of remaining free from disability progression (defined as a confirmed increase of EDSS to ≥ 4.0 sustained for ≥ 24 weeks) is shown for patients initiating treatment with anti-CD20 monoclonal antibodies (red) versus S1PRM (blue). Shaded areas indicate 95% confidence intervals. Numbers at risk at yearly intervals are reported below the graph. Analyses were performed in the inverse probability of treatment weighted (IPTW) population, and no statistically significant difference between treatment groups was observed in the weighted Cox proportional hazards model adjusted for baseline covariates.

EDSS, Expanded Disability Status Scale; IPTW, Inverse probability of treatment weighted

CI 0.48–3.40; $p=0.62$), with corresponding MCF curves shown in the Supplemental Material (Figures S3–S5).

In sex-stratified analyses, no statistically significant differences between S1PRM and anti-CD20 therapies were observed. Among women, hazard ratios for S1PRM compared with anti-CD20 were 0.78 for CDW (95% CI 0.43–1.43; $p=0.42$), 0.68 for PIRA (95% CI 0.35–1.30; $p=0.24$), and 0.62 for PIRMA (95% CI 0.28–1.39; $p=0.25$). Among men, the corresponding hazard ratios were 1.57 for CDW (95% CI 0.65–3.82; $p=0.32$), 1.58 for PIRA (95% CI 0.65–3.85; $p=0.31$), and 1.14 for PIRMA (95% CI 0.35–3.68; $p=0.83$). Interaction tests did not demonstrate significant sex-by-treatment effects. The corresponding MCFs by sex are presented in the Supplemental Material (Figures S6–S8).

Sensitivity analyses with restricted follow-up

In sensitivity analyses restricted to a common 2-year follow-up period, no significant differences between S1PRMs and anti-CD20 therapies were observed for CDW (HR 0.94, 95% CI 0.46–1.89), PIRA (HR 0.82, 95% CI 0.38–1.78), or PIRMA (HR 0.50, 95% CI 0.16–1.53).

Safety outcomes

During follow-up, six severe infection events were observed in six patients, all treated with anti-CD20 therapies. Severe infections included two (33.3%) cases of sepsis, one (16.7%) recurrent or complicated urinary tract infection, one (16.7%) herpes zoster, one (16.7%) opportunistic gastrointestinal infection and one (16.7%) prolonged respiratory infection requiring multiple antibiotic courses. No severe infections were observed

