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Disease activity after discontinuation of disease-modifying therapies in patients with multiple sclerosis in Argentina: data from the nationwide registry RelevarEM

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ABSTRACT

Introduction: The discontinuation of disease-modifying therapies (DMTs) in multiple sclerosis (MS) is commonly seen in real-world settings due to several factors.

Objectives and Methods: The aim of this study is to describe the frequency of disease activity after discontinuation of DMTs in MS patients included in the Argentinean MS and NMOSD registry.Patients with relapsing remitting MS (RRMS) and active secondary progressive MS (SPMS) were included based on the following criteria: they discontinued treatment for more than 6 months, they had been treated with a DMT for ≥2 years, and they had at least 6 months of follow-up in the registry after discontinuation. Demographic and clinical data were collected. Disease activity during follow-up was defined as the presence of a clinical relapse or a new magnetic resonance (MRI) lesion (either new lesions on T2-weighted sequence and/or contrast enhancement). Bivariate analysis was applied to identify clinical and demographic factors related to disease activity.

Results and Conclusions: We included 377 patients (75.5% RRMS, 22.5% SPMS) who had discontinued DMTs. The mean (SD) follow-up after discontinuation was 15.7 (7.9) months. After discontinuation, the presence of relapse was detected in 18.8% and 3.5% in RRMS and SPMS, respectively; and new MRI activity in 22% and 3.5%, respectively. We found that higher risk of relapse and MRI activity was associated with younger age ($p < 0.001$), shorter disease duration ($p < 0.001$), and RRMS phenotype ($p = 0.006$). Males showed higher MRI activity (p 0.011). This study provides real-world data that can guide physicians when considering discontinuation of DMTs.

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Introduction

Multiple Sclerosis (MS) is an inflammatory chronic disease that affects the central nervous system and can lead to a high risk of physical and cognitive impairment [1]. During the last decade, at least 15 disease-modifying therapies (DMTs) have been approved by the Food and Drugs Administration and the European Medicines Agency, which have proved to be effective in reducing relapse rate, MRI activity, and preventing disease progression [2–5].

However, multiple factors can be involved in the discontinuation of DMTs, such as adverse events, lack of perceived efficacy, phenotype change or patient preference [6]. Few studies have been conducted to assess disease activity after DMT discontinuation [7].

Although the course of the disease can be variable, most patients with relapsing remitting MS (RRMS) can progress to secondary progressive MS (SPMS). Despite that, there are limited data on the effectiveness of DMTs in SPMS, and there is little evidence of approved DMTs for progressive forms [5]. In RRMS, permanent interruption of DMTs is associated with the risk of reactivation of the disease, and further evidence is needed to support the decision to discontinue treatment in these cases [6–11]. The aim of this study was to evaluate the activity of the disease after DMT discontinuation in patients with MS included in the Argentinian Multiple Sclerosis Registry.

Methods

Study design and population

RelevarEM is a strictly observational longitudinal registry of patients with MS and neuromyelitis optica spectrum disorders (NCT 03375177) in Argentina. The methodological aspects of the study have been previously described [12]. This study was conducted with data collected during the period from August 2018 to May 2021. The data included demographic characteristics, such as sex, age, and duration of disease (<10 years/>10 years); and clinical characteristics, such as expanded disability status scale (EDSS) at registry entry, presence of lesions in magnetic resonance imaging (MRI), and relapses in the last 6 months. In this study, patients with RRMS and active SPMS phenotypes were defined by validated diagnostic criteria and by clinical course [13,14] were included based on the following criteria: they discontinued treatment for ≥6 months; they had received a DMT for ≥2 years prior to discontinuation; and they had an active follow-up in the registry (for at least 6 months) after discontinuation. Depending on the participating centre, the mean frequency of medical visits was 3–6 months, and the frequency of performing MRIs was 6 months. Late-onset MS was defined as the presence of the first symptom of the disease after the age of 50 years [15].

Assessment of disease activity

Disease activity was evaluated using the following variables:

- **Relapses**: presence of a new or worsening of previous MS symptoms lasting more than 24 hours and not attributed to fever or another explanation. Symptoms must occur at least 30 days from the start of the last relapse [16]. This variable was evaluated in terms of the frequency of occurrence of said event.
- **MRI activity**: new lesions on T2-weighted sequence in two annual brain MRIs and/or gadolinium (Gd)-enhanced lesion on T1-weighted sequence in a single MRI.
- **Disease activity**: a combination of relapses and MRI activity.

