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Usage trend of oral drugs for multiple sclerosis patients in Argentina

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A B S T R A C T

Introduction: Over the past decade, numerous disease modifying drugs (DMDs) for relapsing- remitting multiple sclerosis (RRMS) have been approved in Argentina. The use of oral DMDs (oDMDs) has increased in recent years, although real-life data in our region is limited. We aimed to describe the tendency in the use of oDMDs (as first treatment option or after switch) in relationship with their approval in Argentina.

Methods: A retrospective study in a cohort of MS patients from five Argentinian MS centers was conducted. Regarding the availability of different oDMDs in Argentina, we define three periods (P1-3): P1: 2012 – 2014; P2: 2015 - 2017 and P3: 2018 - 2020. An analysis was performed comparing between these three periods to assess the tendency for oDMDs use over time.

Result: The most frequently prescribed treatment as first DMD was: interferon beta 1a (40%) in P1, fingolimod (37.3%) in P2 and also fingolimod (35%) in P3. We found an increase in the use of oDMTs as initial treatment over time (P1: 17.7%, P2: 63.9% and P3: 65.0%; Chi-square = 41.9 $p < 0.01$). We also found a tendency to increase the use of oDMTs after a first switch (P1: 45.5%, P2: 60.1% and P3 78.3%). Multivariate analysis showed that disease evolution (OR=1.06, p=0.04), and year of treatment initiation (OR=1.01 $p<0.01$) were independently associated with choice of oDMTs.

Conclusion: This study identified an increasing tendency for the use of oDMDs as initial treatment of RMS in relationship with their approval in Argentina.

Introduction

Multiple sclerosis (MS) is an immune-mediated inflammatory demyelinating and neurodegenerative disease of the central nervous system that is a leading cause of disability in young adults (Oh et al., 2018). Current therapy for relapsing-remitting-multiple sclerosis (RRMS) is aimed at reducing inflammation and axonal damage with the goals of limiting relapses and preventing disease progression (Thomas and Wakefield, 2015). Disease-modifying drugs (DMDs) are the cornerstone of treatment for RRMS. The complex physiopathology of MS has led to the development of DMDs that vary substantially in their mechanisms of action as well as in administration methods, dosage, efficacy, safety and tolerability (Derfuss et al., 2020). In 1993 the first study on interferon beta 1b (IFNβ-1b) was published and it was the first drug that proved to be effective in reducing disability and the number of relapses (IFN beta Multiple Sclerosis Study Group, 2001). Shortly thereafter, two different formulations of IFNβ-1a, and glatiramer acetate also became available. Since then, the treatment of MS was dominated for 15 years by injectable DMDs. Some limitations of injectable MS treatment include variable adverse effects, neutralizing antibodies development, that contribute to loss of drug efficacy (related to IFNβ), patient inconvenience and poor adherence associated with parenteral

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administration (Higuera et al., 2016; Lugaresi et al., 2014). Since the beginning of 2010, numerous drugs for treating RRMS have been approved in Argentina, varying in terms of administration, dosing, mechanism of action, efficacy, safety and tolerability. This wider offer of therapeutic options makes the patients' treatment algorithm more complex (Alonso et al., 2018).

Oral treatment options for DMDs in RRMS have substantially increased over the past decade with four approved oral compounds now available: fingolimod, dimethyl fumarate, teriflunomide, and cladribine. Oral DMDs (oDMDs) offer a more convenient route of administration and is reasonable that patients will typically prefer oral drugs over others that require parenteral administration (Utz et al., 2014). Fingolimod, teriflunomide and dimethyl fumarate are some of the continuous MS treatments and are used as escalating treatment regimen early in the disease course (Derfuss et al., 2020). Besides, they have different mechanisms of action, tolerability profiles and different places in the treatment algorithm (Rotstein and Montalban, 2019). On the other hand, oral cladribine is an immune reconstitution therapies and has the potential to induce long-term or even permanent drug-free remission in people with MS. Cladribine is normally used in two treatment cycles that are separated by one year and re-treatment is based on clinical needs (Giovannoni et al., 2010).

