BJPS

Brazilian Journal of Pharmaceutical Sciences

http://dx.doi.org/10.1590/s2175-97902024e23608

Article

Pattern of disease-modifying therapies use and related adverse events among multiple sclerosis patients

Roney Pereira Pinto[1], Charleston Ribeiro Pinto[3,4], Sandro Rodrigues Batista[2], Fernanda Costa Nunes[5], Denise Sisterolli Diniz[1]

[1]Programa de Pós-graduação em Ciências da Saúde, Faculdade de Medicina, Universidade Federal de Goiás Faculdade de Medicina, Goiânia, Brasil, [2]Centro Estadual de Medicação de Alto Custo Juarez Barbosa, Secretaria de Estado da Saúde de Goiás, Goiânia, Brasil, [3]Curso de Farmácia, Departamento de Ciências e Tecnologias, Universidade Estadual do Sudoeste da Bahia, Jequié, Brasil, [4]Faculdade de Farmácia, Universidade Federal da Bahia, Salvador, Brasil, [5]Departamento de Saúde Coletiva do Instituto de Patologia Tropical e Saúde Pública, Universidade Federal de Goiás Faculdade de Medicina, Goiânia, Brasil

This study attempted to describe the disease modifying therapies (DMTs) use patterns and related adverse events in multiple sclerosis (MS) patients assisted by the Brazilian Unified Health System (SUS). This is a cross-sectional study conducted at a reference center in the Midwestern Brazil. Demographic, socioeconomic, and clinical data, and adverse events associated with DMTs were collected. We observed 291 patients with a mean age of 41.4 years, and mostly (68.6%) women. Most patients (58.8%) were using first-line treatment. Fingolimod (29.9%) and beta interferons (23.7%) were the most used drugs. About 74.2% of patients used DMTs for more than six months. In 26.5% of patients, 238 adverse events were reported, 67.2% of which were mild and 32.8% of which were moderate. The most frequent adverse events were headaches (6.9%), myalgia (3.8%), and flu-like symptoms (3.1%). The proportion of adverse events proportion ranged from 17.3% (natalizumab) to 41.2% (dimethyl fumarate). Most MS patients treated by SUS used first-line DMTs. After adjustment, there was noticed that adverse events associated with DTMs are twice as likely to occur in users of the first-line treatment than other lines (OR 1.99, p=0.01). It is essential to develop DMTs safety monitoring strategies to promote their rational use.

Keywords: Adverse Events. Disease Modifying Therapies. Multiple Sclerosis. Treatment.

INTRODUCTION

Multiple sclerosis (MS) is a chronic disease of the central nervous system characterized by inflammation, demyelination, and neurodegeneration (Brasil, 2022; McGinley, Goldschmidt, Rae-Grant, 2021). Recent data suggest a global increase in MS incidence, prevalence, deaths, and disability-adjusted life years (Qian *et al*., 2023; Walton *et al*., 2020). In 2019, there were 59,345 new incident cases of MS globally and 22,439 MS deaths (Qian *et al*., 2023). In Brazil, there are approximately 40,000 cases of MS, which is more present among young adults aged 20 to 50 years old, with most presenting at 30 years of age. MS can lead to physical disability, cognitive impairment, and reduced quality of life (Brasil, 2022). It has a significant economic impact on both Brazilian households and the healthcare system, especially in terms of the use of disease modifying therapies (DMTs), which account for the majority of direct expenditures (da Silva, *et al*., 2016; Kobelt, *et al*., 2019)

There are currently several DMTs approved by the National Health Surveillance Agency (ANVISA)

***Correspondence:** R. P. Pinto. Programa de Pós-graduação em Ciências da Saúde. Faculdade de Medicina. Universidade Federal de Goiás Faculdade de Medicina. Central de Medicamentos de Alto Custo Juarez Barbosa, CEMAC. Rua 16, 97 - St. Central, CEP: 74015-020, Goiânia, GO, Brasil. Phone: +55 64 99655-9327. E-mail: roneyfarmaceutico@hotmail.com. ORCID: https://orcid.org/0000-0003-2442-9023. C. R. Pinto, ORCID: http://orcid.org/0000-0001-9999-054X. S. R. Batista, ORCID: https://orcid.org/0000-0001-7356-522X. F. C. Nunes, ORCID: https://orcid.org/0000-0001-5036-648X. D. S. Diniz, ORCID: https://orcid.org/0000-0002-3078-6804

available for Relapsing-Remitting MS (RRMS), with varying mechanisms of action and routes of administration, including interferons, glatiramer acetate, dimethyl fumarate, azathioprine, fingolimod, teriflunomide, alemtuzumab, mitoxantrone, natalizumab and ocrelizumab (Brasil, 2022; Marques *et al*., 2018).

