A multicentRE observational analysiS of PErsistenCe to Treatmentin the new multiple sclerosis era: the RESPECT study

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Abstract

In this independent, multicenter, retrospective study, we investigated the short-term persistence to treatment with first-line self-injectable or oral disease-modifying treatments (DMTs) in patients with relapsing–remitting multiple sclerosis. Data of patients regularly attending 21 Italian MS Centres who started a self-injectable or an oral DMT in 2015 were collected to: (1) estimate the proportion of patients discontinuing the treatment; (3) explore reasons for discontinuation; (3) identify baseline predictors of treatment discontinuation over a follow-up period of 12 months. We analyzed data of 1832 consecutive patients (1289 women, 543 men); 374 (20.4%) of them discontinued the prescribed DMT after a median time of 6 months (range 3 days to 11.5 months) due to poor tolerability (n = 163; 43.6%), disease activity (n = 95; 25.4%), adverse events (n = 64; 17.1%), convenience (i.e. availability of new drug formulations) and pregnancy planning (n = 21; 1.1%). Although the proportion of discontinuers was higher with self-injectable (n = 107; 22.9%) than with oral DMT (n = 215; 16.4%), the Cox regression model revealed no significant between-group difference (p = 0.12). Female sex [hazard ratio (HR) = 1.39, p = 0.01] and previous exposure to ≥ 3 DMTs (HR = 1.71, p = 0.009) were two independent risk factors for treatment discontinuation, regardless of prescribed DMTs. Our study confirms that persistence to treatment represents a clinical challenge, irrespective of the route of administration.

Introduction

Self-injectable disease-modifying treatments (DMTs)—glatiramer acetate and interferon beta—were, until recently, the only first-line therapies approved for relapsing–remitting multiple sclerosis (RRMS). In the pivotal clinical trials, the rates of DMT persistence at the end of first year on study ranged from 90 to 97% [1–4]. However, these results cannot be adequately extrapolated to the real-world population, as lower rates of treatment persistence have been reported in post-marketing real-world studies, ranging from 78.5 to 90% after 1 year and dropping to 59–72% between the third and fifth year of treatment [5–8]. Indeed, “old” injectable DMTs suffered from a low adherence and a high rate of dis-continuations due to poor tolerance or convenience, or even to “forgetfulness” [9, 10]. Moreover, in real-world practice the presence of comorbidities can also affect persistence to treatment, leading to more frequent therapy changes [11].

In recent years, there has been an increasing availability of DMTs in RRMS, including two oral drugs—teriflunomide and dimethyl fumarate—available in Italy since 2014. Their indication is similar to self-injectable first-line DMTs [12–14], but the common perception is that these first-line oral DMTs may be more accepted and tolerated by patients than self-injectable ones, merely due to their simpler route of administration. Patients with RRMS, indeed, express preferences for oral DMTs even when reasonably satisfied of their ongoing injective therapy [15]. Therefore, oral DMTs are expected to enhance treatment adherence, a key factor to reduce relapse rate, delay disability worsening and lead to better clinical outcomes [16]. However, oral DMTs are also associated with systemic side effects. Recently, persistence to oral DMTs was explored in two studies conducted in different countries (US and Italy), showing a discontinuation rate of 20–40% over 1 year of follow-up in patients treated with teriflunomide and dimethyl fumarate, mainly due to side effects [17, 18]. Consequently, there is no established evidence yet that oral DMTs are superior to self-injectable ones in terms of adherence and persistence to treatment.

In this multicenter retrospective study, we analyzed treatment persistence in a large cohort of patients with RRMS who started a first-line DMT in 2015, with the objective to evaluate and to compare treatment persistence between self-injectable and oral DMTs and to analyze possible predictors of discontinuation.

Methods

Study design

This was an independent, multicenter, post-marketing study based on a retrospective analysis of data collected from patients with RRMS attending 21 tertiary outpatient MS Centres in Italy. Patients were considered eligible if they started a platform therapy with self-injectable or oral first-line DMTs from January to December 2015 and had at least 12 months of follow-up.

We considered the following DMTs: subcutaneous (sc), glatiramer acetate 20 mg, once daily or 40 mg every other day (Copaxone 20 or 40); intramuscular (im) interferon beta (IFNB)-1a 30 mcg, once weekly (Avonex); sc pegylated IFNB-1a 125 mcg, every 2 weeks (Plegridy); sc IFNB-1b 250 mcg, every other day (Betaferon, Extavia); sc IFNB-1a 22 or 44 mcg, thrice per week (Rebif 22 or 44); oral teriflunomide 14 mg, once daily (Aubagio); oral gastro-resistant dimethyl fumarate 240 mg, twice daily (Tecfidera).

