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ORIGINAL COMMUNICATION

Pediatric-onset Multiple Sclerosis treatment: a multicentre observational study comparing natalizumab with fingolimod

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Abstract

Background Pediatric-onset Multiple Sclerosis (POMS) patients show more inflammatory disease compared with adult-onset MS. However, highly effective treatments are limited with only fingolimod being approved in Italy and natalizumab prescribed as off-label treatment.

Objectives to compare the efficacy of natalizumab versus fingolimod in POMS.

Methods This is an observational longitudinal multicentre study including natalizumab- and fingolimod-treated POMS patients (N-POMS and F-POMS, respectively). We collected Annual Relapse Rate (ARR), Expanded Disability Status Scale (EDSS), Symbol Digit Modality Test (SDMT), and MRI activity at baseline (T0), 12–18 months (T1), and last available observation (T2).

Results We enrolled 57 N-POMS and 27 F-POMS patients from six Italian MS Centres. At T0, N-POMS patients showed higher ARR ($p=0.03$), higher EDSS ($p=0.003$) and lower SDMT ($p=0.04$) at baseline compared with F-POMS. Between T_0 and T_1 ARR improved for both N-POMS and F-POMS ($p<0.001$), while EDSS ($p<0.001$) and SDMT ($p=0.03$) improved only for N-POMS. At T_2 (66.1 ± 55.4 months) we collected data from 42 out of 57 N-POMS patients showing no further ARR decrease.

Conclusion Both natalizumab and fingolimod showed high and sustained efficacy in controlling relapses and natalizumab also associated to a disability decrease in POMS. This latter effect might be partly mediated by the high inflammatory activity at baseline in N-POMS.

Keywords Multiple Sclerosis · natalizumab · fingolimod · pediatric multiple sclerosis · disease modifying treatment · real-worldstudy

Introduction

Multiple Sclerosis (MS) is a chronic immune-mediated inflammatory disease of the central nervous system. While MS primarily affects young adults, with an incidence peak between 20 and 40 years, it presents before the age of 18 in approximately 3–10% of cases [1]. The natural history of Pediatric-Onset Multiple Sclerosis (POMS) markedly differs from that of adult-onset MS (AOMS), with POMS showing greater inflammatory activity, reflected in higher relapse rate and accelerated accumulation of new Magnetic Resonance Imaging (MRI) lesions, compared with AOMS [2–7]. Differently from AOMS, POMS cases typically exhibit a slower progression toward significant disability though they reach key disability milestones approximately 10 years earlier than AOMS patients [2].

The risk of disability decreases significantly in individuals promptly treated with high-efficacy Disease-Modifying Therapies (DMTs) [8]. The therapeutic management of patients with POMS is challenging due to the difficulty to perform randomized controlled trials assessing the efficacy and safety in children of DMTs already used to treat adult patients [9]. In Europe, fingolimod is the only approved DMT by EMA and the National Regulatory Agency (AIFA)

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for POMS, based on findings from PARADIGMS trial [10]. In this trial, fingolimod was proven to be effective in reducing relapse rate, new MRI lesions, and brain atrophy accrual over a 2-year period vs interferon beta 1a. Other high-efficacy DMTs (e.g., natalizumab) are prescribed exclusively as off-label treatment given the efficacy and safety profile of the drug reported from observational and prospective real-world data.

Published observational studies reporting off-label natalizumab usage consistently demonstrate the efficacy of natalizumab in reducing disease activity in POMS, including those with aggressive disease, without significant adverse effects [11–13]. However, natalizumab can be prescribed to POMS patients in whom the use of fingolimod is contraindicated, has not been tolerated or has not been shown to be effective, and with specific criteria (two or more disabling relapses in the last year, and 1 or more gadolinium-enhancing lesions on brain MRI or with a significant increase in lesion load at T2 compared to a previous MRI performed at least three months apart [14]). Furthermore, natalizumab is associated with a higher risk of progressive multifocal leukoencephalopathy, caused by the JC virus [15]. Therefore, clinicians are usually cautious to prescrive natalizumab in those patients with higher Anti-JC virus antibodies titres.