DMTs are effective treatments for relevant outcomes in MS, including relapse-reduced risk and improved activity on magnetic resonance imaging (Bose *et al*., 2022; Liu, *et al.,* 2021*).* Despite their benefits, these drugs are associated with adverse events that can lead to poor adherence or treatment discontinuation and consequently negatively impact disease progression, MS-related hospitalization, and mortality rates (Biolato *et al.,* 2021; Ferraro *et al.,* 2018; Washington, Langdon, 2022). Most information on safety of DMTs safety comes from clinical trials, which may provide limited data due to strict eligibility criteria participant and the short follow-up period of the study (Tramacere *et al.,* 2015).

In 2002, the Brazilian Ministry of Health implemented Clinical Protocol and Therapeutic Guidelines (PCDT) for MS treatment, setting DMTs as the first-choice drug (Brasil, 2009). After several protocol updates, therapeutic options have been expanded based on DMTs for the maintenance treatment of individuals with low to high-activity RRMS, including oral drugs (dimethyl fumarate, fingolimod, teriflunomide and azathioprine), injectable drugs (glatiramer acetate, and betainteferon 1a and 1b) and infusion drugs (natalizumab an alemtuzumab) (Brasil, 2022). Despite the increased use of these drugs in the Brazilian public health system, data on utilization profiles and safety are still limited. Real-world evidence from clinical trials have been increasingly used in monitoring after the implementation of technologies in the Brazilian Unified Health System (SUS). It provides additional information on the effectiveness and safety of incorporated technologies, allowing the reallocation of health resources and contributing to the sustainability of the system (Lyrio *et al*., 2023). This study aimed to describe the DMTs use profile in patients with RRMS assisted by the SUS in Goiânia-Goiás and to characterize the associated adverse events.

MATERIAL AND METHODS

Study Design

A cross-sectional study was conducted on a representative sample of patients with RRMS in Goiânia, Midwestern Brazil, and followed up at the State Center for High-Cost Medications Juarez Barbosa (CEMAC-JB), connected to the Goiás State Health Department. It is a state reference center that is responsible for the dispensation of drugs belonging to the Specialized Component of Pharmaceutical Assistance (CEAF) and provides clinical pharmacy services to SUS users. CEMAC-JB assistance to patients with MS involves a systematic evaluation of the effectiveness, safety, and adherence to drug treatment.

During the study period, CEMAC-JB provided the following DMTs: beta-interferon, glatiramer, and teriflunomide, regarded as first or second line of treatment; dimethyl fumarate, second line of treatment; fingolimod, a second/third line of treatment; and natalizumab, fourth line of treatment.

Sample Size

Considering the prevalence of MS in Goiânia (22.2/100,000 inhabitants) (Ribeiro *et al*., 2019) and the frequency of adverse events from DMTs in MS patients ranging from 28.1% to 46.4% (Bossart *et al*., 2022; Tilbery *et al*., 2009), we calculated a sample size of 277 patients as necessary to achieve a power of 80% in a two-sided test with a significance level of 5%.

Eligibility Criteria

Individuals with a diagnosis of RRMS defined by the revised and adapted McDonald criteria in agreement with the eligibility criteria of the PCDT of MS and individuals using the same line of treatment for at least one month were included in this study. Patients using azathioprine and those who refused to participate in the study or sign the informed consent form (ICF) were excluded.

Data collection

From February 2019 to February 2020, demographic (age, gender, skin color, and body mass index), socioeconomic (education, marital status, and family income), and clinical (smoking status, physical activity, medication use, comorbidities, disability status, and quality of life) data were collected from the patients through interviews. The Expanded Disability Status Scale (EDSS) was used to assess patients' status of disability (Kurtzke, 1983; Brasil, 2019).

We used a scale (Lawton, Brody, 1969), with a maximum score of 27 points, to assess instrumental activities of daily living. Scores of less than 7 points indicate total dependence; scores ranging from 7 to 21 points indicate partial dependence; and scores above 21 points indicate that the individual is considered independent.

DMT-related adverse events were assessed using a structured questionnaire with a 30-day recall period. They were classified as mild, moderate, or severe, according to the World Health Organization (2010) severity criteria.

Polypharmacy was defined based on the World Health Organization standard as the concomitant use of 5 or more medications by the same patient (Viktil *et al.*, 2007).

Statistical analysis

All analyses were performed using the IBM SPSS Statistics software package, version 21.0 (IBM Corporation, Armonk, NY, USA). Mean and standard deviation (SD) were calculated for quantitative variables with a normal distribution. The median and interquartile range were used to describe quantitative variables without normal distribution.