In Argentina, reports regarding the use of DMDs in patients with MS are scarce (Alonso et al., 2018). Recently, the first nation-wide MS registry in Argentina was presented (Clinical Trials registry number NCT NCT03375177), providing an updated information on epidemiological features, disease characteristic and treatment of MS and neuromyelitis optica spectrum disorders (NMOSD) in Argentina (Ricardo et al., 2020; Rojas et al., 2020). Real-world observational studies of MS patients are really valuable as they capture the trend of the use of treatments. Our aim was to describe the usage trend of oDMDs, as first treatment option or after switch, in relationship with their approval in Argentina.

Methods

RelevarEM is a longitudinal, strictly observational MS and neuromyelitis optica spectrum disorders (NMOSD) registry in Argentina. The registry is open to all practicing neurologists and to MS specialists and their teams across the country. It tracks the outcomes of routine clinical practice of patients with MS and NMOSD in a web-based platform that allows researchers to register and follow up their patients. The primary objective of the registry was to create an MS physicians network in Argentina that captures pragmatic and relevant information from MS patients in terms of clinical and demographic aspects (Rojas et al., 2019). Any patient diagnosed with MS, a clinically isolated syndrome, a radiologically isolated syndrome, or an NMOSD defined by validated diagnostic criteria can be enrolled into the registry (Thompson et al., 2018; Wingerchuk et al., 2015). To ensure the correct use of the diagnostic criteria for MS and NMOSD in each center, the executive committee invited all MS centers and physicians involved in the care of affected patients in Argentina. To reduce the possibility of bias in the selection, each participating physician was required to include all patients seen in their practice or clinic.

A retrospective study was conducted in a cohort of MS patients follow-upped in five MS centers of Buenos Aires and incorporated in RelevarEM: Hospital Ramos Mejia, Hospital Alemán, Hospital Italiano de Buenos Aires / CEMBA, Hospital de Clínicas de Buenos Aires and Centro de Investigaciones Diabaid. The inclusion criteria for this study were: diagnosis of RRMS, 18 years of age or older and treatment initiation after 2012. Regarding the availability of different oDMDs in Argentina, we define three time periods (P1-3): P1: from 2012 to 2014; P2: from 2015 to 2017 and P3: from 2018 to 2020. An analysis was performed comparing among these three periods to assess the tendency of oDMDs use over time (Alonso et al., 2018). Related to the use of oDMDs, three scenarios were defined: initial treatment, first switch and second switch. In addition, the causes of treatment switch were identified. Treatment failure was defined based on neurologist criteria at moment to perform the treatment change.

Statistical analysis

Data analysis was conducted using SPSS Statistics v22. Descriptive analyses of all variables were carried out. Results were presented as frequencies, percentages, ranges, mean and standard deviation values. Comparisons between groups were analyzed using Chi-square or Fisher's exact tests for categorical variables and, for continuous variables, analysis of variance (ANOVA) with Bonferroni post hoc correction or Kruskal-Wallis test with Dunn post hoc analysis, as appropriate. Logistic regression analysis was applied to identified factors associated with the choice of oDMDs. Statistical significance was set at $p < 0.05$.

Results

Out of 202 RRMS patients, 58% were female, mean age 32.4 ±11.0 years at study entry, mean disease duration 8.0 ±5.5 years, 46 % started with oDMTs and 64% oDMTs was the first choice after a switch. Demographic characteristics of these patients are summarized in Table 1.

Treatments were analyzed according to each time period. The most frequent treatment as first prescribed DMD was: interferon beta 1a (40%) in P1, fingolimod (37.3%) in P2 and also fingolimod (35%) in P3. A total of 40.6% of MS patients switched the treatment at least once and the main cause for the first DMD switch was treatment failure (39%). A second switch of treatment was needed in 14.4% of the patients and the most frequent cause was also treatment failure (52.2%) (Table 2). Issues related to adherence and tolerance of DMDs were the second cause of treatment change, mainly in P1. The tendency among patients who switched due to therapeutic failure was change for a more effective treatment. Injectable therapies were the most frequently withdrawn in comparison with oDMTs and monoclonal antibodies (Chi-square = 23.6; $p<0.01$). We found an increase in the use of oDMTs as initial treatment over time (P1: 17.7%, P2: 63.9% and P3: 65.0%; Chi-square = 41.9 $p<0.01$). We also found a tendency to increase the use of oDMDs after a first switch (P1: 45.5%, P2: 60.1% and P3 78.3%) (Figure 1). Multivariate analysis showed that disease duration (OR=1.06, p=0.04), and year of treatment initiation (OR=1.01 $p<0.01$) were independently associated with the choice of oDMTs.