We included data of both patients who started for the first time a DMT (naives) and those who switched from another first-line DMT (switchers), regardless of the reason for switching treatment.

We excluded patients who started monoclonal antibod-ies (natalizumab and alemtuzumab) and fingolimod because their indication mainly encompasses patients failing a previous first-line DMT and, therefore, this was considered as a “second-line” treatment strategy going beyond the scope of the study. Patients with disease course other than RRMS were also excluded.

Data collection and harmonization

In September 2016, clinicians from each participating Clinical Centre convened to a workshop in Rome where an 'ad hoc' shared electronic spreadsheet was created to collect clinical data for analyses. This electronic spreadsheet was further refined in another workshop held in January 2017 in Rome. Finally, an external subject collected data from each Centre until June 2017 and data were centrally reviewed for discrepancies by the two lead authors in September 2017. Regarding homogeneity of data collection, participating centers were all specialized MS clinics in hospital or University settings, whose neurologists were part of a scientific board called RIREMS (Raising Italian Researchers in MS) that gathers at least twice per year, since 2008, to discuss scientific and medical care issues of MS patients, with the objective of harmonizing the standard of care to patients across Italian MS Centres [19].

The present study was conducted in accordance with specific national laws and the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Given its retrospective design, in no way this study did interfere with the care received by patients

Outcome definition
The main outcome measure was treatment discontinuation within a follow-up period of 12 months.

Reasons for discontinuation were also collected and categorized into four groups:
1. poor tolerability, i.e., when discontinuation was 'patient-driven' due to expected side effects;
2. adverse events, i.e., when discontinuation was 'physician-driven' due to medical concern for expected or unexpected side effects;
3. disease activity, i.e., radiological or clinical events that led physicians to discontinue treatment for lack of efficacy;
4. others, i.e., any reason not included in the previous definitions.

Research questions
Question no. 1: "did the short-term persistence to treatment differ in patients treated with first-line self-injectable or oral DMTs?". To answer this question, we compared the proportions of patients discontinuing a self-injectable or an oral DMT, without any specific distinction across drugs. There-fore, we collapsed Copaxone, Avonex, Plegridy, Betaferon, Extavia, Rebif into a single group (self-injectable DMTs) and Aubagio and Tecfidera into another group (first-line oral DMTs).

Question no. 2: "was there any specific DMT associated with an increased risk of treatment discontinuation in the short-term period?". To answer this question, we conducted a post hoc analysis to compare the proportions of patients discontinuing Copaxone, Avonex, Plegridy, Betaferon/Extavia/Rebif, Aubagio, and Tecfidera. This allowed us to explore if factors other than the administration route, such as treatment schedule or DMT-specific side effects, could affect the short-term treatment persistence.

Question no. 3: "did the short-term persistence to treatment differ in naives patients and in switchers?". To answer this question, we re-ran all the aforementioned analyses after splitting the whole sample into two subgroups (naives and switchers).

Question no. 4: “were there demographic and/or clinical variables associated with an increased risk of treatment discontinuation in the short-term period?” To answer this question, we explored baseline demographic and clinical variables associated with treatment discontinuation, independent of the prescribed DMTs.

Statistical analysis

All research questions were explored in time-to-event analyses. We considered as main time variable the interval (in weeks) elapsed between treatment start (baseline) and treatment discontinuation for patients reaching the outcome, while all the other patients were right censored at 12 months (52 weeks).

Cox proportional hazard regressions, adjusted for gender, age, time since first symptom, EDSS score and number of previously taken DMTs were built to compare self-injectable versus oral treatments (first question), different specific treatments (second question) and naives versus switchers (third question). Another Cox model was built to identify predictors for reaching the outcome by entering the afore-mentioned patients’ characteristics as covariates and the treatment as variable of no interest (fourth question).
All models were stratified by Centre to correct for different prescription habits and rules, taking into account dis-parity across different regions in Italy in terms of treatment availability due to administrative issues.

Results

Participants

We analyzed data of 1832 consecutive patients (1289 women, 543 men) with a mean age of 40.0 (11.2) years, mean time since first symptoms of 9.1 (8.1) years and median EDSS score of 2.0 [0–7.5]. Out of 1832, 626 (34.2%) patients were treatment naïve, while the remaining 1206 (65.8%) were switchers. As expected, naives were younger, had a shorter time since first symptom and lower EDSS score than switchers ($p < 0.001$).

