ORIGINAL ARTICLE

Revista Eletrônica de Enfermagem

Cutaneous reactions caused by injected immunomodulators in the treatment of multiple sclerosis and associated factors

Ligia Nogueira Manso de Oliveira[1]
Hélio Amante Miot[1]
Tais Lopes Saranholi[1]
Luciana Patrícia Fernandes Abbade[1]

[1]Universidade Estadual Paulista Júlio de Mesquita Filho (Unesp), Botucatu, São Paulo, Brazil.

Corresponding author:
Ligia Nogueira Manso de Oliveira
E-mail: lg-nm@hotmail.com

Extract from the Master's Dissertation: "Cutaneous reactions caused by injectable immunomodulators used for the treatment of multiple sclerosis" (In Portuguese, "Reações cutâneas provocadas por imunomoduladores injetáveis associados ao tratamento de esclerose múltipla"), defended in 2016 at the Faculdade de Medicina da Universidade Estadual Paulista Júlio de Mesquita Filho, Botucatu, São Paulo, Brazil.

Submited: 8 August 2023
Accepted: 16 December 2024
Published: 17 April 2025

Executive Editor: Valéria Pagotto
Associated Editor: Cristiana da Costa Luciano

How to cite this article: Oliveira LNM, Miot HA, Saranholi TL, Abbade LPF. Cutaneous reactions caused by injected immunomodulators in the treatment of multiple sclerosis and associated factors. Rev. Eletr. Enferm. 2025;27:76957.https://doi.org/10.5216/ree.v27.76957 English, Portuguese.

ABSTRACT

Objectives: to describe cutaneous reactions caused by injected immunomodulators used for the treatment of multiple sclerosis (MS) and associated factors. **Methods:** a descriptive and analytical cross-sectional study was conducted with a nonprobability sample of MS patients undergoing treatment at a hospital's neuroimmunology center. The data were collected using structured interviews consisting of two instruments. **Results:** the sample consisted of 116 MS patients with an average age of 39.8 years, who were predominantly female (72.4%) and white (98.3%). The most prevalent type of MS was relapsing-remitting MS (70.0%). A total of 101 (87.0%) participants developed one or more cutaneous reactions at the injection site. The most frequent reactions were hyperemia (n = 86; 74%), sclerosis (n = 68; 59%), ecchymosis (n = 59; 51%), oedema (n = 53; 46%) and warmth (n = 50; 43%). Reactions were mostly mild and moderate intensity. The factors associated with reactions were depression (p = 0.01) and Body Mass Index considered to be obese (p = 0.04). **Conclusions:** a significant proportion of patients developed cutaneous reactions at the immunomodulator injection site, and the presence of reactions was associated with depression and obesity.

Descriptors: Multiple Sclerosis; Hypersensitivity; Drug-Related Side Effects and Adverse Reactions.

INTRODUCTION

Multiple Sclerosis (MS) is a chronic autoimmune inflammatory demyelinating and degenerative disease of the central nervous system (CNS) and is disabling in more than 50.0% of cases. It usually affects young adults aged between 20 and 40, its etiology is multifactorial and its exact cause remains elusive[1-4].

It is estimated that MS affects around 2.8 million people worldwide[5,6], with prevalence being highest in North America (140 cases per 100,000) and Europe (108 cases per 100,000)[7]. Brazil is considered an area of low to medium prevalence, with a wide variation in rates across states and regions[8-11].

There are three types of MS: Relapsing-Remitting (RRMS), Secondary-Progressive (SPMS) and Primary-Progressive (PPMS)[11], with the latter two being the most aggressive forms. While most people with MS are initially diagnosed with RRMS, many transition to SPMS over time, probably as a result of neurodegenerative processes[12].

There is currently no cure for MS and treatment is based mainly on the use of immunosuppressive and immunomodulatory agents, as well as disease-modifying therapies[13]. Irrespective of the type of treatment, it is recommended that patients start therapy as early as possible to slow disease progression, reduce the frequency of flare-ups and improve quality of life[14,15].

The immunomodulators available on the public health system in Brazil for the treatment of RRMS are glatiramer acetate, interferon beta-1a and beta-1b (subcutaneous or intramuscular), fingolimod (oral) and natalizumab (intravenous infusion)[9]. The first-choice immunomodulators for the treatment of MS are beta interferons and glatiramer acetate[16], which have been used since 1993 and 1998 respectively, can be self-administered and have a well-established long-term safety profile[17].