Statistical Analysis

Data analysis was conducted using SPSS Statistics v25. Descriptive analyses of all variables were performed. Results were presented as frequencies, percentages, ranges, and mean and standard deviation values. Baseline characteristics of the cohort were reported in percentages for categorical data and median for continuous data. The data comparison between the group with SPMS and the group with RRMS was performed using t-test for quantitative data and Chi-square test for categorical data. A bivariate analysis was performed to identify clinical and demographic factors related to disease activity. Statistical significance was set at $p < 0.05$ [17].

Results

Of the 3125 patients in the registry, 377 MS patients (292 RRMS and 85 active SPMS) who discontinued DMT were included, of which 65.8% were female. Mean follow-up time after interruption was 15.7 ± 7.9 months (range 6–30.7 months), median 14.6 months, and the interquartile range 12.8 months. Demographic characteristics of these patients are summarized in Table 1. The causes of discontinuation of the different treatments are presented in Table 2. Patient decision was the most frequent cause of DMT discontinuation (Table 2).

As expected, we detected a higher frequency of relapses and MRI activity in the RRMS group compared with the active SPMS group, as shown in Figure 1. Only 58 (15.4%) patients had relapses after discontinuation of DMTs, this being more frequent in young people with RRMS phenotype and short duration of disease. There were no differences when

Table 1. Demographic characteristics of enrolled patients.

	RRMS (n = 292)	SPMS (n = 85)
Female, n (%)	196 (67.1)	52 (67.1)
Age, mean (SD)	42.5 (14.1)	58.3 (12.1)
EDSS, median (IQR)	1.5 (2.5)	6.5 (1.5)
Disease duration, mean (SD) – years	11.4 (10.6)	24.1 (9.75)
Relapses*, n (%)	55 (18.8)	3 (3.5)
MRI Scan*, n (%)	118 (40.4)	16 (18.8)
-Gd-enhanced lesions on T1-weighted, n (%)	40 (34)	2 (2.4)
-New lesions on T2-weighted, n (%)	53 (18.2)	3 (3.5)
-New lesions on T2-weighted and Gd-enhanced T1-weighted, n (%)	65 (55)	3 (3.5)

(*) last 6 months.
Abbreviations: RRMS: relapsing remitting multiple sclerosis. SPMS: secondary progressive multiple sclerosis. MRI: magnetic resonance imaging. Gd: Gadolinium. DE: Standard deviation. IQR: Interquartile range.

Table 2. Causes of discontinuation of DMTs.

Causes	n (%)
Patient decision	26 (21.5)
Phenotype change	13 (10.7)
Health coverage problems	21 (17.4)
Adverse effects	16 (13.2)
Treatment failure	14 (11.6)
Planning pregnancy or pregnancy	15 (12.4)
Cancer or another comorbidity	5 (4.1)
Non-adherence to DMTs	3 (2.5)
Change of diagnosis	1 (1.6)
Other	6 (5)

Abbreviations: DMTs: disease-modifying therapies. SPMS: secondary progressive multiple sclerosis.

comparing the EDSS between patients with RRMS and patients with SPMS (p = 0.173). Of the 134 (35.5%) MRI scans performed, 68 (50.7%) showed activity after DMT suspension. Younger age, male sex, RRMS phenotype, short duration of disease, and relapses in the last 6 months were the characteristics associated with higher activity in MRI, as shown in Table 3.

A sub-analysis was performed for an age subgroup with a cutoff value of 45 years; 198 (52.5%) were younger than 45 years. We noticed greater MRI activity in 58 (64.4%) patients and presence of clinical relapses in 50 (25.3%) patients, this being more frequent in the group of patients under 45 years.

A post hoc analysis including 23 (6.1%) patients with late-onset MS was performed. None of these patients showed Gd-enhancing lesions on T1-weighted sequence (p = 0.03). These findings were reproduced in a subgroup analysis that included 74 (19.6%) patients older than 60 years. None of the patients showed Gd-enhancing lesions and only 1 (9.7%) showed new lesions on T2-weighted MRI sequence (p = 0.005 and p = 0.007, respectively).

Discussion

There are limited data on the potential risk of disease reactivation after stopping chronic treatment in MS. There is no randomized controlled clinical trial that can directly address the question of when or why to stop DMTs in MS patients with no evidence of relapsing or disability progression and no new brain lesions [5].

This longitudinal study evaluated the short-term effect of discontinuation of DMTs on clinical and radiological activity in patients with RRMS and SPMS. We detected that 50.7% of the MRI scans showed activity and 15.4% of patients presented relapses in the 6 months following the interruption.