Discussion

In our research we evaluated the usage trend of oDMDs in Argentine RRMS patients over the years, both as the first treatment option and after switch. We observed a significant trend towards the use of oDMDs,

Table 1
General characteristics of patients with RRMS and their treatment.

General characteristics	Total	Period 1	Period 2	Period 3
N	202	79	83	40
Mean age at study entry (±SD)	40.6 (±11.64)	41.6 (±10.67)	41.8 (±11.87)	36.2 (±12.25) *
Female No (%)	117 (57.9)	50 (63.3)	43 (51.8)	24 (60.0)#
Disease duration, y mean ±SD (range)	8.1 ± 5.5 (1-44)	9.6 ± 7.7 (2-34)	7.9 ± 6.1 (2-44)	5.6 ± 4.6 (1-19) *
First treatment (%)				
Injectables	94 (46.5%)	60 (75.9%)	25 (30.0%)	9 (22.5%)
Orals	93 (46%)	14 (17.7%)	53 (63.9%)	26 (65%)
Monoclonal antibodies	15 (7.4%)	5 (6.3%)	5 (6.0%)	5 (12.5%)
	32 (15.8%)	22 (27.8%)	8 (9.6%)	2 (5.0%)
Causes of first switch	27 (13.3%)	21 (26.6%)	6 (7.2%)	-
Treatment failure	23 (11.4%)	9 (11.4%)	14 (16.9%)	-
Related to adherence and tolerance				
Others				

Table 2
Disease-modifying treatment used in the first and second treatment change according to period.

Period	Elegible DMTs	First treatment changeN:75	Second treatment changeN: 31
		Frequency (%)	**Frequency (%)**
Period 1	Injectables	9 (19.1%)	-
	oDMTs	**28 (59.6%)**	**14 (77.8%)**
	Monoclonal antibodies	10 (21.3%)	4 (22.2%)
Period 2	Injectables	2 (7.7%)	-
	oDMTs	**19 (73.1%)**	**10 (83.3%)**
	Monoclonal antibodies	5 (19.2%)	2 (16.7%)
Period 3	Injectables	-	-
	oDMTs	1 (50%)	**1 (100%)**
	Monoclonal antibodies	1 (50%)	-

Abbreviations: DMDs: disease-modifying drugs. oDMDs: oral disease-modifying drugs. T/A: switch frequency due to adherence or tolerance. E: switch frequency due to efficacy. Period 1: 2012 – 2014; Period 2: 2015 - 2017 and Period 3: 2018 – 2020

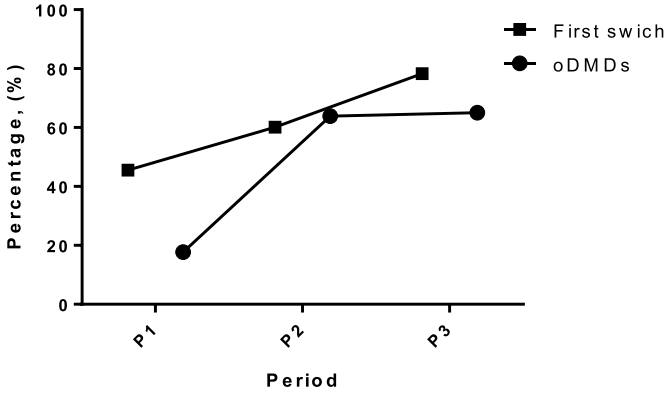

Figure 1. Trends in prescription oDMDs use in MS patients from Argentina P1: 2012 – 2014; P2: 2015 - 2017 and P3: 2018 - 2020. oDMDs: oral disease modifying drugs. oDMDs: P1 17.70%, P2 63.90% and P3 65%. First switch: P1 45.50%, P2 60.10% and P3 78.30%.

after their approval by the local regulatory agency (ANMAT).

Numerous DMDs have appeared on the market over the past decade. Following a worldwide tendency, new molecules for RRMS treatment have been approved in Argentina since 2010 (Alonso et al., 2018). Although all of these new drugs represent important advances in the treatment of MS patients, their efficacy, tolerance, adherence and adverse effects vary. Among oral treatments, the common route of administration of these drugs does not mean that they are equivalent, since oral DMDs encompasses drugs with distinct indications and mechanisms of action, as well as heterogeneous results in terms of efficacy and safety, allowing treatment to be personalized according to each patient's characteristics.