Despite this safety profile, therapy is long-term and subcutaneous (SC) and intramuscular (IM) drugs can induce localized or generalized cutaneous reactions, which adversely affect patient physical and emotional health and contribute to treatment abandonment[18].

It is therefore important to understand the types of cutaneous reactions presented by patients using self-injected immunomodulators and associated factors to help develop effective early interventions and contribute to treatment adherence.

Considering the above, the aim of this study was therefore to describe the occurrence of cutaneous reactions caused by injectable immunomodulators used to treat MS and potential associated factors.

METHODS

A descriptive and analytical cross-sectional study was conducted at a university hospital in the state of São Paulo between January and September 2015. The report was prepared following the recommendations of the STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) statement[19].

The nonprobability sample consisted of MS patients of both sexes aged 18 years and over taking the injectable immunomodulators beta interferons and/or glatiramer acetate and undergoing treatment at the hospital's neuroimmunology center. Patients with a disability that could compromise their understanding of the study information were excluded.

Patients were approached before or after their routine appointment with the doctor, and after the participants signed an informed consent, a structured interview consisting of three instruments was then conducted in a private room.

The first instrument was devised to collect information on patient sociodemographic and clinical characteristics and treatment. MS was classified as Relapsing-Remitting (RRMS), progressive (Secondary-Progressive Multiple Sclerosis – SPMS; Primary-Progressive Multiple Sclerosis – PPMS; and Flare-up Remission Multiple Sclerosis – FRMS) and unspecified.

The second instrument was developed and refined by the researchers to assess cutaneous reactions caused by the injectable drugs using the following classifications: mild cutaneous reaction — presence of hyperemia, dryness, scaling, ecchymosis or hyperpigmentation; moderate reaction — presence of hyperemia plus warmth, hematoma, eczema, oedema or sclerosis; and severe reaction — presence of panniculitis, lipoatrophy, ulcerative lesion or necrosis.

Adherence to treatment was assessed by asking patients about the medications they were taking and compliance with advice given by health professionals. Patients who reported following the prescribed recommendations correctly were deemed to be adhering to treatment.

The data were analyzed using software Statistical Package for the Social Sciences – SPSS, version 21.0 (2012, International Business Machines Corporation, United States). The categorical variables were described using simple and relative frequencies and percentages and compared across subgroups using William's corrected G-test for the polytomous variables, Fisher's exact test for the dichotomous variables and analysis of residuals in contingency tables. The quantitative variables were described using means and Standard Deviation (SD) or median and first and third quartiles (Q1 = P25; Q3 = P75). The parametric data were assessed using the Mann-Whitney and Kruskal-Wallis tests.

The sample non-probabilistic was selected using convenience sampling, including all patients who met the eligibility criteria during the study period.

The study was conducted in accordance with ethical norms and standards for research involving human beings and the recommendations set out in Brazilian National Health Council Resolution 466/2012. The study was approved by the *Botucatu* Medical School's (*Sao Paulo* State University) research ethics committee (Certificate of Submission for Ethical Appraisal Nº 36520714.1.0000.5411).

RESULTS

The sample consisted of 116 MS patients (Table 1) with an average age of 39.8 years (SD ± 11.1). The participants were predominantly women (n = 84; 72.4%), white (n = 114; 98.3%), married (n = 63; 54.3%) and had completed higher education (n = 51; 44.0%). Most were retired or on sick leave due to the disease (n = 46; 39.7%) and had a BMI considered to be obese (n = 59; 50.8%).

In relation to clinical forms of disease, 81 (70.0%) had RRMS and 27 (23.0%) had SPMS or PPMS (Table 1).

Table 2 shows the results regarding the immunomodulators and cutaneous reactions. The vast majority of participants (87.1%) had some kind of cutaneous reaction. Of these, 27 (23.3%) were patients with recent reactions who had also had a history of previous cutaneous reactions.

The median length of time of use of the immunomodulators was as follows: Subcutaneous (SC) interferon beta-1a – 35 months (12 - 48 months); intramuscular (IM) interferon beta-1a – 36 months (24-63 months); SC interferon beta-1b – 36 months (21.5 - 36 months); and glatiramer acetate – 24 months (18 - 36 months). The frequency of cutaneous reactions was higher among patients using only glatiramer acetate (n = 43; 37.0%).