Categorical variables were presented as frequency and proportion. The differences in categorical variables between patients with and without adverse event reports were analyzed using the chi-square test. For comparisons of continuous variables between independent groups, Student's t-test or the Mann-Whitney test was used according to normality. The logistic regression model was used for adjusting potential confounding factors. The criterion for inclusion of variables in the model was based on an association with self-perception of adverse events associated with DTM at a level of $p < 0.20$ in the bivariate analysis. The Odds Ratio (OR) was calculated. The overall prevalence of events was estimated based on the cases reporting at least one adverse event and the total number of patients evaluated. The statistical significance level adopted for all tests was $p < 0.05$.

Ethical consideration

This study was approved by the Leide das Neves Research Ethics Committee of the Goiás State Health Department (CAAE Protocol No. 01908618.2.0000.5082). Before any information was collection, all participants in this study signed the ICF respecting their dignity, autonomy, and confidentiality of information.

RESULTS

This study included 291 eligible patients (Figure 1), of whom 198 (68%) were female, with a mean age of 42.8 ± 12.4 years. Patients with an EDSS score > 2 accounted for 72.2%, and 52.2% were on first-line treatment. Fingolimod and beta interferons were the most commonly used drugs. It was found that 74.2% of patients had been using DMTs for more than six months (median 27 months). The prevalence of polypharmacy in this study was 15.8%.

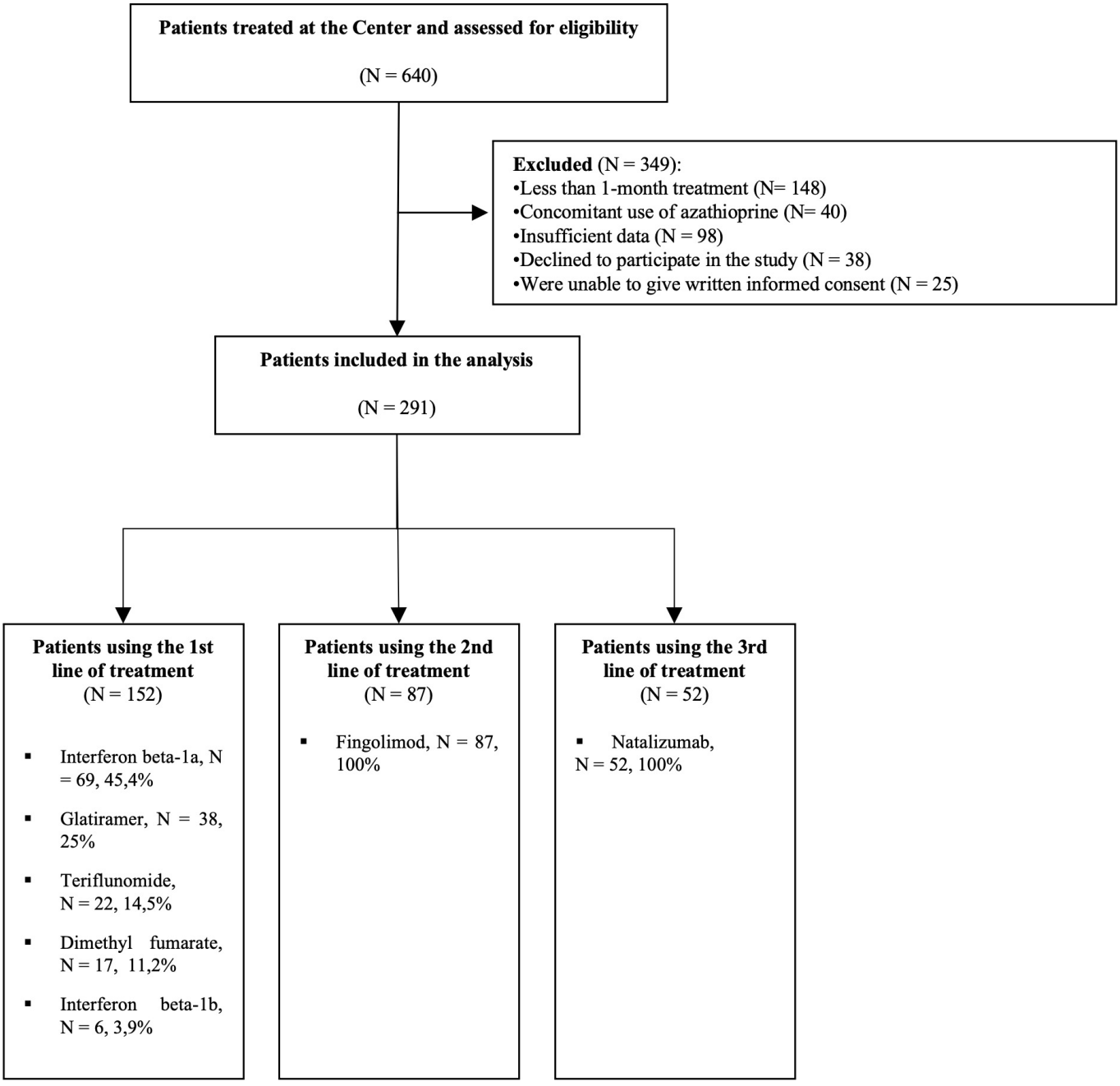

FIGURE 1 - Flow chart of the patients in the study.