Previous studies showed an acute reactivation of the disease within 12–24 months after discontinuation in 58.8% of the patients with RRMS and 11.7% of the patients with SPMS [18]. A prospective cohort study included 43 patients with RRMS who discontinued interferon beta treatment (with at least 25 months of treatment prior to the interruption), and found an increased disease activity after discontinuation. It should be noted that the patients included had high levels of inflammatory activity before treatment initiation and were young [19]. In contrast to these results, a recent study in patients with RRMS with a long duration of treatment and a stable course of the disease did not show recurrent inflammation [20]. These results are in line with those obtained by Pasca et al., which did not show reactivation of the disease in terms of disease activity and annual relapse rate after discontinuation of first-line DMTs. Based on these findings, the authors argue that a sustained long-term remission of disease activity could persist after cessation, even in the absence of treatment [21]. Another prospective cohort, which used data from the MS-Base registry, included patients with MS of unspecified phenotype. Disability progression was compared between patients who had discontinued treatment and those who continued it. Further progression was observed in the EDSS scale in patients with RRMS who had discontinued treatment. Younger age and lower baseline disability were the most significant predictors of risk of relapse in those who discontinued DMTs [19].

Between 11% and 79% of the patients who start medication treatment either suspend it or switch to another alternative drug during the first year of treatment [22,23]. The primary cause of early suspension, before the first year, is adverse effects; whereas late suspension, after the first year, is due to the lack of perceived efficacy [24]. However, the reason for discontinuation in most of the patients in our cohort was patient preference.

Our study evaluated predictors of disease activity in patients who discontinued treatment. We detected

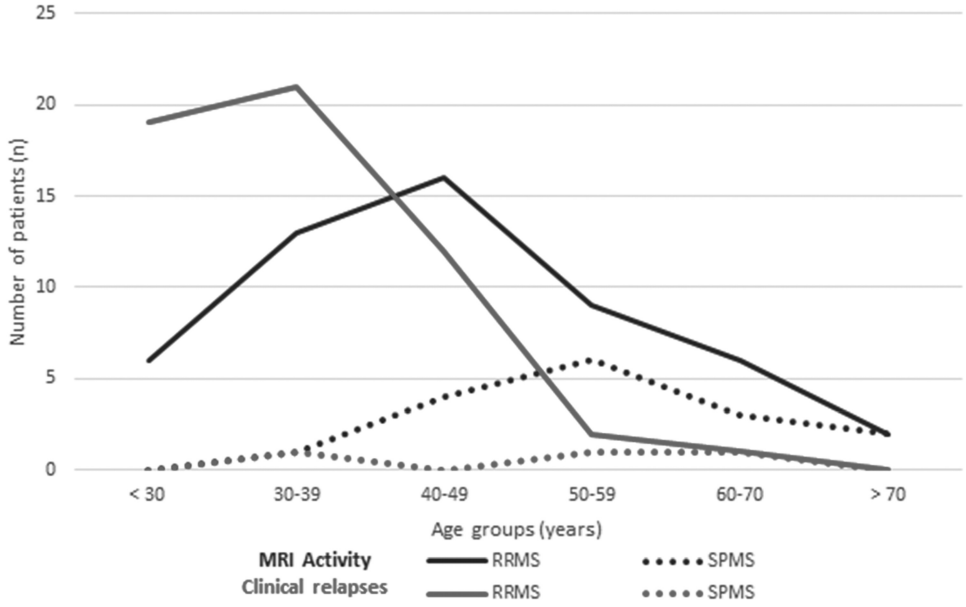

Figure 1. Clinical relapses and MRI activity in RRMS and SPMS patients.

Table 3. Factors associated with relapses and MRI activity.

	MRI ACTIVITY			RELAPSES		
	Present (n = 68)	Absent (n = 66)	P value	Present (n = 58)	Absent (n = 319)	P value
Female, n (%)	39 (57.4)	51 (77.3)	0.011*	35 (60.3)	213 (66.8)	0.343
Age, mean (SD)	34.6 (10.2)	47 (13.5)	<0.001*	35.1 (10.2)	48.3 (14.9)	<0.001*
Disease duration, mean (SD)	6.4 (5.7)	13.4 (11.5)	<0.001*	6.12 (6.9)	15.9 (11.8)	<0.001*
MS phenotype:						
RRMS	65 (95.6)	53 (80.3)	0.006*	55 (94.8)	237 (72.3)	<0.001*
SPMS	3 (4.4)	13 (19.7)	0.006*	3 (5.2)	82 (25.7)	<0.001*
EDSS, median (IQR)	2 (2.5)	2 (5)	0.246	2 (2)	2.5 (5.5)	0.282
Relapses**, n (%)	41 (82)	9 (18)	<0.001*	-	-	-

(*) last 6 months.
Abbreviations: RRMS: relapsing remitting multiple sclerosis. SPMS: secondary progressive multiple sclerosis. MRI: magnetic resonance imaging. Gd: Gadolinium. DE: Standard deviation. IQR: Interquartile range.

greater activity of the disease after suspension in the following cases: male patients, patients younger than 45 years, relapsing-remitting phenotype, and short duration of the disease.