Regarding the severity of cutaneous reactions (Table 2), glatiramer acetate accounted for the highest frequency of moderate (n = 49; 66.2%) and severe (n = 16; 21.6%) reactions, showing a

Table 1 - Sociodemographic and clinical characteristics of multiple sclerosis patients (n = 116), Botucatu (SP), Brazil, 2015

Variables	
Sex – n (%)	
Female	84 (72.4)
Male	32 (27.6)
Age – mean (SD[A]) in years	39.8 (11.1)
Color n (%)	
White	114 (98.3)
Black	2 (1.7)
Marital status – n (%)	
Married	63 (54.3)
Single	41 (35.4)
Divorced	8 (6.9)
Widowed	4 (3.4)
Education level – n (%)	
Primary education	22 (19.0)
Secondary education	43 (37.0)
Higher education	51 (44.0)
Occupation – n (%)	
Intellectual worker	22 (19,0)
Services	29 (25,0)
Retired or on leave	46 (39.6)
Other	19 (16.4)
BMI[B] – classification, median (P[C]25–P75)	
Below weight	6 (5.2)
Normal weight	51 (44)
Obese	59 (50.8)
Type of MS[D] – n (%)	
RRMS[E]	81 (70.0)
SPMS[F] or PPMS[G]	27 (23.0)
Unspecified	8 (7.0)
Length of time with the disease – median (P[C]25–P75), months	72 (38–126)
Length of time since the first flare-up - median (P[C]25–P75), months	96 (52–168)
Length of time since the last flare-up - median (P[C]25–P75), months	24 (12–48)
Length of time since initiation of treatment using immunomodulators - median (P[C]25–P75), months	63 (36–132)

Notes: [A]SD: standard deviation; [B]BMI: Body Mass Index; [C]P: percentile; [D]MS: Multiple Sclerosis; [E]RRMS: Relapsing-Remitting Multiple Sclerosis; [F]SPMS: Secondary-Progressive Multiple Sclerosis; [G]PPMS: Primary-Progressive Multiple Sclerosis

statistically significant difference when compared to interferon beta-1a (IM) ($p < 0.01$ – William's corrected G-test).

The most frequent cutaneous reactions (Figure 1) were hyperemia (n = 86; 74.0%), sclerosis (n = 68; 59.0%), ecchymosis (n = 59; 51.0%), edema (n = 53; 46.0%) and localized warmth (n = 50; 43.0%), and the least frequent reactions were lipoatrophy (n = 17; 15.6%), hyperpigmentation (n = 15; 13.8%), dryness (8; 7.3%), panniculitis (n = 7; 6.4%), necrosis (n=3; 2.8%) and eczema (n =2; 1.8%).

The most affected injection sites were the side of the thigh (74; 64%) and the abdomen (73; 63%), followed by the arms (54; 47%).

Fifty-two patients (52; 44.8%) reported that they self-injected (Table 3), with the rest saying they asked for help from a family member or health professional. The injection technique and use of an autoinjector were described correctly by 46 (40.0%) patients, partially correctly by 43 (37.0%) patients and incorrectly by 27 (23.3%) patients. Eighty-eight (76.0%) patients used the autoinjector provided by the immunomodulator manufacturer, 84 (72.4%) received previous training on self-injection and injection site care provided by the manufacturer and/or referral centers, and 88 (75.8%) adhered to the proposed treatment.

The presence of cutaneous reactions was associated with depression ($p < 0.01$) and obesity based on BMI ($p < 0.01$) (Table 4).

No association was found between the presence of cutaneous reactions and type of MS (Table 5).

DISCUSSION

While immunomodulators are described in the literature as safe medications, a previous study showed that 90.0% of MS patients using SC formulations and 33% of those using IM formulations developed mild localized cutaneous reactions[20]. Similar results were found in the current study, which showed that 87.0% (n = 100) of patients experienced this adverse event.

Cutaneous reactions can adversely affect treatment adherence[18] and patient quality of life. It is therefore important to provide guidance on injection site rotation, the correct injection technique and continuous monitoring of the injection site to ensure early identification of reactions.

The most frequent cutaneous reactions in the present study were, in general, mild (hyperemia and ecchymosis) and moderate (sclerosis at the injection site and oedema). The most frequent severe reactions were panniculitis and lipoatrophy. Previous studies have also reported higher incidence of mild and moderate localized skin reactions, including hyperemia, erythema, oedema, pruritus, inflammation and hardening of the surrounding area[21,22]. While mild and moderate cutaneous reactions have less serious clinical outcomes, they can cause discomfort and undermine patient commitment to ongoing treatment[23]. Injection-site reactions may occur less frequently when the autoinjector provided by the manufacturer is used[24].