The most frequently prescribed treatment was Tecfidera (n = 1046; 57.1%), followed by Aubagio (n = 277; 15.1%); Copaxone 20 or 40 mg (n = 173; 9.4%); Betaferon, Extavia, Rebif 22 or 44 mcg (n = 163; 8.9%); Avonex (n = 102; 5.6%); and Plegridy (n = 71; 3.9%).

Outcome

A total of 374 (20.4%) patients discontinued the prescribed DMT after a median time of 6 months [ranging from 3 days to 11.5 months; see also Fig. 1] due to poor tolerability (n = 163; 43.6%), disease activity (n = 95; 25.4%), adverse events (n = 64; 17.1%—see also Table 1 for details) and other reasons (n = 52; 2.8%) that included convenience (i.e., availability of new drug formulations, such as witch from Copaxone 20–40 mg and from Avonex to Plegridy—n = 31; 1.7%) and pregnancy planning (n = 21; 1.1%).

To conform with our primary study purpose, that was to investigate persistence to treatment in 12 months period, we excluded from further analyses those patients who discontinued treatment for convenience and pregnancy planning (n = 52). These latter two situations cannot be indeed considered properly as two reasons of short persistence to treatment. Therefore, the next analyses are based on an overall sample of 1780 patients of whom 322 were discontinuers. Notably, time to discontinuation differed according to rea-

sons for discontinuation, as shown in Fig. 2. In more detail, discontinuation due to persistent disease activity occurred later than discontinuation due to either adverse events or poor tolerability ($p < 0.001$ by the log-rank test).

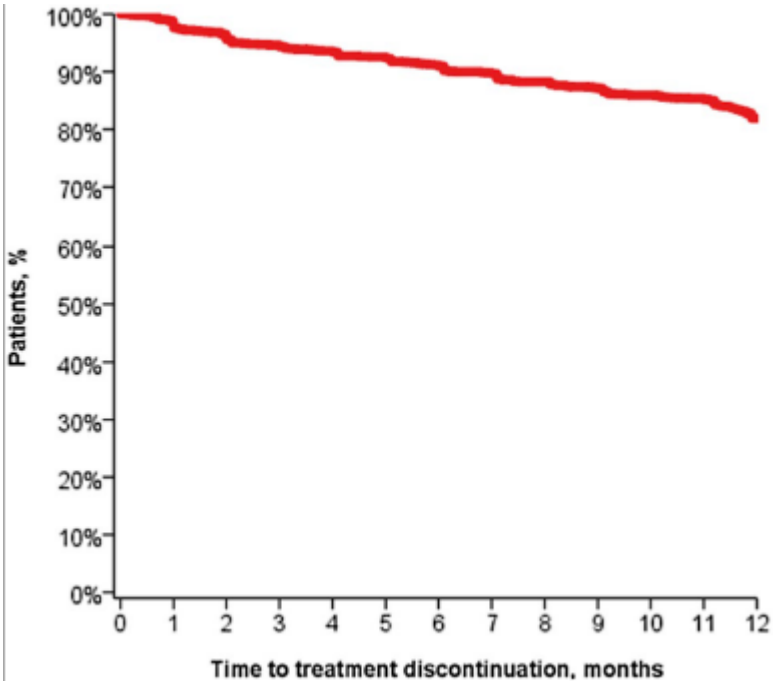

Fig. 1 Kaplan–Meier curve showing time to treatment discontinuation in the whole study sample (n = 1832)

Table 1 Frequency of adverse events leading to treatment discontinuation

Disease-modifying treatment	Description	*n*
Tecfidera (*n* = 38)	Lymphopenia	20
	Gastrointestinal disturbance	5
	Skin rash with pruritis	5
	Liver enzyme increase	5
	Others	3
Aubagio (*n* = 13)	Liver enzyme increase	5
	Hair thinning	3
	Hypertension	2
	Leukopenia	2
	Intracranial hemorrhage	1
Copaxone 20 or 40 (*n* = 5)	Erythema	4
	Lymphadenopathy	1
Betaferon, Extavia, Rebif 22 or 44 (*n* = 3)	Liver enzyme increase	2
	Mood disorders	1
Avonex (*n* = 2)	Liver enzyme increase	1
	Lymphadenopathy	1
Plegridy (*n* = 3)	Leukopenia	2
	Erythema	1

Answer no. 1

Overall, we analyzed data of 468 patients who started a self-injectable DMT and 1312 who started an oral DMT. Although the proportion of discontinuers was higher with self-injectable (n = 107; 22.9%) than with oral DMT (n = 215; 16.4%), the Cox regression model revealed no significant between-group difference (hazard ratio [HR] = 0.81; 95% confidence intervals [CIs] 0.62–1.05; p = 0.12). Figure 3 shows the survival graph according to group assignment. Different route of administration was associated with different reasons for discontinuation (Fig. 4a), poor tolerability being more common in patients treated with self-injectable DMT and adverse events more common in patients treated with oral drugs (p = 0.015 by the Chi-squared test). Discontinuation due to disease activity did not differ between self-injectable and oral DMTs.