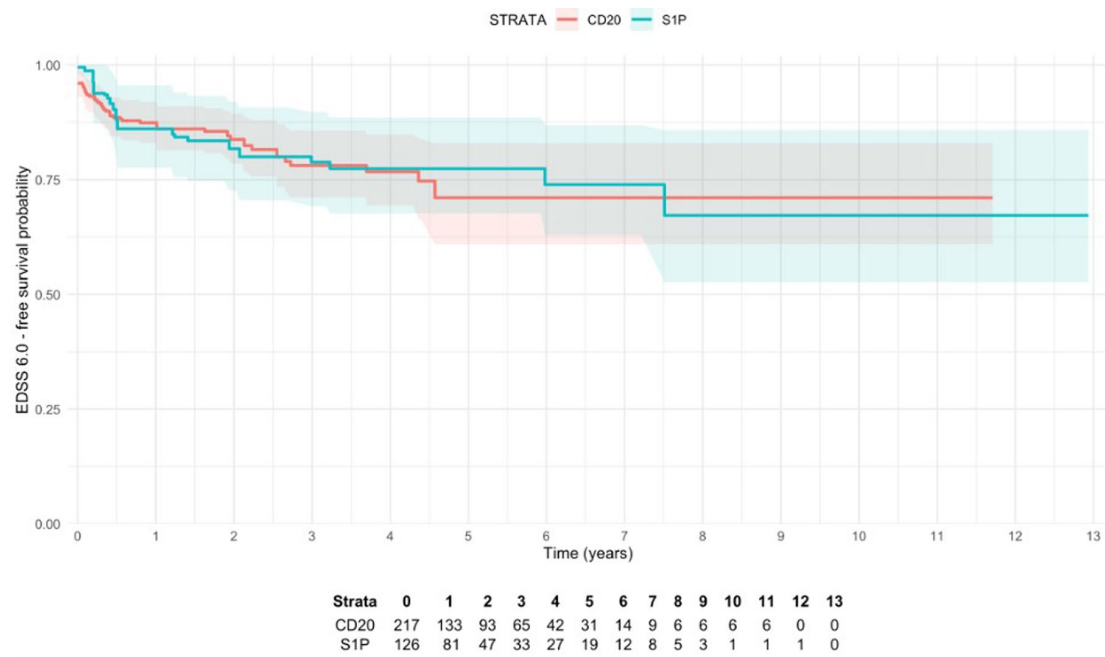


Figure 3. Kaplan–Meier curves for time to EDSS ≥4.0. The probability of remaining free from disability progression (defined as a confirmed increase of EDSS to ≥4.0 sustained for ≥24 weeks) is shown for patients initiating treatment with anti-CD20 monoclonal antibodies (red) versus S1PRM (blue). Shaded areas indicate 95% confidence intervals. Numbers at risk at yearly intervals are reported below the graph. Analyses were performed in the inverse probability of treatment weighted (IPTW) population, and no statistically significant difference between treatment groups was observed in the weighted Cox proportional hazards model adjusted for baseline covariates.

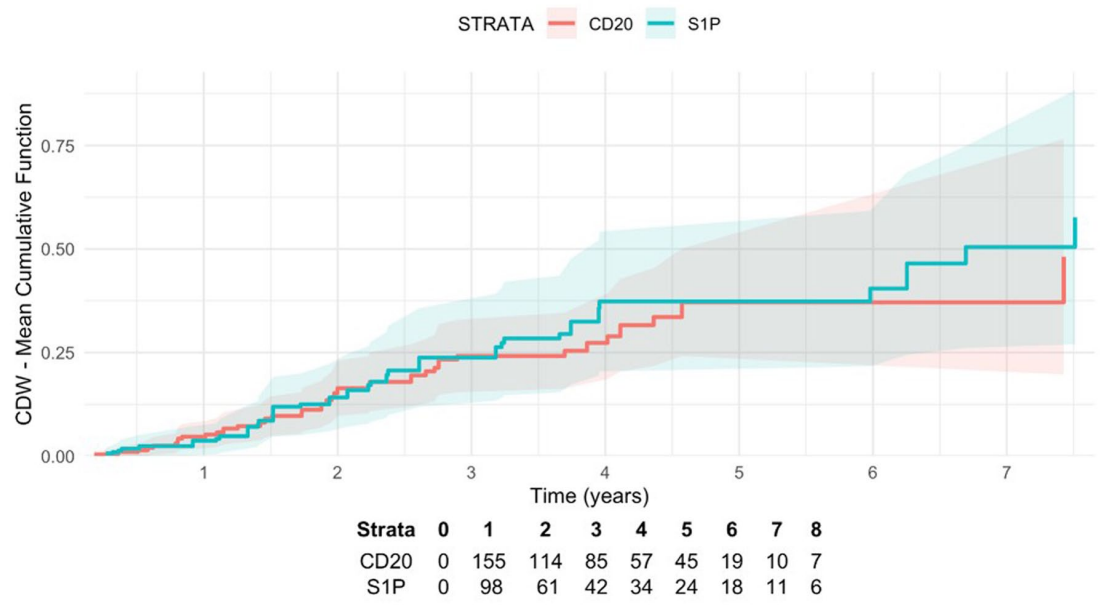


Figure 4. Mean cumulative function of CDW. Mean cumulative function estimates for CDW events are shown for patients treated with anti-CD20 therapies (red) and S1PRM (blue). Shaded areas represent 95% confidence intervals. The MCF accounts for recurrent events, allowing visualisation of the cumulative burden of disability worsening over time. Numbers below the x-axis indicate the number of patients at risk in each treatment group at the corresponding time points. Analyses were performed in the inverse probability of treatment weighted (IPTW) population. CDW, confirmed disability worsening; MCF, mean cumulative function; S1PRM, sphingosine-1- phosphate receptor modulators.