Studies comparing prescription patterns of natalizumab and fingolimod in clinical settings (i.e., patients population addressed to either fingolimod or natalizumab) or comparing treatment effectiveness are still lacking. Different real-world studies comparing long-term and short-term safety and efficacy between the two drugs in the adult population have reported contrasting results, with some studies showing a trend favoring natalizumab [16–20]. A recent study analyzing data from three MS registries showed that natalizumab had higher efficacy compared with fingolimod in AOMS patients [21]. Considering the scarcity of available data in the pediatric population, we conducted a multicentre longitudinal observational study in Italy to describe the use of available high-efficacy therapies in POMS. The objective is to evaluate clinical utilization of fingolimod and natalizumab in real-world settings and to compare the efficacy of the two drugs accounting for the possible selection biases.

Methods

This is a multicentre longitudinal retrospective study. We included POMS patients from 6 Italian MS Centres (1.Federico II University, Naples; 2. Bambino Gesù Hospital IRCCS, Rome; 3. Sapienza University of Rome, Rome; 4. University of Campania, Naples; 5.University of Florence, Florence; 6. SS. Annunziata University Hospital, Chieti), satisfying the following inclusion criteria: (1) MS diagnosis according to Krupp criteria [22] (2) POMS with treatment with natalizumab or fingolimod start before 18 years of age; (3) age at last available follow-up < 25 years old; (4) patients starting on fingolimod (F-POMS) or natalizumab (N-POMS) treatment with at least 12 month of follow-up; (5) body weight between 50 and 100 kg allowing a standard treatment dosage; (6) no other major systemic, psychiatric or neurologic diseases. POMS patients treated with both fingolimod and natalizumab in sequence were included only for the DMT started earlier (see Fig. 1).

Standard protocol approvals, registrations, and patient consents

Approval was received from the 'Comitato Etico Campania 3' (approval number:0023943). All subjects and parents, when necessary, gave written informed consent prior to study participation. The study was performed in accordance with good clinical practices and the Declaration of Helsinki.

Clinical assessment

We retrospectively included patients treated with natalizumab and fingolimod, with at least two clinical assessment 12–18 months apart: at baseline corresponding treatment start (T_0) and after 12–18 months (T_1). Since natalizumab has been used for longer time in clinical settings, we also collected clinical and radiologic data up to the last available assessment (T_2) for N-POMS.

Patients treated with natalizumab received intravenous 300 mg administration of natalizumab each 28 days. Patients treated with fingolimod received oral 0.5 mg per day.

At T_0 we recorded clinical and demographic data (mandatory data: age, sex, disease duration expressed in months, number of previous disease modifying treatments, previous DMT, reasons for switching from previous disease modifying treatments, annualized relapse rate, Expanded Disability Status Scale (EDSS) [23]; Paediatric Multiple Sclerosis Severity Score (Ped-MSSS) [24]; supplemental data: lesion load based on conventional T2-weighted MRI scan [low if < 10lesions; medium if lesions number between 10 and 25; high if lesions > 25] assessed from neurologists involved in the study with demonstrated expertise in reviewing MRI images as for conventional radiologic reporting systems [25], contrast-enhancing lesions [yes/no], symbol digit modality test (SDMT) [26], JCV positivity [yes/no]). At T_1 and T_2 we recorded the following clinical data: time from previous assessment, EDSS, relapse occurrence and time to relapse, occurrence of DMT switch, time to DMT switch and reason for DMT switch (inefficacy, tolerability [lack of adherence to drug administration protocol for personal choice or willingness of different mode of administration], safety concerns), lesion load based on conventional T2-weighted

MRI scan (low if < 10lesions; medium if lesions number between 10 and 25; high if lesions > 25), contrast-enhancing lesions (yes/no), SDMT, JCV positivity (yes/no). MRI activity was defined based on the radiologic report provided from the radiologist blinded to patients' treatment. MRI activity was defined either as contrast-enhancing lesion and/or new/enlarging T2 lesions at follow-up scans.

Statistical analysis

Statistical analyses were performed using the Stata software (version 13; StataCorp LP, College Station, TX). Demographic, clinical and radiologic features of study subjects are presented as means, medians or proportions as appropriate. All demographic, clinical and laboratory variables were checked for normality using the Shapiro–Wilk normality test. Differences between F-POMS and N-POMS for demographic and clinical features at T_0 were assessed through *t*-Test, Mann–Whitney *U* or Chi-squared as appropriate.

Paired-Samples *t* test or Wilcoxon matched-paired signed-rank test was used to compare Annual Relapse Rate (ARR), EDSS and SDMT among different time points for each drug.