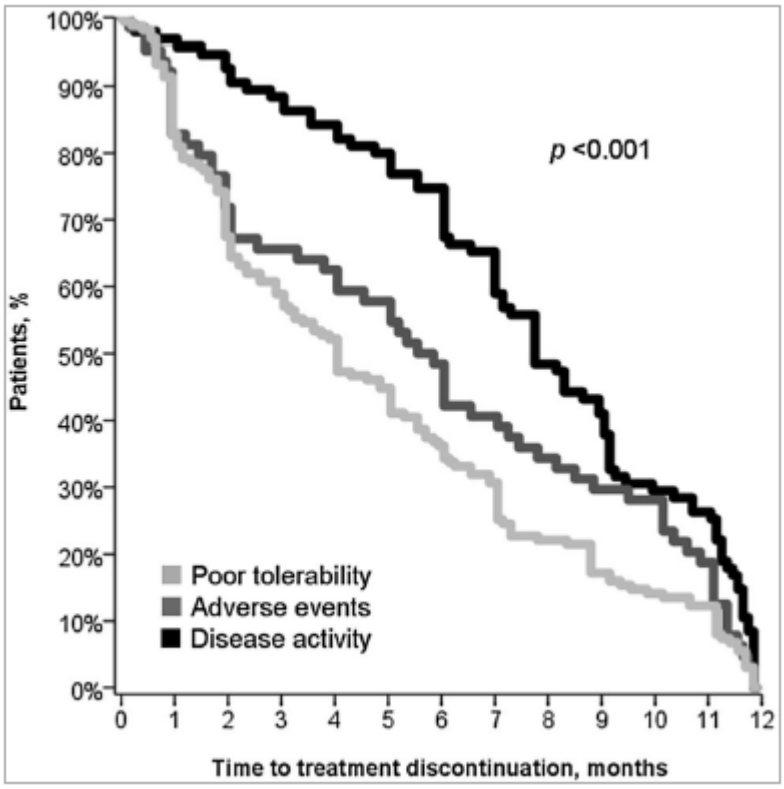

Fig. 2 Kaplan–Meier curves showing time to treatment discontinuation in patients who interrupted the prescribed disease-modifying treatment (n = 322), according to reasons for discontinuation

Answer no. 2

The highest discontinuation rate was observed in patients treated with Plegridy (45.1%) than with all the other DMTs, whose discontinuation rates ranged from 15.6 to 19.6% (p < 0.001 by the Chisquared test; see also Fig. 5). The Cox regression model revealed a more than doubled-increased risk of treatment discontinuation with Plegridy when compared with Tecfidera, which was the DMT with the lowest discontinuation rate (see also Table 2). Reasons for discontinuation were significantly different across different types of DMT (p = 0.008 by the Chi-squared test; see also Fig. 4b).