Age represents an important prognostic factor considering that young patients are at a higher risk of relapse [6,19,25,26]. After discontinuation of treatment, greater activity on MRI and relapses were seen in patients younger than 45 years, as previously published [27].

Another aspect to consider is the sex of the patient. Similar to the data obtained in a recent Austrian study, we found greater activity of the disease in male patients [28]. This contrasts with the results obtained by Kister et al., which showed that female patients were at a higher risk of relapse and progression of disability [19].

A long duration of the disease was associated with progression of disability after discontinuation of DMTs but not with disease activity in patients with RRMS [6]. In our population, the median baseline EDSS was 1.5 and 6.5 for the RRMS and SPMS phenotypes, respectively. This factor was not associated with increased disease activity. A study that included patients with RRMS and baseline EDSS between 0 and 1.5 showed a similar result in terms of disease activity after DMT discontinuation [26]. In contrast, another study showed a faster time to progression of EDSS in the group of patients who discontinued first-line treatment [19].

In our study, only 35.5% of the patients included had a recent MRI scan and of these, half showed MRI activity. Taking into account existing evidence on the natural history of brain lesions, these are less frequent as the disease progresses. We found this in our study, in which there was no MRI activity in patients with late-onset MS. Some authors suggest that the interruption of DMTs should be avoided in patients with new recent brain lesions [7]. In line with our findings, a previous study showed a low frequency of MRI lesions (4.9% of the new T2-weighted lesions and 14.9% of the Gd-enhanced lesions on T1-weighted sequence) and relapses (0.6%) after suspension of treatment in patients older than 60 years [29].

In patients with SPMS, we detected low frequency of relapses (3.5%) and activity in MRI (3.5%). A previous study evaluated the impact of DMT discontinuation in 21 patients with SPMS. It reported 14.3% relapses, increased EDSS, and new lesions on MRI during the 12 months after discontinuation [30]. A French study that included 100 patients with SPMS did not show an increase in the annual relapse rate between the first and third year after the interruption of treatment; and it detected that 19% of the patients presented activity on MRI after treatment interruption compared to the 3 years prior to the discontinuation. The main factor related to disease reactivation was MRI activity, suggesting that this could be a more sensitive tool than clinical evaluation to identify persistent activity after discontinuation of treatment [31]. However, both studies were limited by a small sample size. Therefore, more studies are required to establish the minimum time without activity in SPMS prior to the decision of treatment interruption. To date, there are no defined clinical, imaging, or immunological criteria to determine the moment when SPMS becomes inactive. However, several of the factors evaluated could help to make decisions regarding the discontinuation of treatment in this phenotype.

Limitations and strengths of this study

Several limitations of this study should be noted. Firstly, we do not have data about the drug previously used or the frequency of relapses before discontinuation. This may have resulted in an unmeasured confounding bias. Secondly, among the inclusion criteria, patients had to be off treatment for at least 6 months to ensure that we included patients who had actually stopped treatment rather than changed it, which could entail sample bias. Finally, unfortunately more than half of the patients had not had MRI scans after the interruption. This aspect should be interpreted with caution, especially when considering the small sample of patients with late-onset MS and patients older than 60 years included in our sample. Despite these limitations, this study provides valuable data on the effect of discontinuation of therapies in our patients with MS and provides the variables to consider when deciding whether to suspend treatment, taking into account the limited data available that address this issue in our field. Future prospective studies are essential to determine the best time to continue or discontinue treatment in MS.

Conclusions

This real-life study is fundamentally useful in determining which patients are candidates for the discontinuation of treatment in MS. Unfortunately, there are no biological markers of drug efficacy that can guide decision-making in this area. However, the monitoring of recurrent disease activity is mandatory after stopping treatment.

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Gisela Zanga and Marcos Sorbara contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Gisela Zanga, Marcos Sorbara, Carla Portinari, Josefina Barber, Tomas Ibañez and Lucia Brolese. The first draft of the manuscript was written by Gisela Zanga and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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