The general characteristics of the patients evaluated in this study are shown in Table I. At least one adverse event was reported by 26.5% (n=77) of the patients. After adjustment, there was noticed that adverse events associated with DTM are twice as likely to occur in users of the first-line treatment than other lines (OR 1.99, p = 0.015) (Table II).

TABLE I - General characteristics of multiple sclerosis patients. (N = 291)

Characteristic	Presence of adverse events		P-value*
	No	Yes	
	(N=214, 73.5%)	(N=77, 26.5%)	
Gender			
Female	141 (65.9)	57 (74)	0.189
Male	73 (34.1)	20 (26)	
Age, years			
< 30	32 (15)	11 (14.3)	0.288
30 – 39	55 (25.7)	21 (27.3)	
40 – 49	71 (33.2)	20 (26)	
50 – 59	34 (15.9)	20 (26)	
≥ 60	22 (10.3)	5 (6.5)	
Marital Status			
Without partner	103 (48.1)	32 (41.6)	0.321
With partner	111 (51.9)	45 (58.4)	
Per capita family income, number of times the NMW			
≤ 2	78 (36.4)	31 (40.3)	0.769
3 – 4	67 (31.3)	21 (27.3)	
≥ 5	69 (32.2)	25 (32.5)	
Schooling, years			
≤ 8	31 (14.5)	6 (7.8)	0.309
9 – 11	64 (29.9)	26 (33.8)	
≥ 12	119 (55.6)	45 (58.4)	
Health insurance plan			
No	69 (32.2)	18 (23.4)	0.145
Yes	145 (67.8)	59 (76.6)	
Self-reported race			
White	132 (61.7)	47 (61)	0.921
Non-white	82 (38.3)	30 (39)	
Smoking status			
Never smoker	193 (90.2)	68 (88.3)	0.767
Former smoker	16 (7.5)	6 (7.8)	
Smoker	5 (2.5)	3 (3.9)	

TABLE I - General characteristics of multiple sclerosis patients. (N = 291)

Characteristic	Presence of adverse events		P-value*
	No	Yes	
	(N=214, 73.5%)	(N=77, 26.5%)	
Practice of physical activity			
No	90 (42.1)	33 (42.9)	0.903
Yes	124 (57.9)	44 (57.1)	
BMI, Kg/m^2 [a]	25.20 ± 4.70	25.75 ± 4.51	0.376
Number of comorbidities			
< 5	143 (66.8)	50 (64.9)	0.672
≥ 5	91 (33.2)	27 (35.1)	
Lowton Scale of dependency			
Total independence	126 (58.9)	43 (55.8)	0.644
Dependency (partial or total)	88 (41.1)	34 (44.2)	
Score EDSS [a]	2.26 ± 1.49	1.97 ± 1.20	0.121
DMTs treatment time, months [b]	27 (6 – 51)	29 (5 – 47)	0.679
Treatment Line			
First	102 (47.7)	50 (64.9)	0.009
Second or Third	112 (52.3)	27 (35.1)	

NMW: National Minimum Wage; BMI: body mass index; EDSS: Expanded Disability Status Scale; DMT: Disease Modifying Therapies. Statistical analysis: Data are shown as N (%); chi-square test. [a]Student's t-test: mean (standard deviation); [b]Mann-Whitney test: median (interquartile range); *p-value < 0.05 was defined as statistically significant.

TABLE II - Result of logistic regression regarding the self-perception of adverse events associated with disease modifying therapies. (N = 291)

CharaLcteristic	OR	Adjusted P-value*
Gender, Female	1.42	0.246
Health insurance plan, yes	1.50	0.210
Score EDSS	0.93	0.490
Treatment Line, First	1.99	0.015

EDSS: Expanded Disability Status Scale; Statistical analysis: *p-value < 0.05 was defined as statistically significant.

The adverse events frequency reported for each DMT is shown in Table III. A total of 238 adverse events were reported, the most common being headache (6.9%), myalgia (3.8%), and flu-like symptoms (3.1%). Of these, 67.2% (n= 160) were classified as mild and 32.8% (n=78) as moderate. Of the total number of events, 160 (67.2%) were classified as mild and 78 (32.8%) as moderate. Only 2.0% (n=4) of patients discontinued treatment due to adverse events.