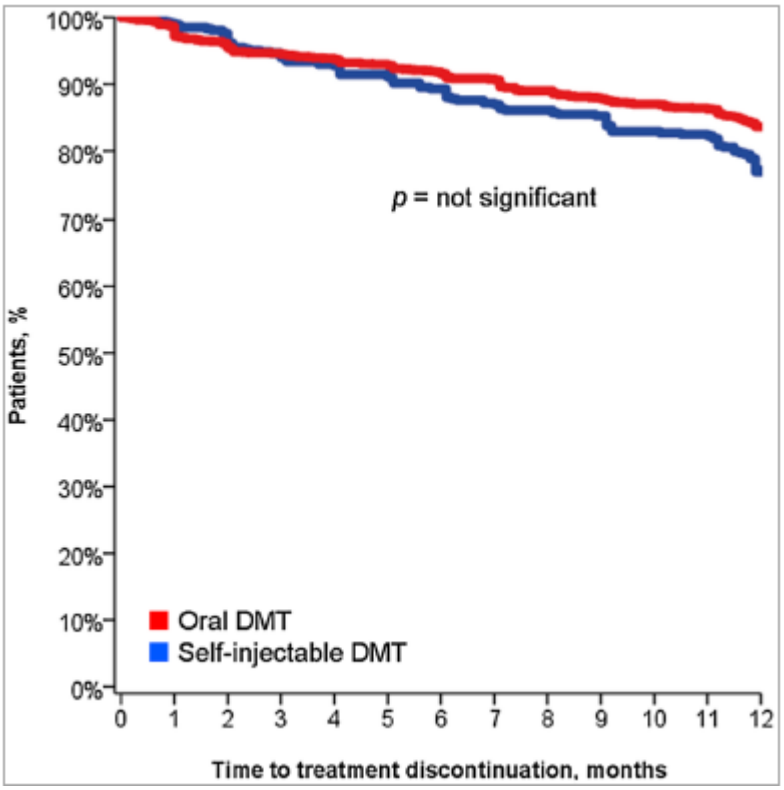

Fig. 3 Kaplan–Meier curves showing time to treatment discontinuation in patients who started a self-injectable (n = 468) and in those who started an oral disease-modifying treatment (n = 1312)

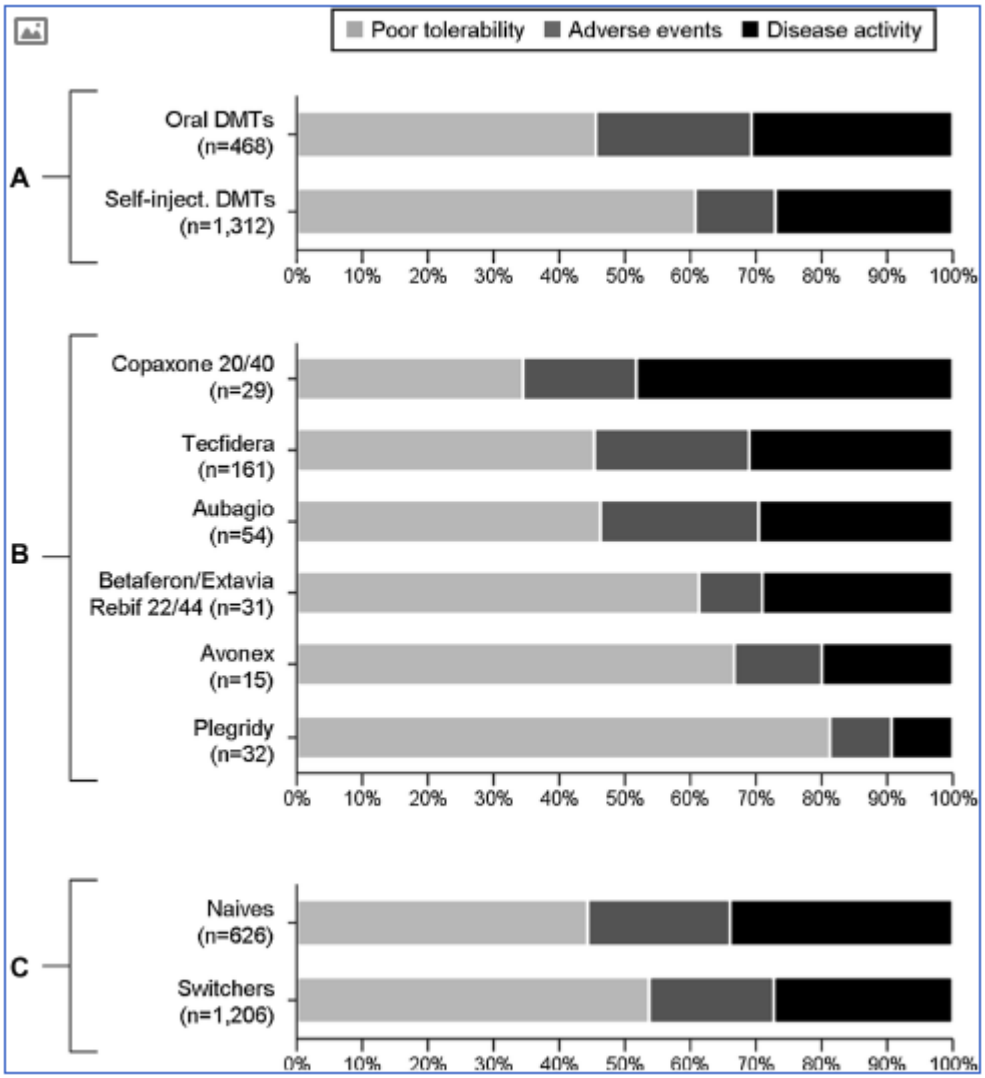

Fig. 4 Reasons for discontinuation of the prescribed disease-modifying treatment: a self-injectable versus oral; b across different types of disease-modifying treatments; c naives versus switchers

Answer no. 3

We found no difference regarding short-term persistence to treatment in naïve patients versus switchers (HR = 1.14, 95% CIs 0.87–1.49; p = 0.35). Also reasons for discontinuation were not different between these two groups (p = 0.28; see also Fig. 4c). There was no difference between naïve patients and switchers even after considering each DMT separately, with the only exception for Tecfidera (p = 0.006 by the Chi-squared test). Tecfidera discontinuation for disease activity occurred indeed more frequently in naive patients (17/39; 43.6%) than in switchers (33/122; 27.0%). Accordingly, discontinuation for poor tolerability occurred more frequently in switchers (64/122; 52.5%) than in naïve patients (9/39; 23.1%).