We performed a propensity score (PS) matching analysis accounting for possible differences in clinic-demographic variables at T_0 in the two arms too explore natalizumab or fingolimod associated with relapse occurrence or DMT switching over the follow-up.

Specifically, to balance observed covariates (i.e., age, sex, EDSS, Ped-MSSS, ARR and number of previous treatment) between F-POMS and N-POMS we employed the PS method. A Binary Logistic Regression Model, with treatment group as dependent variable, was applied for the calculation of the PS. The PS was calculated as the predicted probability of occurrence of the event (treatment group allocation). To obtain two groups not differing for considered covariates we performed a 1-to-1 matching with no replacement methods using a caliper of 0.2 as maximum PS score distance to match groups. We applied the matching technique instead of the adjusting PS technique as to be more conservative. Using the created groups we performed analysis of survival by Cox Regression model, for time to DMT switch and time to first relapse occurrence. A p value < 0.05 was considered statistically significant. Results are presented with 95% confidence interval (95%CI) or p values.

Data availability

The anonymised dataset used and analyzed during the current study is available from the corresponding author upon reasonable request.

Results

Clinical and MRI measures at baseline

Demographic and clinical data from subjects enrolled in the study are summarized in Table 1. We included 84 MS patients (27 patients treated with fingolimod [disease duration (mean ± SD): 16.3 ± 26.1 months] and 57 patients treated with natalizumab [disease duration: 13.5 ± 15.4 months]). Compared with F-POMS, N-POMS showed higher number of total relapse before T_0 (median [range]: 2 [0–10] vs 1 [1–6], $p = 0.02$), higher ARR before T_0 (1 [0–5.2] vs 1 [0.1–4.4], p = 0.03), higher EDSS at T_0 (median [range]: 2 [0–6] vs 1.5 [0–3.5], $p = 0.003$), higher Ped-MSSS [mean ± SD: 7.2 ± 2.9 vs 5.2 ± 3.2, $p = 0.005$], higher prevalence of patients switching from previous DMT due to inefficacy (72% vs 37%, $p = 0.02$) and lower SDMT ((mean ± SD): 49.4 ± 7.9 vs 60.2 ± 9.2, $p = 0.04$).

Clinical and MRI measures at T_1

Overall, patients were followed-up for a mean follow-up time at T_1 of 13.9 ± 3.8 months with no differences in follow-up time between F-POMS and N-POMS ($p = 0.95$). Between T0 and T1, the percentage of patients switching to another DMT was not different between F-POMS (3 out of 27 [11.1%]) and N-POMS (6 out of 57 [10.5%]) ($p = 0.93$). F-POMS mostly switched for inefficacy () compared with N-POMS, who mostly switched for safety concerns due to JCV antibody positivity (2 out of 3 F-POMS vs 5 out of 6, $p = 0.13$). Time to first DMT switch was not different between the two groups ($p = 0.76$).

Both F-POMS and N-POMS showed ARR reduction between T_0 and T_1 (F-POMS: 1 [0.1–4.4] vs 0 [0–0.1], $p < 0.001$; N-POMS: 1 [0–5.2] vs 0 [0–0.2], $p < 0.001$). Eight out of 27 F-POMS (30%) and 8 out of 57 (14%) N-POMS experienced at least one relapse between T_0 and T_1 ($p = 0.09$). Time to first relapse was not different between the two groups ($p = 0.76$). Two N-POMS patients switched to fingolimod after 6 and 11 months from T_0 because of JCV sieroconversion. None of the F-POMS switched to natalizumab.

F-POMS did not show EDSS change between T_0 and T_1 (1.5 [0–3.5] vs 1.5 [0–2.5], $p = 0.56$). Conversely, N-POMS showed EDSS reduction between T_0 and T_1 (2 [0–6] vs 2 [0–6], $p < 0.001$). MRI data at T_1 were available for 73 out of 81 patients. Five out of 21 (23.8%) F-POMS and 11 out of 52 (21.2%) N-POMS showed MRI activity between T_0 and T_1 ($p = 0.80$). Finally, only 1 out of 5 F-POMS performed a SDMT assessment at T_1 showing thus changes were not assessed whereas 7 out of 8