Panniculitis generally develops after around two months of glatiramer acetate treatment, regressing spontaneously within three months of stopping therapy[20]. One of the possible causes of this reaction is a local inflammatory reaction triggered by the drug's direct toxic effect on adipocytes. The inflammatory phase is then followed by hypersensitivity reactions and residual lipoatrophy[20].

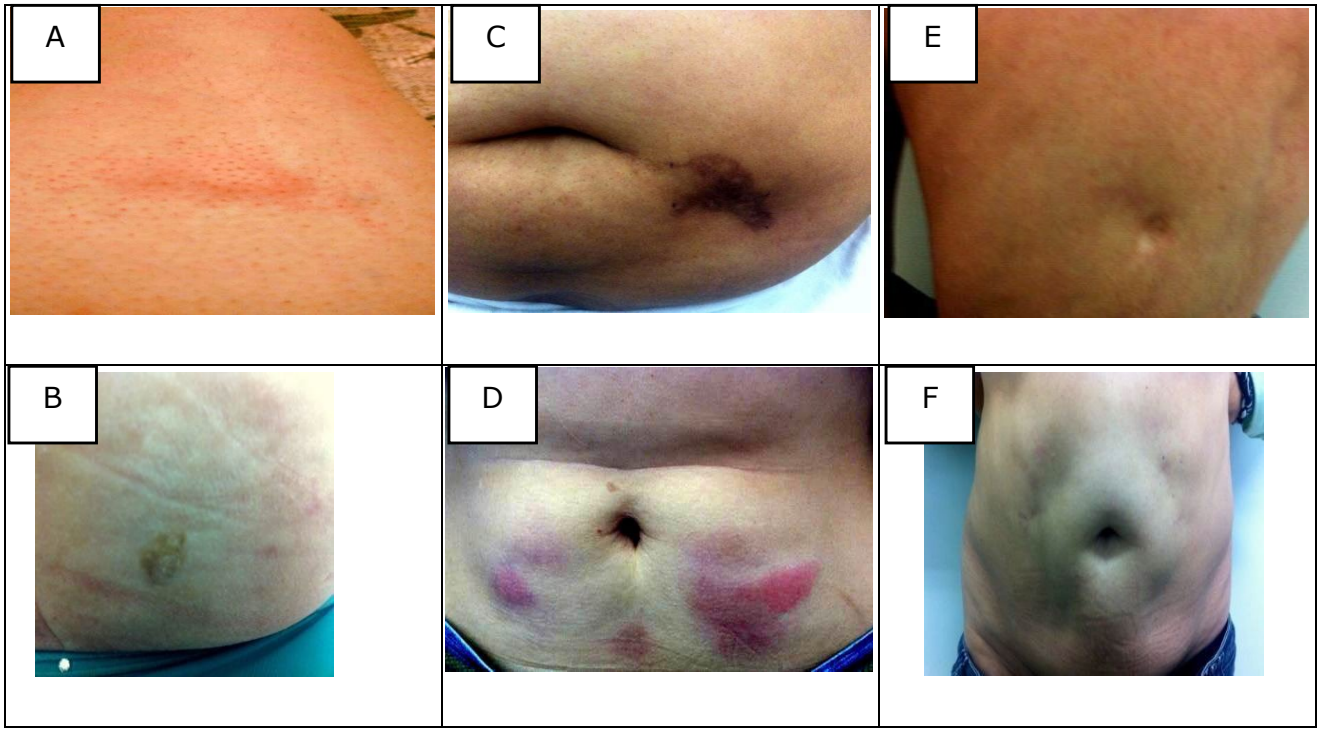
Lipoatrophy is a severe adverse event reported in patients taking these injectable immunomodulators[25]. In the present study 17 patients (15.6%) developed this type of reaction.

Table 2 - Injectable immunomodulators for the treatment of multiple sclerosis and cutaneous reactions (n=116), Botucatu (SP), Brazil, 2015