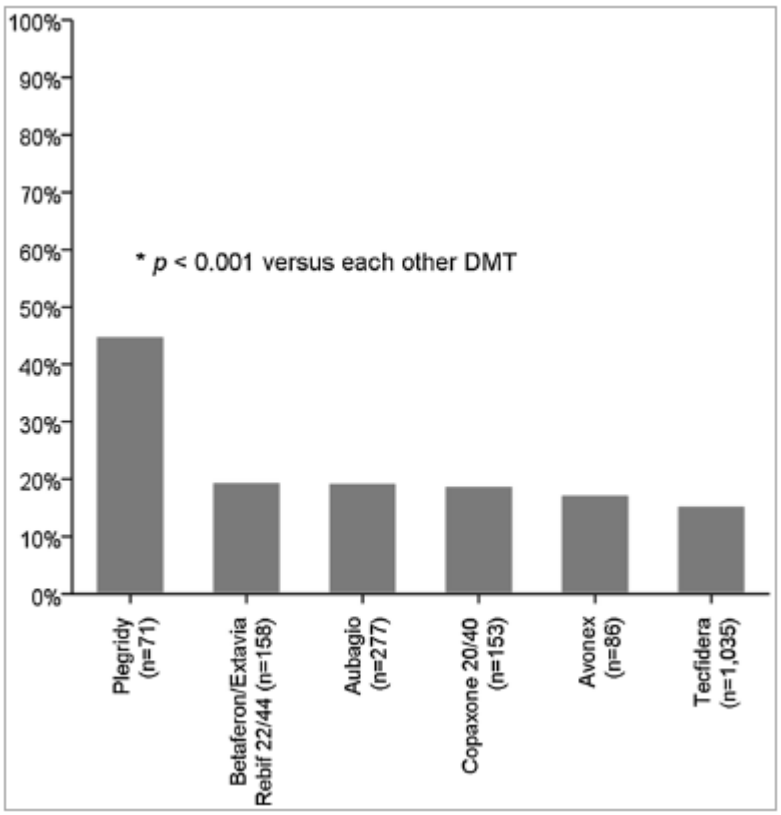

Fig. 5 Discontinuation rates according to different types of disease-modifying treatments

Table 2 Cox proportional hazard regression model comparing the risk of treatment discontinuation across different types of disease-modifying treatments (n = 1780)

	N	Discontinuation (%)	HR	95% CIs	*p*
Tecfidera	1035	15.6	1.00	–	–
Aubagio	277	19.5	1.11	0.78–1.57	0.55
Rebif 22/44, Betaferon/Extavia	158	19.6	1.07	0.70–1.63	0.76
Copaxone 20/40	153	19.0	0.91	0.59–1.38	0.64
Avonex	86	17.4	1.22	0.68–2.19	0.50
Plegridy	71	45.1	**2.15**	**1.44–3.21**	**<0.001**

Stratified by MS Clinics and adjusted for sex, age, time since first symptom, EDSS score, and no. of previously taken DMTs
HR hazard ratio, 95% CIs 95% confidence intervals
In bold are reported values significant at a two-sided α-level of 0.05

Answer no. 4
Female sex (HR = 1.39, p = 0.01) and previous exposure to ≥ 3 DMTs (HR = 1.71, p = 0.009) were two independent risk factors for treatment discontinuation, regardless of prescribed

DMTs. Notably, reasons for discontinuation did not differ between women and men and between patients with prior exposure to ≥ 3 DMTs and those who received < 3 DTMs. We also found a statistical trend for a shorter persistence to treatment in patients with higher EDSS score (HR = 1.08, p = 0.06) (see also Table 3).

Discussion

In this multicenter study, we performed a retrospective observational analysis on a large cohort of patients with RRMS who began a first-line drug in 2015, to assess their short-term persistence after the availability of new oral drugs.

The overall rate of discontinuation was approximately 20% at 12 months, mainly for poor tolerability (> 40%). This prevalence is higher than expected from RCTs and shows the evident differences between the "ideal" experimental setting and the real-world practice. Moreover, we observed longer time to discontinuation for disease activity than for adverse events and poor tolerability. These data seem to reflect the longer follow-up necessary to assess DMT effectiveness in clinical practice, since most DMTs show a certain latency before being considered active, requiring a "re-baseline" several months after treatment initiation [20]. On the other hand, poor tolerability is typically an immediate complication leading to early discontinuation.