Table 1 Demographic and clinical features for the enrolled patients

	Fingolimod	Natalizumab	*p* value
Subjects	27	57	
Center			
Federico II University, *N* (%)	7 (26)	20 (35)	
University of Florence, *N* (%)	2 (7)	2 (3)	
University of Campania, *N* (%)	4 (15)	6 (10)	
Hospital Bambino Gesù, *N* (%)	9 (34)	18 (32)	
University of Rome 'La Sapienza', *N* (%)	2 (7)	9 (17)	
Sant' Annunziata University Hospital, *N* (%)	3 (11)	2 (3)	
Sex			
Female, *N* (%)	19 (70)	40 (70)	0.98
Male, *N* (%)	8 (30)	17 (30)	
Age, mean ± SD (years)	16.2 ± 2.7	15.6 ± 2	0.26
Age of onset, mean ± SD (years)	14.3 ± 3.4	14 ± 2.3	0.71
Age of diagnosis, mean ± SD (years)	14.9 ± 3.3	14.4 ± 2,2	0.54
Disease duration, mean ± SD (month)	16.3 ± 26.1	13.5 ± 15.4	0.54
EDSS, median (range)	1.5 (0–3.5)	2 (0–6)	0.003
Ped-MSSS, mean ± SD	5.2 ± 3.2	7.2 ± 2.9	0.005
Number of relapse pre T_0, median (range)	1 (1–6)	2 (0–10)	0.02
ARR pre T_0, median (range)	1 (0.1–4.4)	1 [0–5.2]	0.03
N° Previous DMT T_0, median (range)	1 (0–2)	1 (0–2)	0.38
Previous DMT T_0[a]			
Interferon, *N* (%)	14 (87)	25 (86)	0.06
Glatiramer acetate, *N* (%)	1 (6.5)		
Dimethyl fumarate, *N* (%)	1 (6.5)	3 (10)	
Mitoxantrone, *N* (%)		1 (4)	
Reason for switch			
Inefficacy, *N* (%)	6 (37)	21 (72)	0.02
Tollerability, *N* (%)	10 (63)	8 (28)	
Safety concerns, *N* (%)			
MRI lesion load[b]			
Low, *N* (%)	3 (12)	9 (17)	0.77
Medium, *N* (%)	12 (44)	21 (39)	
High, *N* (%)	12 (44)	24 (44)	
MRI contrast enhancement[c]			
Yes, *N* (%)	14 (58)	40 (78)	0.07
No, *N* (%)	10 (42)	11 (22)	
JCV status[d]			
Positive, *N* (%)	10 (53)	7 (15)	0.002
Negative, *N* (%)	9 (47%)	39 (85)	
SDMT T0, mean ± SD[e]	60.2 ± 9.2	49.4 ± 7.9	0.04

DMT Disease modifying treatment, *EDSS* Expanded disability status scale, Ped-*MSSS* Paediatric Multiple Sclerosis Severity Score, *SD* standard deviation, *SDMT* Symbol Digit Modality Test

(a) over total patients switching treatment; (b) data available for 81 patients; (c) data available for 75 patients; (d) data available for 65 patients (e) data available for 13 patients;

*Chi-squared, t test or Wilcoxon rank-sum as appropriate

N-POMS performed a SDMT assessment at T_1 showing increase in the SDMT score (48.4 ± 8.1 vs 54.2 ± 5.7, $p = 0.03$).

Propensity score matching analysis

After PS matching, we included 42 POMS patients in the analysis (21 F-POMS and 21 N-POMS). Groups were

comparable for age ($p=0.96$), gender ($p=0.52$), ARR at T_0 ($p=0.89$), EDSS at T_0 ($p=0.62$), Ped-MSSS ($p=0.64$) and number of previous DMT at T_0 ($p=1.0$). Clinical features of patients included in the analysis following PS-matching are reported in Table 2. The time to first relapse occurrence as well as time to DMT switch was not different between the two groups ($p=0.17$ [see Fig. 1] and $p=0.85$, respectively).

Clinical and MRI measures at T_2 for N-POMS

Forty-two out of 57 N-POMS patients were followed-up at T_2 with a mean follow-up time of 66.1 ± 55.4 months. Between T_1 and T_2, 9 out of 42 (21%) N-POMS switched to another DMTs after mean time of 64.4 ± 39.4 months with 8 patients switching for safety concerns and 1 patients switching for inefficacy. Seven out of 42 (17%) N-POMS experienced at least one relapse between T_1 and T_2 after 71.5 ± 47.2 months. EDSS and ARR did not change between T_1 and T_2. MRI data at T_2 were available for 37 out of 42 patients. Eight out of 37 (22%) N-POMS showed MRI activity between T_1 and T_2. Finally, we collected SDMT from 5 out of 7 N-POMS who already performed SDMT assessment at T_1 and no changes were observed ($p=0.79$). Over the follow-up none of the patient experienced any serious adverse event including PML, hospitalization due to relapse severity or infections.