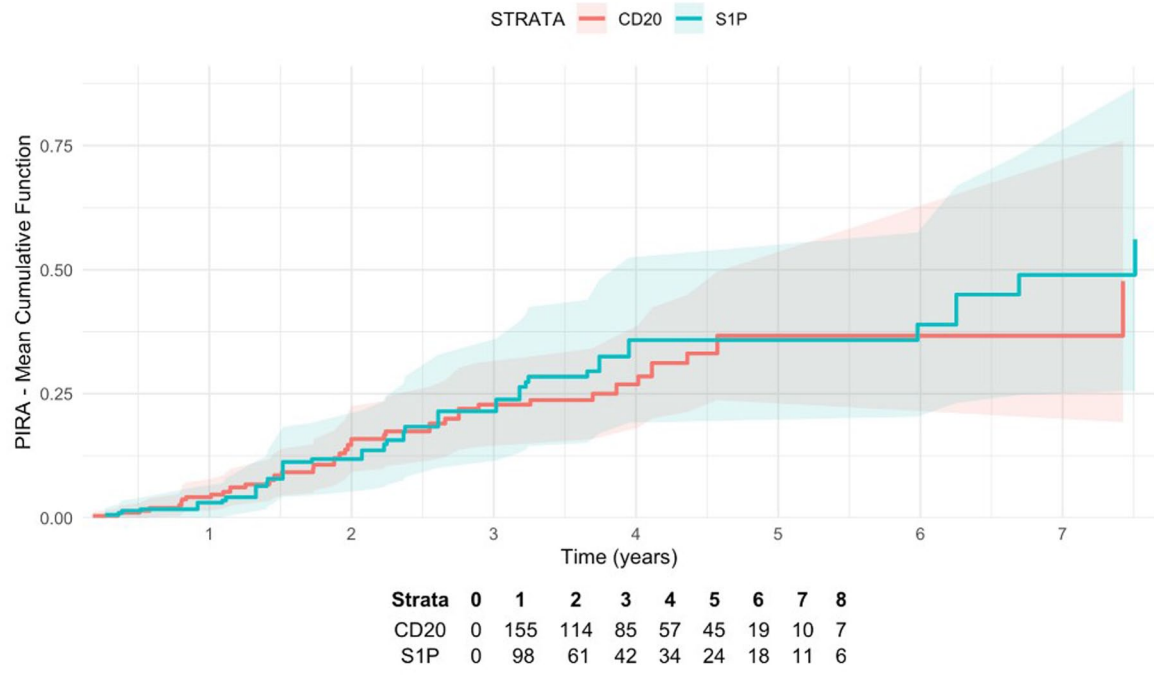


Figure 5. Mean cumulative function of progression independent of relapse activity (PIRA). Mean cumulative function estimates for PIRA events are shown for patients treated with anti-CD20 therapies (red) and S1PRM (blue). Shaded areas represent 95% confidence intervals. The MCF framework accounts for recurrent events, providing an estimate of the cumulative burden of disability progression independent of relapses over time. Numbers below the x-axis indicate the number of patients at risk in each treatment group at the corresponding time points. Analyses were performed in the inverse probability of treatment weighted (IPTW) population. MCF, mean cumulative function; PIRA, progression independent of relapse activity; S1PRM, sphingosine-1-phosphate receptor modulators.

among patients treated with sphingosine-one-phosphate receptor modulators.

In addition, 16 malignancy events were observed in nine patients. Malignancies included five (31.3%) breast cancers, one (6.3%) lung carcinoma, one (6.3%) prostate carcinoma, one (6.3%) cervical carcinoma, one (6.3%) bladder cancer, one (6.3%) bowel carcinoma, one (6.3%) lymphoma, one (6.3%) melanoma, one (6.3%) lentigo maligna, and one (6.3%) carcinoma not otherwise specified. Among these, 14 malignancy events occurred in 7 patients treated with anti-CD20 therapies, while 2 events occurred in 2 patients treated with sphingosine-1-phosphate receptor modulators, both breast cancers.