Table 3 Cox proportional hazard regression model showing variables associated with an increased risk for treatment discontinuation (n = 1780)

	HR	95% CIs	*p*
Female sex	**1.39**	**1.07–1.81**	**0.01**
Age (each year)	1.01	0.99–1.02	0.35
Time since first symptom (each year)	0.99	0.98–1.01	0.43
EDSS score (each unit)	1.08	1.00–1.18	0.06
No. of previously taken DMT			
0	1.00	–	–
1	0.95	0.70–1.28	0.73
2	1.04	0.72–1.51	0.82
≥ 3	**1.71**	**1.14–2.57**	**0.009**

Stratified by disease characteristics and adjusted for DMT categories HR hazard ratio, 95% CIs 95% confidence intervals

In bold are reported values significant at a two-sided α-level of 0.05

Through our analysis, we answered to four main research questions: first, we found no differences in persistence to the self-injectable DMTs and the new oral ones. However, different routes of administration were associated with different reasons for discontinuation, with poor tolerability being by far the main obstacle in MS therapy with self-injectable DMTs. Of note, oral DMT suffered from more adverse events, while discontinuation rates due to disease activity were similar within the two categories, these results are somewhat surprising since clinicians and patients generally anticipate greater persistence to treatment with oral than injectable DMTs. However, the better tolerability of

oral DMTs seems to be counter parted by the more frequent adverse events (and similar efficacy) compared to self-injectable DMTs, at least in the short term. We must admit that modern treatments are burdened by more unexpected adverse events and less confidence in their management by neurologists, due to the relatively short experience matured by MS specialists. Hopefully, with the enlarging of real-life experience, adverse events will be better taken in charge and even avoided, leading to better persistence. Moreover, our study suggests a similar impact on clinical activity in the short term, but this specific finding should be interpreted with caution since our study was not designed to assess short-term effectiveness, due to the absence of MRI data and different time of efficacy latency of the various DMTs.

The second question regarded differences in discontinuation among drugs: we found the highest discontinuation rate in patients treated with Plegridy, with a more than doubled-increased risk when compared with Tecfidera, which showed the lowest discontinuation rate. Reasons for discontinuation were significantly different also across different types of DMTs, with interferons being poorly tolerated, Copaxone burdened by a relatively higher rate of discontinuation for poor efficacy, and the two oral DMTs sharing the same dis-continuation profile. Although the small subgroup sample size does not allow to draw definitive conclusions on effectiveness, the poor tolerability of Plegridy seems to emerge unequivocally, confirming the notion that it is associated with flu-like reactions and local side effects, ranging from pruritus to pain, edema and erythema in 66% of patients, despite its proven safety and effectiveness [21].

The third question was related to the possible difference regarding short-term persistence to treatment in naïve patients versus switchers. We found no differences in both discontinuation rates and reasons for discontinuation, with the only exception for Tecfidera being the discontinuation rate for disease activity more frequent in naives than in switchers, while discontinuation for poor tolerability occurred more frequently in switchers than in naïves. This likely reflects the fact that naïve patients starting Tecfidera had a more active disease at treatment initiation, maybe due to a perceived better efficacy of this drug compared to other first-line options [22].

Eventually, our aim was to identify predictors of treatment discontinuation. Several studies tried to identify patients at risk of discontinuation, with conflicting results. In our cohort, female sex and previous exposure to more than two DMTs were two independent risk factors for treatment discontinuation, regardless of prescribed DMTs and in the absence of differences for reasons for discontinuation. We also found a trend for a shorter persistence to treatment in patients with higher EDSS score. Regarding gender differences, it has been already shown that female subjects with MS experience poorer persistence to treatment [16], and tolerate less local effects of interferon injections [23]. The reduced persistence to treatment in patients who already changed more than two therapies might have different interpretations: it might depend on either a more aggressive form of disease, with frequent switches due to poor efficacy, or to an individual predisposition to poor tolerability. The trend towards more frequent discontinuations in patients with higher EDSS is an expected result, since it was already observed in several studies [24, 25]; this latter finding may be explained, in our opinion, by a more “aggressive” therapeutic attitude of MS specialists, who are concerned about disability accrual in patients with worse baseline disability, leading to

frequent switches to more active drugs. In our report, these data did not reach statistical significance probably because discontinuation for persistent clinical activity requires longer time than for poor tolerability or even side effects, as already discussed.