TABLE III - Frequency and severity of adverse events according to disease-modifying therapy used by study patients. (N = 291)

Variable		Medication*, N (%)					
Fingolimod (N = 87, 29.9%)		**Interferon beta-1a (N = 69, 23.7%)**	**Natalizumab (N = 52, 17.9%)**	**Glatiramer (N = 38, 13.1%)**	**Teriflunomide (N = 22, 7.6%)**	**Dimethyl fumarate (N = 17, 5.8%)**	
Report of at least one adverse event, N (%)		18 (20.7%)	23 (33.3%)	9 (17.3%)	14 (36.8%)	6 (27.3%)	7 (41.2%)
Adverse Event, N (%)				**Severity**			
Headache	Moderate	7 (8.0)	9 (13.0)	3 (5.8)	0 (0.0)	1 (4.5)	0 (0.0)
Eye pain	Mild	4 (4.6)	1 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Dizziness	Mild	4 (4.6)	1 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Numbness	Mild	4 (4.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hair loss	Moderate	4 (4.6)	0 (0.0)	0 (0.0)	0 (0.0)	4 (18.2)	0 (0.0)
Flu symptoms	Mild	3 (3.4)	2 (2.9)	2 (3.8)	2 (5.2)	0 (0.0)	0 (0.0)
Myalgia	Mild	1 (1.1)	9 (13.0)	0 (0.0)	0 (0.0)	1 (4.5)	0 (0.0)
Redness of the face	Mild	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	7 (41.2)
Muscle weakness	Mild	0 (0.0)	7 (10.1)	0 (0.0)	0 (0.0)	1 (4.5)	0 (0.0)
Skin problems	Mild	0 (0.0)	0 (0.0)	0 (0.0)	6 (15.8)	0 (0.0)	0 (0.0)
Hot flushes	Mild	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	6 (35.3)
Anxiety	Moderate	0 (0.0)	5 (7.2)	0 (0.0)	3 (5.8)	0 (0.0)	0 (0.0)
Redness at the application site	Mild	0 (0.0)	5 (7.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Joint pain	Mild	0 (0.0)	0 (0.0)	5 (9.6)	0 (0.0)	0 (0.0)	0 (0.0)
Tiredness	Mild	1 (1.1)	1 (1.4)	5 (9.6)	0 (0.0)	0 (0.0)	0 (0.0)
Nausea	Mild	0 (0.0)	1 (1.4)	1 (1.9)	0 (0.0)	1 (4.5)	4 (23.5)

* There were only 6 patients using Interferon beta-1b. None of them reported adverse events.

Different prevalences of adverse events were recorded among DMTs, ranging from 17.3% among natalizumab users to 41.2% for those using dimethyl fumarate. Comparing the most frequent adverse event among the DMTs assessed, we observed: headache (8.0%) for fingolimod; headache and myalgia (both 13%) for beta interferon-1a; headache (5.8%) for natalizumab; skin disorders (15.8%) for glatiramer; hair loss (18.2%) for teriflunomide; and facial redness (41.2%) for dimethyl fumarate.

DISCUSSION

In our study, the DMTs most used by the patients were fingolimod (29.9%) and beta interferon-1a (23.7%). A previous study demonstrated a different result when evaluating the pattern of DMTs use among MS patients receiving Medicare in the United States and identified the use of beta interferon-1a and fingolimod in 30.7% and 6.9%, respectively (Hartung *et al.,* 2022). Another recent Swiss study, however, found a pattern of medication use closer to the reality of our study, with fingolimod being the most frequently DMT used (33.4%) (Bossart *et al*., 2022). It is also important to highlight that these differences may be related to the period in which each study was conducted, the characteristics of the population, and the list of medications approved in different countries as well as their associated costs. For example, in Brazil there is a public policy for free access to medicines for EM. In USA, most patients with MS are covered by some form of healthcare insurance, but plan designs and formulary restrictions can create access barriers for some patients (Hartung *et al*., 2022; Mathis, Owens, 2014). These patients can face high out-of-pocket costs to have access to DMTs (Hartung *et al*., 2022).

Interferons beta and glatiramer acetate were the most used drugs as first-line treatment of RRMS. These findings correspond to those observed in previous national studies with retrospective data that reported both medications as the most used first-line treatments (Bianco et al, 2020; Souza et al. 2023). Furthermore, this pattern of use is accordance with current clinical guidelines for MS of the Brazilian Ministry of Health (Brasil, 2022).