Exploratory machine-learning analyses

In the causal forest analysis and BLP projections, we observed signals favouring anti-CD20, particularly in patients with shorter disease duration (≤ 2 years from diagnosis; CDW HR 0.965 (95% CI 0.933–0.998), $p=0.039$; PIRA HR 0.947

(95% CI 0.909–0.987), $p=0.010$), lower baseline disability (EDSS < 3 ; CDW HR 0.937 (95% CI 0.904–0.972), $p=0.001$; PIRA HR 0.891 (95% CI 0.852–0.932), $p<0.001$; PIRMA HR 0.958 (95% CI 0.941–0.976), $p<0.001$), and earlier age at onset (50–55 years) compared with > 55 years (CDW HR 0.917 (95% CI 0.891–0.943), $p<0.001$; PIRA HR 0.904 (95% CI 0.873–0.936), $p<0.001$; PIRMA HR 0.984 (95% CI 0.970–0.998), $p=0.028$). These findings are hypothesis-generating and should be interpreted with caution; full results are presented in Table 2 and Figure 7.

Discussion

In this large, real-world cohort of LOMS, we did not observe significant differences in relapse or disability outcomes between patients treated with S1PRMs and those treated with anti-CD20 monoclonal antibodies. These results are consistent with previous real-world studies suggesting an overall attenuation of DMT efficacy in older patients.^{31,32}

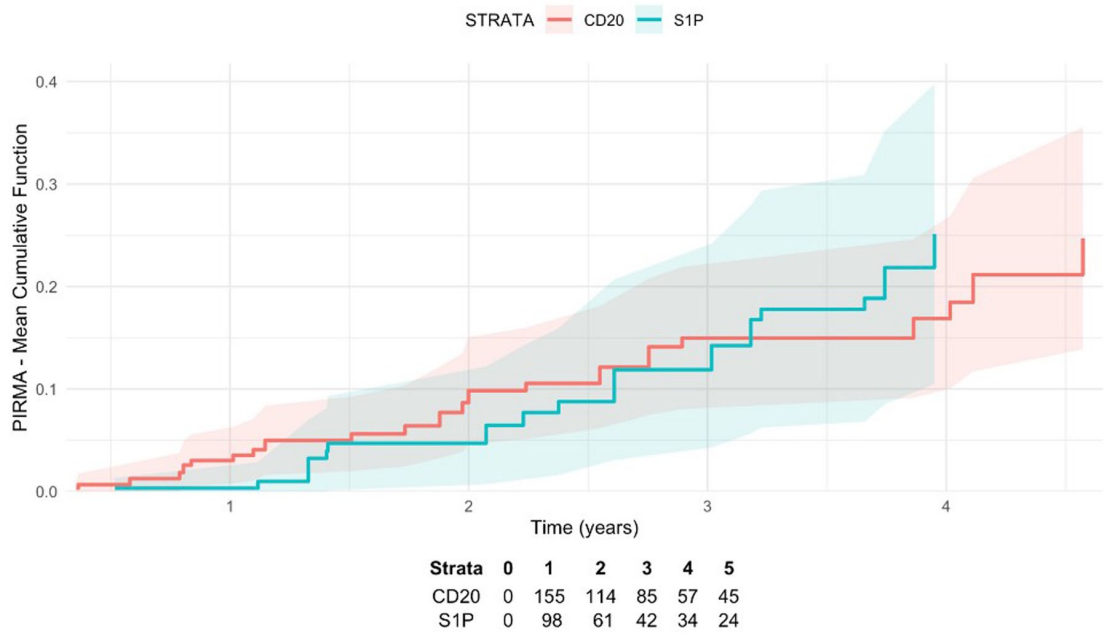


Figure 6. Mean cumulative function of progression independent of relapse activity with no MRI activity (PIRMA). Mean cumulative function estimates for PIRMA events are shown for patients treated with anti- CD20 therapies (red) and S1PRM (blue). Shaded areas represent 95% confidence intervals. The MCF framework accounts for recurrent events and allows visualisation of the cumulative burden of disability progression independent of relapses and in the absence of new or enlarging MRI activity. Numbers below the x-axis indicate the number of patients at risk in each treatment group at the corresponding time points. Analyses were performed in the IPTW population.
MCF, mean cumulative function; IPTW, inverse probability of treatment weighted; PIRMA, progression independent of relapse activity with no MRI activity; S1PRM, sphingosine-1-phosphate receptor modulators.