We acknowledge that our study suffers from some limitations due to the real-life setting, such as absence of data on baseline radiological characteristics (that might have influenced treatment choice), non-homogeneity of recruitment in different Centres and obviously different behaviors of clinicians, since the definition of reasons for discontinuation was based on the neurologist opinion. Furthermore, the higher number of patients starting Tecfidera and, to a lesser extent, Teriflunomide, likely reflects the recent availability of these new DMTs and we cannot exclude that prescription habits are changing in the next years. However, real-world data are necessary to analyze large number of patients, not pre-selected as in trials, and to provide more generalizable and useful information to help clinicians for decision-process making in clinical practice.

In conclusion, our study adds valuable information of short-term persistence to first-line DMTs in the contemporary era. We found an approximately 20% discontinuation rate over 12 months, with a similar persistence to self-injectables and oral DMTs, the first poorly tolerated but the second ones burdened by more frequent adverse events. Research should be aimed at improving tolerability of self-injectable DMTs, through molecular structure modifications or device development, and to reduce adverse event risk related to oral DMTs, by improving safety and follow-up procedures, and by defining patients' individual risk, since persistence to treatment still represents a clinical challenge, irrespective of the route of administration.

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Compliance with ethical standards

Conflicts of interest RL: personal fees and financial support from Almirall, Novartis, Merck Serono, Biogen, Teva, Genzyme. LP: consulting fees from Biogen, Novartis and Roche; speaker honoraria from Biogen, Genzyme, Merck Serono, Novartis and Teva; travel grants from Biogen, Genzyme, Novartis and Teva; research grants from the Italian MS Society (Associazione Italiana Sclerosi Multipla) and Gen-zyme. RF: honoraria for speaking or consultation fees from Almirall, Merck Serono, Novartis, Sanofi, Teva, Biogen; advisory board mem-bership of Teva, Biogen, Merck Serono, Novartis. MM has nothing to disclose. VN has nothing to disclose. CG: fees as invited speaker or travel expenses for attending meeting from Biogen, Merck-Se-rono, Teva, Sanofi, Novartis, Genzyme. CT: honoraria for speaking and travel grant from Biogen, Sanofi-Aventis, Merck Serono, Bayer-Schering, Teva, Genzyme, Almirall and Novartis. PA: honoraria for lecturing and participation in advisory boards, and travel expenses for attending congresses and meetings from Merck Serono,

Biogen, Teva, Sanofi-Aventis, Almirall, Roche and Novartis. PC: honoraria for consultancy or speaking from Almirall, Biogen, Merck-Serono, Novartis, Sanofi-Genzyme, Teva. MR has nothing to disclose. SM has nothing to disclose. VTC: advisory board membership of Novartis and Merck-Serono; funding for traveling and honoraria for speaking or writing from Teva, Biogen, Genzyme, Merk-Serono and Almirall; support for research project by Almirall. LB has nothing to disclose. FB: advisory board membership of Teva and Merck Serono; honoraria for speak-ing or consultation fees from Almirall, Biogen Idec, Genzyme, Merck Serono, Novartis, Teva. PR: honoraria for consultancies, speaking, or travel expenses from: Biogen idec, Merck Serono, Novartis, Sanofi-Genzyme and Teva pharmaceuticals. GTM: travel assistance and/or honoraria for advice to Biogen, Novartis, Genzyme, Sanofi-Aventis and Merck-Serono. MDF: nothing to disclose. MCB: advisory board membership and honoraria for speaking from Teva, Novartis, Sanofi, Merck Serono and Biogen. FP has nothing to disclose. AG has nothing to disclose. EC has nothing to disclose. GC has nothing to disclose. IP has nothing to disclose. AL has nothing to disclose. AG: research sup-port from Fondazione Cariverona, Novartis Pharma and Merck Sero-no; honoraria to participate in advisory boards and travel support from Merck Serono. MC: honoraria for research or speaking from Sanofi-Genzyme, Merck-Serono, Biogen Idec, Bayer, Novartis Pharma and funds for travel from Sanofi-Genzyme, Merck-Serono, Biogen Idec, Teva, Novartis Pharma, Roche and Bayer. VT has nothing to disclose. CS: advisory board membership of the following companies: Biogen and Merck Serono; speaking honoraria from Bayer-Schering, Biogen, Merck Serono, Almirall, Teva, Genzyme; research grants and support from the Italian MS Society Research Foundation (Fondazione Italiana Sclerosi Multipla).

Ethical standard Due to the retrospective design and since all clinical assessments were part of clinical practice in a University or Hospital specialized Centre setting, specific ethical approval was not required.

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