In the present study, we showed that more than a quarter (26.5%) of MS patients reported at least one adverse event related to DMTs use. The frequency of the adverse events identified in our study was lower than that observed in other national and international studies (Bossart *et al*., 2022; Tilbery *et al*., 2009). This difference may be related to the fact that the patients evaluated were followed up in a reference center with clinical pharmacy services to users. In this setting, pharmacists are actively involved in MS patient care, promoting access and rational use of DMTs through the systematic assessment of potential adverse events, where patients are encouraged to discuss their concerns and expectations regarding the treatment.

A study conducted in São Paulo evaluated 118 MS patients and estimated the prevalence of adverse events related to the use of DMT at 42.7%, a value higher than that found in our study (Tilbery *et al*., 2009). The difference found can be explained by the different safety profiles of the most frequently used DMTs in each study. It is worth noting that most patients in the present study were using the second or third line of treatment (52.2%), with fingolimod being the most frequently used drug (29.9%), as opposed to the study in São Paulo, where beta interferon-1a was the most frequently used drug (49.9%). Previous studies have shown that fingolimod has a better long-term tolerability profile compared to beta interferon-1a (Bossart *et al*., 2022; Jalkh *et al*., 2020).

Another recent study conducted in Switzerland also found higher values than those found in our study, with a prevalence of adverse events ranging from 28.1% (DMTs initiated more than six months ago) to 46.4% (DMTs initiated less than six months ago) Bossart *et al*., 2022). The difference may be related to the average time of DMTs use identified in the studies. In our study, most patients (74.2%) had been using DMTs for > 6 months, with a median duration of use equal to 27 months. Previous studies have shown that patients at the beginning of treatment with DMTs tend to report a higher frequency of adverse events (Bossart *et al*., 2022; Khatri, 2016; Rafiee *et al*., 2019).

Headache was the adverse event most frequently reported by interferon beta-1a and natalizumab users. This event is significantly more frequent in MS patients treated with interferons compared to the placebo group (Filippini *et al*., 2003). Interferon-beta may cause headaches, which can be an important trigger for worsening migraines (Mantia, Prone, 2015; Villani *et al*., 2012). It is estimated that about 70% of patients without headache prior to treatment may develop a new headache after the inclusion of interferons (Filippini *et al*., 2003). Headache was also identified in 5.8% of patients using natalizumab. This value was surprisingly identical to that found in a cross-sectional study that assessed the prevalence and profile of adverse events caused by natalizumab in MS patients

at infusion centers in 9 Brazilian states (Fragoso, *et al*., 2013). The pivotal study of natalizumab found a higher frequency of headaches in the group of individuals treated with natalizumab (5%) than in the placebo group (3%) (Polman *et al*., 2006). Evidence suggested, however, that natalizumab did not exacerbate comorbid migraine in MS patients (Villani *et al*., 2012).

Despite the established effectiveness of DMTs in MS treatment, these drugs have a complex risk-benefit profile and their use requires careful patient monitoring due to a higher risk of serious adverse events (Simbrich, 2019). Adverse events related to the use of DMTs are known to affect a significant percentage of patients and are an important factor associated with treatment abandonment and poor adherence. A previous study evaluated how MS patients perceive the risks and benefits of DMT treatment and identified a history of discontinuation of these drugs due to adverse events (Bruce *et al*., 2018). The risks of DMTs tend to be underestimated by many patients. A systematic review identified that many MS patients prefer treatments that offer extremely low levels of adverse event risks (Reen, Silber, Langdon, 2017). The same study, however, revealed that many patients are willing to accept higher risks in exchange for substantial long-term improvements. In this sense, health professionals involved in the care of MS patients should be aware of and monitor for possible adverse events and complications of DMTs, in order to minimize risks associated with treatment.

This study has some limitations. Although the questionnaire given to patients was designed to explore the events associated with the use of DMTs, we cannot ignore the possibility that some patients reported adverse events that may be related to other causes, such as MS-related symptoms, comorbidities, and continuous use of other medications. Another limitation of our study may be related to the cross-sectional design, which establishes an association, but not causality between events and the use of DMTs. The strength of our study, however, lies in the sample size, which is representative of the MS population in Goiânia.

Most patients with RRMS treated within the public health system in Goiânia were using first-line treatment. Fingolimod and beta interferons were the most used drugs. Adverse events related to DMTs were reported by more than a quarter of the patients in the study, being significantly more frequent among individuals on first-line treatment compared to those on second or third-line treatment. The DMTs most frequently associated with adverse events were dimethyl fumarate and glatiramer, with headache and myalgia being the events most commonly reported by patients. Strategies for monitoring the safety of DMTs in MS patients are needed in order to promote the rational use of these drugs in clinical practice. Our results also reinforce the importance of pharmacovigilance to acquire new safety data on the long-term use of DMTs. Future studies with prospective designs are needed to evaluate the long-term effect of DMTs adverse events on treatment adherence in MS patients.