A particularly relevant observation is that, among treatment-naïve patients, the direction and magnitude of treatment effects were similar to those seen in the overall cohort, with no statistically significant difference between anti-CD20 and S1PRM therapies. However, treatment-naïve status should not be equated with early treatment initiation. In our exploratory analyses, patients who commenced therapy within 2 years from diagnosis—regardless of prior treatment exposure—tended to derive greater benefit from anti-CD20 therapies. This aligns with evidence from randomised trials and large registries showing that initiating high-efficacy treatments early, rather than after switching, is associated with improved long-term outcomes in younger populations (28–30). Our findings suggest that this advantage may be attenuated in LOMS, although the limited number of events and follow-up duration in this subgroup warrant cautious interpretation.^{33–35}

Sex-stratified analyses also did not show clear treatment differences. Neuropathological studies have shown that men with MS tend to experience faster

neurodegeneration and greater grey matter atrophy, while women more often display stronger inflammatory activity.³⁶ However, these biological differences have not been consistently associated with divergent responses to disease-modifying therapies, as systematic reviews of sex-stratified outcomes have failed to demonstrate clear treatment effects by sex.³⁷ In our cohort, hazard ratios for disability outcomes diverged in direction, suggesting a relative advantage of anti-CD20 therapies in men and of S1PRM in women, but none of these results reached statistical significance. Taken together, these findings should be regarded as exploratory and underline the need for dedicated sex-stratified analyses in larger LOMS populations.

In addition to the IPTW analyses, the exploratory causal forest and BLP indicated a favourable association of anti-CD20 therapies over S1PRMs across all disability outcomes (CDW, PIRA, and PIRMA), particularly driven by subgroups of patients with earlier age at onset (50–55 years compared with >55 years), shorter disease duration (≤2 years from diagnosis), and lower baseline disability (EDSS < 3).

Table 2. Best linear projector (BLP) estimates of treatment effect modification.

Endpoint	Modifier	HR (95% CI)	p-Value
CDW	Naïve	1.019 [0.981–1.059]	0.329
	Female	0.981 [0.954–1.009]	0.181
	Spinal onset	1.009 [0.978–1.042]	0.561
	Brainstem onset	0.995 [0.960–1.032]	0.783
	Disease duration ≤ 2 years	0.965 [0.933–0.998]	0.039
	Baseline EDSS < 3	0.937 [0.904–0.972]	0.001
	Previous DMT < 2	1.030 [0.933–1.137]	0.555
	Age at onset 50–55 years	0.917 [0.891–0.943]	0.000
PIRA	Naïve	1.015 [0.969–1.064]	0.526
	Female	0.972 [0.940–1.006]	0.108
	Spinal onset	0.987 [0.950–1.026]	0.513
	Brainstem onset	0.984 [0.941–1.029]	0.478
	Disease duration ≤ 2 years	0.947 [0.909–0.987]	0.010
	Baseline EDSS < 3	0.891 [0.852–0.932]	0.000
	Previous DMT < 2	1.051 [0.931–1.186]	0.425
	Age at onset 50–55 years	0.904 [0.873–0.936]	0.000
PIRMA	Naïve	1.002 [0.982–1.022]	0.851
	Female	0.989 [0.975–1.003]	0.123
	Spinal onset	1.002 [0.986–1.019]	0.770
	Brainstem onset	0.991 [0.973–1.010]	0.352
	Disease duration ≤ 2 years	0.987 [0.971–1.004]	0.146
	Baseline EDSS < 3	0.958 [0.941–0.976]	0.000
	Previous DMT < 2	1.027 [0.976–1.080]	0.303
	Age at onset 50–55 years	0.984 [0.970–0.998]	0.028
Hazard ratios (HR) with 95% confidence intervals (CI) and p-values are reported for CDW, PIRA, and PIRMA. Values < 1 indicate associations favoring anti-CD20 over S1PRM. Bold values indicate statistically significant coefficients ($p < 0.05$).			

Given the limited sample size, low event rates, and multiple subgroup dimensions explored, these findings should be regarded as strictly hypothesis-generating and interpreted with caution.