Variables	
Cutaneous reaction - n (%)	
Yes	101 (87.1)
No	15 (12.9)
Time since cutaneous reaction - n (%)*	
Recent	27 (26.7)
Previous	74 (73.3)
Length of time using glatiramer acetate – median P[A]25-P75	24 (18-36)
Length of time using interferon beta – median P[A]25-P75	
Subcutaneous 1a	35 (12–48)
Intramuscular 1a	36 (25–63)
Subcutaneous 1b	36 (21.5–36)
Immunomodulator with presence of cutaneous reaction – n (%)*	
Glatiramer acetate (SC[B])	43 (37.0)
Interferon beta-1a (IM[C])	13 (13.0)
Interferon beta-1a (SC[B]) and glatiramer acetate (SC[B])	10 (10.0)
Interferon beta-1b (SC[B])	4 (4.0)
Interferon beta-1a (IM[C]) and glatiramer acetate (SC[B])	6 (6.0)
Interferon beta-1a(SC[B]) and interferon beta-1b (SC[B])	2 (2.0)
Interferon beta-1a(IM[C]), interferon beta-1a (SC[B]) and interferon beta-1b (SC[B])	1 (1.0)
Interferon beta-1a (SC[B]), interferon beta-1a (IM[C]) and glatiramer acetate (SC[B])	1 (1.0)
Interferon beta-1a (SC[B]), interferon beta-1a (IM[C])	1 (1.0)
Interferon beta-1a (IM[C]), interferon beta-1b (SC[B]) and glatiramer acetate (SC[B])	1 (1.0)
Interferon beta-1a (IM[C]), interferon beta-1a (SC[B]), interferon beta-1b (SC[B]) and glatiramer acetate (SC[B])	1 (1.0)
Interferon beta-1a (SC[B]), interferon beta-1b (SC[B]) and glatiramer acetate (SC[B])	1 (1.0)
Total	101 (100.0)
Severity of cutaneous reaction by immunomodulator – n (%)	
Interferon beta-1a (SC[B])	
Mild reaction[D]	8 (25.8)
Severe reaction	6 (19.3)
Interferon beta-1a (IM[C])	
Mild reaction[D]	13 (43.3)
Moderate reaction[E]	15 (50.0)
Severe reaction[F]	2 (6.4)
Interferon beta-1b (SC[B])	
Mild reaction[D]	7 (31.8)
Moderate reaction[E]	12 (54.5)
Severe reaction[F]	3 (13.6)
Glatiramer acetate (SC[B])	
Mild reaction[D]	9 (12.1)
Moderate reaction[E]	49 (66.2)
Severe reaction[F]	16 (21.6)

Notes: [A]P: percentile; [B]SC: subcutaneous; [C]IM: intramuscular; [D]mild reaction: hyperemia, dryness, scaling, ecchymosis and hyperpigmentation; [E]moderate reaction: hyperemia plus warmth, ecchymosis, hematoma, eczema, edema and hardening; [F]severe reaction: panniculitis, lipoatrophy, ulcerative lesion and necrosis.
*n = 101.

Figure 1 - Cutaneous reactions at medication injection sites in multiple sclerosis patients, Botucatu (SP), Brazil, 2015



Notes: Mild reactions: images A (hyperemia) and B (hyperpigmentation); Moderate reactions: images C (ecchymosis - violaceous macule in the periumbilical region) and D (panniculitis - hardened painful patches - erythema nodosumon – on the abdomen); and Severe reactions: images E (lipoatrophy in a single depression on the side of the thigh) and E (lipoatrophy in multiple depressions on the abdomen).

Table 3 - Patient characteristics by injection technique, use of an autoinjector and previous training on self-injection (n = 116), Botucatu (SP), Brazil, 2015

Variables	n	%
Who applies the injection		
Patient (self-injection)	52	44.8
Patient and family member	27	23.2
Family member	16	13.8
Patient and health professional	8	6.9
Health professional	4	3.4
Family member and health professional	2	1.7
Missing information	7	6.0
Injection technique		
Correct	46	40.0
Partially correct	43	37.0
Incorrect	27	23.3
Use of autoinjector		
Yes	88	76.0
No	28	24.1
Previous training		
Yes	84	72.4
No	32	27.5
Adherence to treatment		
Yes	88	75.8
No	28	24.1

Moderate and severe localized cutaneous reactions were more frequent in patients using glatiramer acetate when compared to those taking betainterferone. Cutaneous reactions caused by glatiramer acetate were also identified by a previous study, in which nine out of 12 patients with RRMS (75.0%) developed early lesions with urticated erythematous patches and nodules, while the remaining participants had late lesions such as lipoatrophy (n = 2; 16.6%) and morphoea (n = 1; 8.4%)[26-29].

Interferon beta can trigger skin reactions due to the drug's potential cutaneous toxicity, with mild reactions being more common[28], which is in line with the findings of the present study.