REFERENCES

Bianco J, Damasceno A, Becker J, Casarin F, Carlos N, Martins T, et al. Prevalência da esclerose múltipla em pacientes tratados com medicamentos modificadores do curso da doença utilizando dados do Sistema Único de Saúde brasileiro. J Bras Econ Saúde. 2023;15(1):12-23.

Biolato M, Bianco A, Lucchini M, Gasbarrini A, Mirabella M, Grieco A. The Disease-Modifying Therapies of Relapsing-Remitting Multiple Sclerosis and Liver Injury: A Narrative Review. CNS Drugs. 2021;35(8):861-880.

Bose D, Ravi R, Maurya M, Pushparajan L, Konwar M. Impact of disease-modifying therapies on MRI outcomes in patients with relapsing -remitting multiple sclerosis: A systematic review and network meta-analysis. Mult Scler Relat Disord. 2022;61.

Bossart J, Kamm C, Kaufmann M, Stanikić M, Puhan M, Kesselring J, et al. Real-world disease-modifying therapy usage in persons with relapsing-remitting multiple sclerosis: Cross-sectional data from the Swiss Multiple Sclerosis Registry. Mult Scler Relat Disord. 2022;60:103706.

Brasil. Ministério da Saúde. Secretaria de Atenção Especializada à Saúde. Portaria Portaria no375. Aprova o Protocolo Clínico e Diretrizes Terapêuticas da Esclerose Múltipla [Internet]. Brasilia: Ministério da Saúde; 2009. Available from: https://bvsms.saude.gov.br/bvs/saudelegis/sas/2009/prt0375_10_11_2009.html

Brasil. Ministério da Saúde. Secretaria de Atenção Especializada à Saúde. Portaria Portaria no375. Aprova o Protocolo Clínico e Diretrizes Terapêuticas da Esclerose Múltipla [Internet]. Brasília: Ministério da Saúde; 2019. Available from: https://bvsms.saude.gov.br/bvs/saudelegis/Saes/2019/poc0007_11_07_2019.html

Brasil. Ministério da Saúde. Secretaria de Atenção Especializada à Saúde. Portaria Conjunta no1, de 07 de janeiro de 2022. Aprova o Protocolo Clínico e Diretrizes Terapêuticas da Esclerose Múltipla. [Internet]. Brasília: Ministério da Saúde; 2022. Available from: https://bvsms.saude.gov.br/bvs/saudelegis/saes/2022/poc0001_31_01_2022.html

Bruce J, Jarmolowicz D, Lynch S, Thelen J, Lim S-L, Smith J, et al. How patients with multiple sclerosis weigh treatment risks and benefits. Health Psychol. 2018;37(7):680-690.

da Silva N, Takemoto M, Damasceno A, Fragoso Y, Finkelsztejn A, Becker J, et al. Cost analysis of multiple sclerosis in Brazil: a cross-sectional multicenter study. BMC Health Serv Res. 2016;16:102.

Ferraro D, Camera V, Baldi E, Vacchiano V, Curti E, Guareschi A, et al. First-line disease-modifying drugs in relapsing-remitting multiple sclerosis: an Italian real-life multicenter study on persistence. Curr Med Res Opin. 2018;34(10):1803-1807.

Filippini G, Munari L, Incorvaia B, Ebers G, Polman C, D'Amico R, et al. Interferons in relapsing remitting multiple sclerosis: a systematic review. Lancet. 2003;361(9357):545–552.

Fragoso Y, Alves-Leon S, Arruda W, Carvalho M de J, Comini-Frota E, Corrêa É, et al. Natalizumab adverse events are rare in patients with multiple sclerosis. Arq Neuropsiquiatr. 2013;71(3):137-141.

Hartung DM, Johnston KA, McGregor JC, Bourdette DN. Characteristics of prescription drug use among individuals with multiple sclerosis in the us medicare population. Int J MS Care. 2022;24(2):90-97.

Jalkh G, Abi Nahed R, Macaron G, Rensel M. Safety of newer disease modifying therapies in multiple sclerosis. Vaccines (Basel). 2020;9(2):12.

Khatri BO. Fingolimod in the treatment of relapsing-remitting multiple sclerosis: long-term experience and an update on the clinical evidence. Ther Adv Neurol Disord. 2016;9(2):130-147.

Kobelt G, Teich V, Cavalcanti M, Canzonieri A. Burden and cost of multiple sclerosis in Brazil. PLoS One. 2019;14(1):e0208837.

Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology. 1983 Nov;33(11).

Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. Gerontologist. 1969;9(3):179-86.

Liu Z, Liao Q, Wen H, Zhang Y. Disease modifying therapies in relapsing-remitting multiple sclerosis: A systematic review and network meta-analysis. Autoimmun Ver. 2021;20(6).