Discussion

In this study, we investigated the efficacy of fingolimod and natalizumab in POMS in a multicentre setting. We reported that overall natalizumab was prescribed to patients with much higher disease activity. Notwithstanding this bias in patient selection, over the follow-up both natalizumab and fingolimod were able to control the ARR as well as the EDSS, and SDMT. The beneficial effect of natalizumab on clinical outcomes was also confirmed longitudinally. However, if groups were balanced for disease severity at baseline, the two DMTs showed comparable efficacy profiles over time.

The first finding concerns the attitude of neurologists in prescribing natalizumab to POMS patients with greater disease activity, forecasting higher disability risks over the follow-up. Specifically, in our cohort, N-POMS showed higher relapse rate, physical and cognitive disability and mostly switched from previous DMTs due to inefficacy. Previous reports in AOMS have already shown that clinicians are usually more prone in prescribing natalizumab instead of fingolimod in highly active patients notwithstanding fingolimod shows a better ease of use (oral vs intravenous administration) and a lesser extent of life-threatening adverse event (i.e., progressive multifocal leucoencephalopathy) [16, 21].

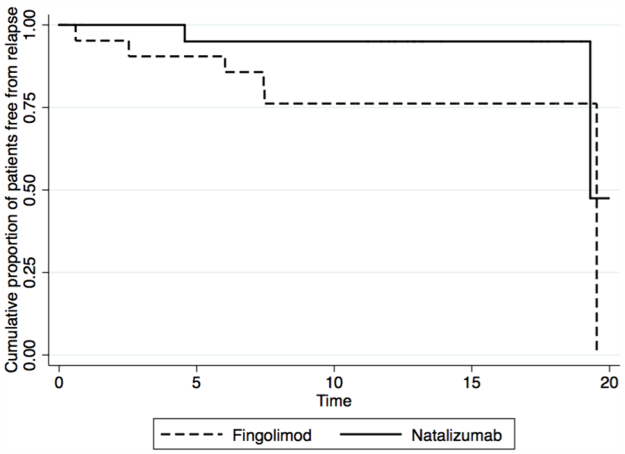

Fig. 1 Analysis of time to relapse: Cox regression analysis after propensity score matching showing no differences in time to first relapse between N-POMS and F-POMS

In a recent registry-based study, the same attitude was also demonstrated for POMS and, hence, our study is in line with the report [27, 28]. However, the reason underpinning such attitude is still unclear. In clinical settings, natalizumab was proven to be more effective in controlling fatigue with a better patients' perception vs fingolimod [28, 29]. Possibly, clinicians also consider these aspects and their impact on the on the overall disability, and, thus, tend to prescribe more often natalizumab in those patients with higher risk of disability accrual over the follow-up.

In addition, natalizumab was proven to be able to rapidly promote disability improvement after clinical relapses possibly through rapid resolution of acute inflammation allowing proper repair actions [30]. It was also demonstrated that delayed natalizumab start was associated with increases relapse frequency and motor disability [31–33]. These factors might provide rationale for selecting natalizumab over fingolimod treatment in POMS with more severe disease onset.

Another aspect that might drive clinicians to use natalizumab over fingolimod in patients with more severe disease activity is the treatment efficacy profile. In both adults and pediatric MS patients, previous studies evaluating treatment efficacy for fingolimod and natalizumab suggested an outperformance of the latter in halting disability accrual and disease flares over the follow-up [16–19].