While early or late severe cutaneous reactions are less prevalent, the development of these events is extremely undesirable. Even if them occurs in a single patient, they can have a negative impact on the quality of life of patient, as shown by a study[27] that found necrosis of the skin and subcutaneous tissue around the interferon beta 1b (SC) injection site after 10 years of administration in a 55-year-old male patient.

The findings of the present study revealed an association between cutaneous reaction and obesity. To the best of our knowledge this is the first time this finding has been documented in the literature. However, it is known that obesity affects skin physiology and the skin barrier, collagen structure, wound healing, as well as the sebaceous and sweat glands, and circulatory and lymphatic systems. Obesity also has metabolic effects and is associated with inflammatory skin diseases. In this sense, localized traumas caused

Table 4 - Sociodemographic and clinical characteristics and frequency of cutaneous reactions in multiple sclerosis patients (n =116), Botucatu (SP), Brazil, 2015

Variables	Drug reaction		*p*-value
	Yes	No	
Age – mean (SD[A]) in years	39.5 (12.5)	41.7 (10.9)	0.89[B]
Sex n (%)			
Female	76 (65.5)	8 (7.0)	0.23[C]
Male	25 (26.0)	7 (6.0)	
Education level n (%)			
Primary education	18 (15.5)	4 (3.4)	0.84[D]
Secondary education	36 (31.0)	7 (6.0)	
Higher education	47 (40.5)	4 (3.4)	
Occupation n (%)			
Retired or on sick leave	41 (41.0)	5 (33.3)	0.78[D]
Intellectual worker	19 (18.8)	3 (20.0)	
Other	17 (16.8)	2 (13.3)	
Diabetes n (%)			
Yes	97 (96.0)	14 (93.3)	0.49[C]
No	04 (3.9)	1 (6.6)	
Depression n (%)			
Yes	27 (26.7)	0	0.01[C]
No	74 (73.3)	15 (100)	
Body Mass Index n (%)			
Low weight	04 (66.7%)	2 (33.3%)	0.04[D]
Normal weight	43 (84.3%)	8 (15.7%)	
Obese	54 (91.5%)	5 (8.4%)	

Notes: [A]SD: standard deviation; [B]Student's t-test; [C]Fisher's test; [D]William's corrected G-test

Table 5 - Association between cutaneous reactions and type of multiple sclerosis (n = 116), Botucatu (SP), Brazil, 2015

Type	Cutaneous reaction		*p*-value[F]
	Yes n (%)	No n (%)	
RRMS[A]	70 (60.3)	11 (9.5)	
SPMS[B]	16 (13.8)	4 (3.5)	
PPMS[C]	4 (3.5)	0	$p = 0.99$
EMSR[D]	3 (2.5)	0	
UMS[E]	8 (6.9)	0	

Notes: [A]RRMS: Relapsing-Remitting Multiple Sclerosis; [B]SPMS: Secondary-Progressive Multiple Sclerosis; [C]PPMS: Primary-Progressive Multiple Sclerosis; [E]UMS: Unspecified Multiple Sclerosis; [F]Fisher's test $p < 0.05$.

by subcutaneous and intramuscular injections can exacerbate inflammatory processes in the skin and adjacent muscle[30].

As well the present study reveals an association between cutaneous reactions caused by using immunomodulators and depression, reinforcing the notion that effects of MS can adversely affect patient quality of life, leading to disability, fatigue, depression[29], cognitive impairment and unemployment[31].

Patient adherence to therapy is vital to ensure treatment efficacy. It is therefore important to provide adequate guidance to patients on treatment expectations, adverse effects and the treatment strategies adopted to address these problems[27]. The present study shows that 88 (75.8%) patients adhered to treatment, which is higher than the adherence rate found by a previous study[29]. Similar results were found by another study showing that treatment adherence was greater in patients using intramuscular drugs once a week. Several authors have pointed out a potential association between treatment regime complexity and adherence[32,33], while others found a strong association between perceived benefits of using immunomodulators and treatment adherence[34,35]. Factors associated with adherence are patient-centered and reflect individual expectations[36]. Treatment adherence is also related to support from family members[37].

Another study also found high levels of treatment adherence, showing an association between adherence and guidance on the disease received from health professionals before starting treatment, with patients who were well-guided showing a significatively higher level of adherence[38].

In contrast, complex and/or painful treatment regimens with unpleasant side effects and frequent changes to the treatment plan increase the chances of not adhering to treatment[27]. The absence of immediate improvements in the patient's clinical condition, progression of the disease and disability caused by MS can also compromise treatment adherence[39].

It is important to emphasize that consistencies and differences in adherence rates across studies can be explained by differences in the variables used to assess this outcome.