Safety considerations are particularly important in late-onset multiple sclerosis, as older patients

are generally more susceptible to treatment-related adverse events due to immunosenescence, comorbidities, and cumulative treatment exposure.^{38–40} Anti-CD20 therapies have been consistently associated with age- and exposure-dependent risks of infections and hypogammaglobulinemia,⁴¹ as well as attenuated vaccine responses,⁴²

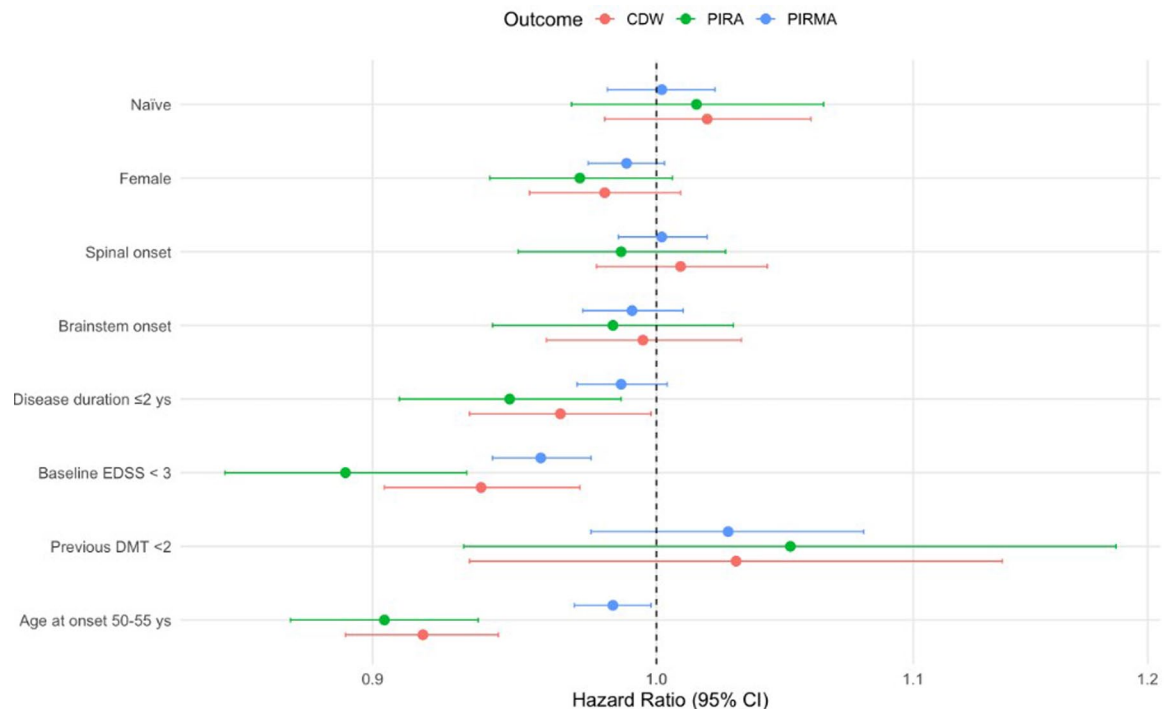


Figure 7. Forest plot showing the effect modifiers of treatment response (CD20 vs S1P) across the three outcomes (CDW, PIRA, PIRMA). Points represent hazard ratios (HR) with 95% confidence intervals. HR < 1 indicates a relatively greater treatment benefit in the subgroup of interest compared to the reference group (Male, Spinal onset absent, Brainstem onset absent, Disease duration >2 years, Baseline EDSS ≥ 3 , ≥ 2 previous DMTs, Age at onset >55 years, Non-naïve). CDW, confirmed disability worsening; MCF, mean cumulative function; PIRMA, progression independent of relapse activity with no MRI activity; S1PRM, sphingosine-1-phosphate receptor modulators.

whereas S1P receptor modulators are characterised by distinct safety concerns, including cardiovascular adverse events,⁴³ macular oedema,⁴⁴ and the risk of disease rebound following treatment discontinuation.⁴⁵ In the present registry-based analysis, safety outcomes were assessed descriptively. Severe infections and malignancies were observed predominantly among patients treated with anti-CD20 therapies, while fewer events were recorded in patients receiving sphingosine-1-phosphate receptor modulators. However, given the limited number of events, the heterogeneity of reported outcomes, and the potential for under-reporting inherent to real-world registries, no causal inference or comparative risk assessment can be drawn.