Lyrio A, Mega T, Lopes A, Ferré F, Barreira A, Portugal C, et al. OP152 Use of Real-world Evidence By The Brazilian Health Technology Assessment Committee (Conitec) For Monitoring Of Health Technologies. Int J Tech Assess Health Car. 2023;39(S1):S45-S45.

Mantia L, Prone V. Headache in multiple sclerosis and autoimmune disorders. Neurol Sci. 2015;36(Suppl 1):S75–S78.

Marques V, Passos G, Mendes M, Callegaro D, Lana-Peixoto M, Comini-Frota E, et al. Brazilian Consensus for the Treatment of Multiple Sclerosis: Brazilian Academy of Neurology and Brazilian Committee on Treatment and Research in Multiple Sclerosis. Arq Neuropsiquiatr. 2018;76(8):539-554.

Mathis A, Owens G. Implications for multiple sclerosis in the era of the Affordable Care Act: the shifting managed care landscape. Am J Manag Care. 2014;20(11 Suppl):S242-53.

McGinley MP, Goldschmidt CH, Rae-Grant AD. Diagnosis and treatment of multiple sclerosis: A review. JAMA. 2021;325(8):765-779.

Polman H, O'Connor P, Havrdova E, Hutchinson M, Kappos L, Miller D, et al. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. N Engl J Med. 2006;354(9):899-910.

Qian Z, Li Y, Guan Z, Guo P, Zheng K, Du Y, et al. Global, regional, and national burden of multiple sclerosis from 1990 to 2019: Findings of global burden of disease study 2019. Front Public Health. 2023;17(11):1073278.

Rafiee A, Ghadimi K, Ataei A, Askari M, Sheikhinia N, Tavoosi N, et al. Mechanism and adverse effects of multiple sclerosis drugs: a review article. Part 2. Int J Physiol Pathophysiol Pharmacol. 2019;11(4):105-114.

Reen GK, Silber E, Langdon DW. Multiple sclerosis patients' understanding and preferences for risks and benefits of disease-modifying drugs: A systematic review. J Neurol Sci. 2017;15(375):107-122.

Ribeiro T, Duarte A, Silva D, Borges F, Costa V, Papais-Alvarenga R, et al. Prevalence of multiple sclerosis in Goiania, Goias, Brazil. Arq Neuropsiquiatr. 2019;77(5):352-356.

Simbrich A, Thibaut J, Khil L, Berger K, Riedel O, Schmedt N. Drug-use patterns and severe adverse events with disease-modifying drugs in patients with multiple sclerosis: a cohort study based on German claims data. Neuropsychiatr Dis Treat. 2019;28(15):1439-1457.

Souza K, Diniz I, Lemos L, Junior N, Zuppo I, Teodoro J, et al. Effectiveness of first-line treatment for relapsing- remitting multiple sclerosis in Brazil: A 16-year non-concurrent cohort study. PLoS ONE. 2020;15(9):e0238476.

Tilbery CP, Fazzito MM, Jordy SS, Thomaz RB, Fernandes IR. Efeitos adversos no tratamento da Esclerose Múltipla com drogas imunomoduladoras: experiência em 118 casos. Rev Neurocienc. 2009;17(3):220-225.

Tramacere I, Del Giovane C, Salanti G, D'Amico R, Filippini G. Immunomodulators and immunosuppressants for relapsing-remitting multiple sclerosis: a network meta-analysis. Cochrane Database Syst Rev. 2015;2015(9).

Villani V, Prosperini L, De Giglio L, Pozzilli C, Salvetti M, Sette G. The impact of interferon beta and natalizumab on comorbid migraine in multiple sclerosis. Headache. 2012;52(7):1130-5.

Viktil KK, Blix HS, Moger TA, Reikvam A. Polypharmacy as commonly defined is an indicator of limited value in the assessment of drug-related problems. Br J Clin Pharmacol. 2007;63(2):187-195.

Walton C, King R, Rechtman L, Kaye W, Leray E, Marrie RA, et al. Rising prevalence of multiple sclerosis worldwide: Insights from the Atlas of MS, third edition. Mult Scler. 2020;26(14):1816-1821.

Washington F, Langdon D. Factors affecting adherence to disease-modifying therapies in multiple sclerosis: systematic review. J Neurol. 2022;269(4):1861-1872.

World Health Organization. WHO. Division of Patient Safety. Department of Quality in Healthcare ([2010)]. Conceptual framework for the international classification for patient safety version 1.1: final technical report January 2009. Geneva: World Health Organization; 2010. 145 p.

Received for publication on 27th August 2023
Accepted for publication on 25th February 2024