While this study provides important insights into cutaneous reactions caused by injected immunomodulators, one of the limitations of this study is recall bias, with participants finding it difficult to recall illness and treatment history, especially with regard to the immunomodulators used and length of treatment. Another limitation is research design, as cross-sectional studies are limited in their ability to determine the direction of causality in the relationship between associated factors.

It is worth noting that, while not one of the objectives, one of the contributions of this study to clinical practice was the production of a guide on the management of MS in patients using injected immunomodulators containing information for health professionals to help with patient guidance[40].

In light of our findings, future research should explore the factors causing adverse reactions in MS patients with long-term use of injected immunomodulators and the relationship between reactions and number of injections, doses, part of the body, obesity and depression.

CONCLUSION

Most of the MS patients using injected immunomodulators developed mild, moderate or severe cutaneous reactions at the in-

jection site. The most frequent reactions were hyperemia, sclerosis and ecchymosis and the least frequent reactions were lipoatrophy, panniculitis and necrosis. Obesity and depression were associated with a higher frequency of adverse reactions.

REFERENCES

1. Dobson R, Giovannoni G. Multiple sclerosis – a review. Eur J Neurol. 2019 Oct 9;26(1):27-40. https://doi.org/10.1111/ene.13819

2. Azami M, YektaKooshali MH, Shohani M, Khorshidi A, Mahmudi L. Epidemiology of multiple sclerosis in Iran: a systematic review and meta-analysis. PLoS One. 2019 Apr 9;14(4):e0214738. https://doi.org/10.1371/journal.pone.0214738

3. Thompson AJ, Baranzini SE, Geurts J, Hemmer B, Ciccarelli O. Multiple sclerosis. Lancet. 2018 Apr 21;391(10130):1622-36. https://doi.org/10.1016/S0140-6736(18)30481-1

4. Yamout BI, Alroughani R. Multiple sclerosis. Semin Neurol. 2018 Apr;38(2):212-25. https://doi.org/10.1055/s-0038-1649502

5. Leray E, Moreau T, Fromont A, Edan G. Epidemiology of multiple sclerosis. Rev Neurol (Paris). 2016 Jan;172(1):3-13. https://doi.org/10.1016/j.neurol.2015.10.006

6. Walton C, King R, Rechtman L, Kaye W, Leray E, Ann Marrie R, et al. Rising prevalence of multiple sclerosis worldwide: insights from the Atlas of MS, third edition. Mult Scler. 2020 Dec;26(14):1816-21. https://doi.org/10.1177/1352458520970841

7. Doshi A, Chataway J. Multiple sclerosis, a treatable disease. Clin Med (Lond). 2016 Dec;16(Suppl 6):s53-s59. https://doi.org/10.7861/clinmedicine.16-6-s53

8. Vasconcelos CCF, Thuler LCS, Rodrigues BC, Calmon AB, Alvarenga RMP. Multiple sclerosis in Brazil: a systematic review. Clin Neurol Neurosurg. 2016 Dec;151:24-30. https://doi.org/10.1016/j.clineuro.2016.07.011

9. Kobelt G, Teich V, Cavalcanti M, Canzonieri AM. Burden and cost of multiple sclerosis in Brazil. PLoS One. 2019 Jan 23;14(1):e0208837. https://doi.org/10.1371/journal.pone.0208837

10. Passos GR, Becker J, Varela DL, Fröhlich AC, Rech BC, Mattos ACS, et al. Prevalence of multiple sclerosis in key cities of Brazil: a study in Passo Fundo, Southern Brazil. Arq Neuropsiquiatr. 2021 Aug;79(8):692-6. https://doi.org/10.1590/0004-282X-anp-2020-0221

11. Marques VD, Passos GR, Mendes MF, Callegaro D, Lana-Peixoto MA, Comini-Frota ER, 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 Aug;76(8):539-54. https://doi.org/10.1590/0004-282X20180078

12. Baldassari LE, Fox RJ. Therapeutic advances and challenges in the treatment of progressive multiple sclerosis. Drugs. 2018 Oct;78(15):1549-66. https://doi.org/10.1007/s40265-018-0984-5

13. Gholamzad M, Ebtekar M, Ardestani MS, Azimi M, Mahmodi Z, Mousavi MJ, et al. A comprehensive review on the treatment approaches of multiple sclerosis: currently and in the future. Inflamm Res. 2019 Jan;68(1):25-38. https://doi.org/10.1007/s00011-018-1185-0