However, these studies also highlight the difference for clinical and demographic baseline features for patients in the two groups, suggesting caution should be taken when interpreting or planning a randomized clinical trial. To overcome the lack of a randomized clinical trial, statistical tools could be applied to assess treatment efficacy in real-world setting, adjusting analyses for baseline features between groups. PS matching is the most frequently used among

Table 2 Demographic and clinical features for patients included in the propensity-score matched analysis according to treatment allocation

	T0		*p* value*	T1			*p* value **	T2	*p* value***
	Fingolimod	Natalizumab		Fingolimod	*p* value**	Natalizumab		Natalizumab	
Subjects	27	57		27		57	–	42	–
Age at T_0, mean ± SD	16.2 ± 2.7	15.6 ± 1.9	0.26						
Sex									
Female, *N* (%)	19 (70)	40 (70)	0.98	19 (70)	–	40 (70)	–	31 (16)	–
Male, *N* (%)	8 (30)	17 (30)		8 (30)	–	17 (30)	–	11 (84)	–
EDSS, median (range)	1.5 (0–3.5)	2 (0–6)	0.003	1.5 (0–2.5)	0.56	2 (0–6)	$p < 0.001$	2 (0–7)	0.15
ARR, median (range)	1 (0.1–4.4)	1 (0–5.2)	0.03	0 (0–0.1)	$p < 0.001$	0 (0–0.2)	$p < 0.001$	0 (0–0.005)	0.86
SDMT, mean ± SD	60.2 ± 9.2[a]	49.4 ± 7.9[b]	0.04	–	–	54.2 ± 5.7	0.03	55 ± 7.6	0.79
	T0-PS adjusted		*p* value *	T1-PS adjusted			*p* value **	T2-PS adjusted	*p* value ***
	Fingolimod	Natalizumab		Fingolimod	*p* value **	Natalizumab		Natalizumab	
Subjects	21	21		21	–	21	–	17	–
Age at T_0, mean ± SD	15.9 ± 2.8	15.9 ± 1.8	0.96	–	–	–	–	–	–
Sex									
Female, *N* (%)	14 (67)	12 (57)	0.52	14 (67)	–	12 (57)	–	11 (65)	–
Male, *N* (%)	7 (33)	9 (43)		7 (33)	–	9 (43)	–	6 (35)	–
EDSS, median (range)	1.5 (0–3.5)	1.5 (0–3)	0.62	1.5 (0–2.5)	0.98	1 (0–2.5)	0.18	1.5 (0–7)	0.46
ARR, median (range)	1 (0.3–4.4)	1 (0.5–3.2)	0.89	0 (0–0.01)	< 0.001	0 (0–0.01)	< 0.001	0 (0–0.001)	0.52
Ped-MSSS, mean ± SD	5.7 ± 3.0	5.3 ± 2.9	0.64	–	–	–	–	–	–
SDMT, mean ± SD	60.5 ± 10.6[c]	48.3 ± 1.5[d]	0.11	–	–	51 ± 1.4	0.11	–	–

EDSS Expanded Disability Status Scale, *Ped-MSSS* Paediatric Multiple Sclerosis Severity Score, *SD* standard deviation, *SDMT* Symbol Digit Modality Test, *ARR* Annualizes Relapse Rate

*Chi-squared, t test or Wilcoxon rank-sum as appropriate

**Paired *t* test or Wilcoxon rank-sum as appropriate compared to T0

***Paired *t* test or Wilcoxon rank-sum as appropriate compared to T1

(a) data available for five patients; (b) data available for 8 patients; (c) data available for four patients; (b) data available for three patients

these tools allowing the definition of subgroups from larger groups with a balance for selected variables. This score has been widely applied in many therapeutic areas, including MS, to adjust for the uncontrolled assignment of treatment in observational studies [34]. As we already demonstrated in adults [16], when accounting for clinical features at baseline, natalizumab and fingolimod exert similar effect in modifying disease activity and, hence, could be used in a similar clinical landscape. Indeed, when evaluating the switch from platform therapies in patients with active disease, natalizumab is more effective than fingolimod in adult MS patients [35].

Finally, we also demonstrated the long-term efficacy of natalizumab in POMS. Specifically, natalizumab showed sustained efficacy in reducing disability accrual and relapse occurrence up to 5 years. Treatment with fingolimod was previously associated with favorable outcomes in adult-adult onset onset multiple sclerosis patients [36] as well as in POMS [37–40] as assessed through randomized clinical trials. On the other hand, we do not have proper randomized clinical trial assessing the efficacy of natalizumab vs fingolimod in POMS in the long run. This prevents natalizumab from being approved by regulatory agencies as treatment for POMS. To circumvent this shortage, several real-world studies highlighting the sustained efficacy of natalizumab are accumulating [12, 16–18, 27]. Therefore, to not necessarily prescribe natalizumab as an off-label treatment when considering natalizumab treatment as first line therapy in POMS, even below 12 years of age, our data would further support the drug-approval process from regulatory agencies. In addition, besides intravenous treatment, natalizumab could be prescribed as subcutaneous administration in adult patients after 1 year of intravenous infusion, reducing the burden for clinical facilities needed to administer infusion treatment.