To date, reports regarding the use of oDMDs in RRMS patients are scarce in our country. Analyzing patients included in RelevarEM, we have identified an increasing tendency in the use of oDMDs and that there would be a learning curve among neurologists in Argentina in relation to the availability of the drug. This increase in the use of oDMDs was not only found among patients who started treatment, but also in those who switched treatment. Desai R. J. et al. described time trends and identified factors associated with oDMDs using the health care utilization claims database from Aetna, a large national health insurer in the United States (period 2009 to 2014). Oral DMDs initiation and switching steadily increased from 5% to 16% and 35% to 84%, respectively, between 2011 and 2014, with dimethyl fumarate being the most commonly used agent (Desai et al., 2019). We also found that in patients who changed their treatment to an oDMDS, the most frequent cause of switch was therapeutic failure. Issues related to adherence and tolerance of DMDs were the second cause of treatment change, mainly in period 1. There can be many reasons to justify switching from one drug, such as tolerance problems, lack of adherence, family planning, access barriers and therapeutic failure among others. When considering efficacy from the viewpoint of disease pathophysiological, DMDs have different mechanisms of action, and the highly heterogeneous nature of MS and the lack of a biological marker make it difficult to predict which drug will be optimal in a specific patient (Coyle, 2013). It also has to be considered that 30% of patients may show suboptimal responses during the first years of treatment, and there are different studies claiming that the annual rate of relapses and residual disability are related (Coyle, 2008, 2013; Lublin et al., 2003; Rio et al., 2012). In a previous study that analyzed a cohort of Argentinean patients, the main cause of change in treatment was also therapeutic failure (43% in patients who started their treatment before 2010 and 62% in patients who started after 2010). Furthermore, the most frequently selected drug in patients who failed after 2010 was fingolimod (Alonso et al., 2018). The availability of several therapeutic options has increased the possibility of tailoring the DMD to the individual patient but, so far, no universal guidelines exist to encompass all the scenarios a physician may encounter, nor address patient perspectives 21. Currently, the individualization of the patient is the engine of the change in the treatment trend, evaluating the aggressiveness of the disease and, consequently, choosing the treatment. Lack of treatment efficacy and adverse events remain the main driving force behind a therapeutic switch. In a recent study, among 303 (90.2% of 336) patients switching, the most common reason was "lack of efficacy" (58.4% of 303) (Patti et al., 2020).

Increasing evidence showed that there is a limited window of opportunity to intervene effectively in RRMS management (Meuth et al., 2010; Ziemssen et al., 2016). We identified a few factors predictive of oDMDs initiation or switching (disease evolution and year of starting treatment). A previous study found that a recent neurologist consultation (OR = 1.60; 95% CI = 1.20-2.15) and emergency department visit (OR = 1.43; 95% CI = 1.01-2.01) were significantly associated with oDMDs initiation (Desai et al., 2019). A weakness of this research, and also ours, is that patient and/or physician preferences could not be evaluated. There are also other limitations to our study that should be mentioned. First, this is a retrospective study which could not evaluate all the variables related to the choice of treatments. Second, we were unable to assess disease activity as well as comorbidities or contraindications for the use of some DMDs. Third, we did not have data on some potentially important patient factors, such as preferences, cognitive level, educational attainment, patients reported outcome (PRO), which limited our ability to explore disparities in use of oDMDs by these factors. Therefore, we could not differentiate whether patients who initiated therapy on oDMDs explicitly requested such treatment or whether provider preferences drove these patterns. This cohort has a relatively small population size, although prevalence in Argentina is low-medium (Melcon et al., 2008). Finally, we did not collect data on access, which may be an important factor in determining treatment decisions in MS patients.

Conclusions

This is the first study that evaluates the use of oDMDs and makes a special focus on the tendency in their use in Latin America MS patients. Our study demonstrated a significant trend towards the use of oDMDs in routine clinical practice as alternatives to others DMDs for MS (especially injectables). The rapid increase in the use of oDMDs observed in our study highlights the need for future research in our region.

Disclosure of conflicts of interest

The authors declare no financial or other conflicts of interest.

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