Several limitations should be acknowledged. The most prominent limitation of this study is its limited statistical power, resulting from the relatively small number of patients included in the weighted analysis and the low number of clinical events, particularly for disability outcomes and subgroup

analyses. Given that disability progression typically accrues slowly in older multiple sclerosis populations, the study may have been underpowered to detect modest but clinically meaningful differences between treatment groups, with a substantial risk of type II error.

In addition, the classification of PIRMA relies on consistent MRI surveillance; heterogeneity in MRI availability and protocols across centres may have led to misclassification of subclinical inflammatory activity and biased results toward null differences between treatment groups.

Accordingly, the absence of statistically significant differences should not be interpreted as evidence of therapeutic equivalence, and clinically relevant effects cannot be excluded, as reflected by the wide confidence intervals around most estimates. Despite careful covariate balancing with IPTW and additional spline adjustments, residual confounding cannot be excluded. In particular, treatment allocation in LOMS is likely

influenced by unmeasured factors such as comorbidity burden, prior infection risk or malignancy history, physician treatment preference, and local prescribing policies, which are not fully captured within the registry. In addition, the exclusion of patients with missing baseline covariates may have reduced generalizability by preferentially retaining more closely monitored or less clinically complex cases. These factors may have contributed to indication bias and should be considered when interpreting the results. Lastly, safety outcomes were reported descriptively only, and the risk of underreporting and heterogeneity in adverse event capture inherent to registry-based data should be acknowledged.

Taken together, our findings indicate a possible more favourable profile of anti-CD20 therapies compared with S1PRMs in specific subgroups of LOMS, namely individuals with an age at onset not exceeding 55 years, a shorter disease duration (≤ 2 years from diagnosis), and lower baseline disability (EDSS < 3). By contrast, in patients with later onset, longer disease duration or higher baseline disability, the effectiveness of a high-efficacy therapy such as anti-CD20 appears to converge with that of moderate-efficacy treatments.

Collectively, these findings support the hypothesis that anti-CD20 therapies may be most beneficial when introduced early in carefully selected patient populations. Prospective, age-stratified clinical trials and biomarker-informed approaches will be essential to validate these observations and guide individualised therapeutic strategies in LOMS.

Conclusion

In this real-world study of LOMS, we did not observe statistically significant differences in relapse or disability outcomes between anti-CD20 therapies and S1P receptor modulators. Exploratory analyses suggested potential heterogeneity of treatment effects, with signals favouring anti-CD20 in selected subgroups (age at onset ≤ 55 years, disease duration ≤ 2 years from diagnosis, and baseline EDSS < 3); these findings should be considered hypothesis-generating and interpreted with caution. Given the limited sample size and low event rates, clinically meaningful differences cannot be excluded. Overall, these results highlight the need for individualised treatment decisions in LOMS, and for prospective

studies integrating both effectiveness and safety outcomes to guide therapy selection over the disease course.

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki. The use of MSBase registry data was approved by the MSBase Scientific Leadership Group, which provides scientific and ethical governance for studies using MSBase data. In addition, local ethical approval was obtained from the Comitato Etico della Romagna (CEROM) on 05 November 2021 (approval code: 3139). Informed consent for participation in the MSBase registry was obtained from all participants in accordance with MSBase registry protocols. The approvals cover the analyses performed in this study, including data collected up to April 2025.

Consent for publication

Not applicable.

Author contributions

Andrea Surcinelli: Conceptualisation; Data curation; Formal analysis; Methodology.

Tomas Kalincik: Data curation; Methodology; Supervision; Validation.

Izanne Roos: Supervision; Validation.

Emanuele D'Amico: Data curation; Methodology; Supervision; Validation; Writing – review & editing.

Jeannette Lechner-Scott: Data curation; Methodology; Supervision.