We do acknowledge that this study is not without limitations. First, while this is a longitudinal study, given the retrospective nature of the study, previously collected data might not be complete and recorded in a systematic way. Furthermore, while the multicentre nature of the study allows the

possibility of enrolling a larger sample size, this would also carry greater variability in data collection ad clinicians' behavior in treatment prescription. Indeed, while the study is multicentre in nature, enrolling centres are tertiary centres where usually more severe cases are addressed. Hence, our findings might not reflect the attitude of clinicians toward less severe cases. Second, we relied on clinicians' evaluation for radiologic report of the MRI activity without a centralized MRI assessment. Since no specific MRI protocols were defined, data might not be uniform throughout participating centres. Similarly, SDMT assessment was not a standard procedure for the study and, consequently, we only collected few data on the cognitive status of the patients. This led to the absence of valuable information on the effect of natalizumab and fingolimod on cognitive function in POMS. Finally, although PS is a powerful tool to correct for group differences in terms of clinic-demographic variables, differently from randomization, it might lack a proper group balance for unobserved variables.

In conclusion, in our study, we observed that clinicians usually prescribe natalizumab more frequently than fingolimod in POMS patients showing higher inflammatory activity. Natalizumab showed a greater effect in controlling relapses and reducing disability in POMS, although this effect seems to be mostly attributable to the high inflammatory activity of patients treated with natalizumab. Therefore, it might be valuable to select natalizumab over fingolimod in patients with more severe inflammatory activity. Indeed, when balancing group for disease-specific features, the two treatments showed the same efficacy profile. Finally, we reported that natalizumab showed a sustained beneficial effect in the long run, without safety concerns in POMS, thus, adding further finding in support of the approval process for the natalizumab treatment in young patients.

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Declarations

Conflicts of interest AC has received research grants from Almirall, research grants from ECTRIMS-MAGNIMS and honoraria from Almirall, Biogen, Roche, Sanofi-Genzyme, Merck, Ipsen and Novartis. MM has received research grants from the ECTRIMS-MAGNIMS, the UK MS Society, and Merck; honoraria from Biogen, BMS Celgene, Ipsen, Janssen, Merck, Novartis, Roche, and Sanofi-Genzyme. MP has received research grants from Italian MS Foundation and Baroni Foundation, honoraria from HEALTH&LIFE S.r.l. and Biogen and sponsorship for travel/meeting expenses from Novartis, Roche and Merck. RL has received honoraria from Biogen, Merck, Novartis, Roche, and Teva. VBM has received research grants from the Italian MS Society, and Roche, and honoraria from Bayer, Biogen, Merck, Mylan, Novartis, Roche, Sanofi-Genzyme, and Teva. MV has received grants by Biogen, Roche, Lusofarmaco and Angelini. ALS, CDM, FN, DDS, CI, GS, LP, GDL, CM, MT have nothing to disclose. VT has received research and travel support and honoraria from the Biogen, BMS Celgene, Janssen, Merck, Novartis, Roche, Sanofi-Genzyme Almirall, Viatris, Lundbeck. Carlo Pozzilli has served on scientific advisory boards for Bristol Meyer, Novartis, Merck, Biogen, Roche, Janssen, Alexion, Almirall and has received research support from Merck, Biogen, Bristol Meyer, Novartis and Roche. AI received consulting fees from Janssen. ES received personal compensation from Almirall, Biogen, Sanofi, Novartis, Roche, Horizon, Alexion, Merck, Mylan and Teva for traveling and advisory boards. GB received honoraria and consulting fees from Almirall, Biogen, BMS, Janssen, Merck, Novartis, Sanofi and Roche. GL received speaker honoraria and/or consultancy from Biogen, Teva, Genzyme, Merck, Novartis, Almirall and Roche. EP received compensation for travel grants, participation in advisory board and/or speaking activities from Biogen, Merck Serono, Sanofi, Teva, and Novartis; serves on the editorial board of Frontiers in Neurology and Brain Sciences. MPA 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.

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