Serkan Ozakbas: Supervision; Validation.

Pavel Hradilek: Resources; Supervision; Validation.

Dana Horáková: Supervision; Validation.

Marta Vachova: Supervision; Validation.

Ivan Panzera: Supervision; Validation.

Stefano Ruzza: Data curation; Formal analysis; Methodology.

Maria Grazia Piscaglia: Supervision; Validation.

Oliver Gerlach: Supervision; Validation.

Jose Eustasio Meca-Lallana: Supervision; Validation.

Gabriel Valero-López: Supervision; Validation.

Allan G. Kermode: Supervision; Validation.

Marzena J Fabis-Pedrini: Supervision; Validation.

Julie Prevost: Supervision; Validation.

Radek Ampapa: Supervision; Validation.

Suzanne Hodgkinson: Supervision; Validation.

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Nevin A John: Supervision; Validation.

Marek Peterka: Supervision; Validation.

Jana Houskova: Supervision; Validation.

Eva Recmanova: Supervision; Validation.

Zuzana Rous: Supervision; Validation.

Vahid Shaygannejad: Supervision; Validation.

Raed Alroughani: Supervision; Validation.

Jens Kuhle: Supervision; Validation.

Gregor Brecl Jakob: Supervision; Validation.

Pierre Grammond: Supervision; Validation.

Francesco Patti: Supervision; Validation.

Anneke Van der Walt: Supervision; Validation.

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Competing interests

A.S. has received honoraria for lecturing or advisory board participation from Roche, Novartis, Merck, Biogen and Sanofi. T.K. has served on scientific advisory boards or as a consultant for MS International Federation and World Health Organisation, Therapeutic Goods Administration, BMS, Roche, Janssen, Genzyme, Novartis, Merck and Biogen, and received conference travel support and/or speaker honoraria from WebMD Global, Merck, Sandoz, Novartis, Biogen, Roche, Eisai, Genzyme, Teva and BioCSL, and received research or educational event support from Biogen, Novartis, Genzyme, Roche, Celgene and Merck. I.R. has served on scientific advisory boards and received conference travel support and/or speaker honoraria from Roche, Novartis, Merck and Biogen. E.D. has participated in the Roche Steering Committee and have served on advisory boards for Merck, Sanofi, Novartis, Roche, Neuraxpharm, and Biogen. J.L.-S. has received travel compensation from Novartis, Biogen, Roche and Merck. Her institution receives honoraria for talks and advisory board commitments as well as research grants from Biogen, Merck, Roche and Novartis. S.O. reports no relevant disclosures. P.H. has received compensations for travel, speaker honoraria and/or consultant fees from Biogen, Novartis, Merck KGaA, Sanofi, Roche, Janssen and Teva. D.H. was supported by the Charles University Cooperatio Program in Neuroscience, and the National Institute for Neurological Research (EXCELES, ID LX22NPO5107) funded by the EU Next Generation Programme, and by the General University Hospital in Prague project MH CZ-DRO-VFN64165. She has also received compensation for travel, speaker honoraria and consultant fees from Biogen Idec, Novartis, Merck, Bayer, Sanofi Genzyme, Roche, and Teva. M.V. has received compensation for travel, speaker honoraria and/or consultant fees from Biogen, Merck KGaA, Novartis, Roche, Sanofi, Teva and Janssen-Cilag. I.P. has received honoraria for lecturing or advisory board participation from Alexion and Novartis. Stefano Ruzza reports no relevant disclosures. M.G.P. has received honoraria for

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Availability of data and materials

The data underlying this article were provided by the MSBase Foundation under licence and are not publicly available due to participant privacy, governance, and data-sharing agreements with contributing centres. De-identified individual-level data may be available upon reasonable request to the MSBase Scientific Leadership Group (see www.msbase.org) and subject to ethics approvals and a data-use agreement. Aggregated data supporting the findings are available within the article and its Supplementary Material.

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Supplemental material

Supplemental material for this article is available online.

Reporting guideline

This observational cohort study was designed and reported in accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) and RECORD (REporting of studies Conducted using Observational Routinely collected health Data) statements. A completed STROBE checklist is available in the Supplementary Materials.

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