14. Harding-Forrester S, Roos I, Nguyen AL, Malpas CB, Diouf I, Moradi N, et al. Disability accrual in primary and secondary progressive multiple sclerosis. J Neurol Neurosurg Psychiatry. 2023 Sep;94(9):707-17. https://doi.org/10.1136/jnnp-2022-330726

15. Lee Mortensen G, Rasmussen PV. The impact of quality of life on treatment preferences in multiple sclerosis patients. Patient Prefer Adherence. 2017 Oct 19; 11:1789-96. https://doi.org/10.2147/PPA.S142373

16. Saiz A, Mora S, Blanco J. Cumplimiento terapéutico con terapias modificadoras de la enfermedad de primera línea en pacientes con esclerosis múltiple. Estudio COMPLIANCE. Neurología. 2015 May;30(4):214-22. https://doi.org/10.1016/j.nrl.2013.12.008

17. Wencel-Warot A, Michalak S, Warot M, Kalinowska-Lyszczarz A, Kazmierski R. The cross-reactivity of binding antibodies with different interferon beta formulations used as disease-modifying drugs in multiple sclerosis patients. Medicine (Baltimore). 2016 Nov;95(45):e5337. https://doi.org/10.1097/MD.0000000000005337

18. van Rossum JA, Peters MAD, van der Valk P, de Jong BA. Severe cutaneous adverse event in a daclizumab-treated multiple sclerosis patient. Mult Scler Relat Disord. 2019 Sep;34:38-40. https://doi.org/10.1016/j.msard.2019.06.006

19. Malta M, Cardoso LO, Bastos FI, Magnanini MMF, Silva CMFP. Iniciativa STROBE: subsídios para a comunicação de estudos observacionais. Rev Saúde Pública. 2010;44(3):559-65. https://doi.org/10.1590/S0034-89102010000300021

20. Balak DMW, Hengstman GJD, Çakmak A, Thio HB. Cutaneous adverse events associated with disease-modifying treatment in multiple sclerosis: a systematic review. Mult Scler. 2012 Dec;18(12):1705-17. https://doi.org/10.1177/1352458512438239

21. Leal JM, Souza GH, Marsillac PF, Gripp AC. Skin manifestations associated with systemic diseases – Part II. An Bras Dermatol. 2021 Nov-Dec;96(6):672-87. https://doi.org/10.1016/j.abd.2021.06.003

22. Dantas KM, Lacerda LG, Mendes RF, Coelho VAT, Nascimento ES, Ferraz RL, et al. Esclerose múltipla: eficácia no tratamento por meio de imunomoduladores injetáveis. In: Silva PR. Promoção da saúde: conceito, estratégia e prevenção em pesquisa. 1st ed. São Paulo: Editora Científica Digital; 2023. p. 76–86. https://doi.org/10.37885/230613372

23. Andrade Andrade I, Tejedor Tejada E, Macías Cortés E, Muñoz Fernández C, Martínez Martínez M. Adherence to treatment with injectable immunomodulators in patients with multiple sclerosis and cognitive disorder. Rev Científica Soc Enferm Neurológica. 2021 July 24;56:11–7. https://doi.org/10.1016/j.sedeng.2021.04.001

24. Kołtuniuk A, Chojdak-Łukasiewicz J. Adherence to therapy in patients with multiple sclerosis—review. Int J Environ Res Public Health. 2022 Feb 15;19(4):2203. https://doi.org/10.3390/ijerph19042203

25. Udawatta M, Mateen FJ. Nicolau syndrome following glatiramer acetate for multiple sclerosis: case and review of reports. Ann Clin Transl Neurol. 2024 Apr;11(4):1080-5. https://doi.org/10.1002/acn3.52044

26. Mozafari N, Saffaei A, Alizadeh M, Shabani M. Cutaneous necrotic lesion: a wonderful delay adverse effect of interferon beta-1b injection for multiple sclerosis treatment. J Cosmet Dermatol. 2020 Apr;19(4):951-3. https://doi.org/10.1111/jocd.13104

27. Maurelli M, Bergamaschi R, Antonini A, Fargnoli MC, Puma E, Mallucci G, et al. Interferon-beta injection site reactions in patients with multiple sclerosis. J Dermatol Treat. 2018 Dec;29(8):831-4. https://doi.org/10.1080/09546634.2018.1467539

28. Morillo Verdugo R, Ramírez-Herráiz E, Fernández-Del Olmo R, Roig Bonet M, Valdivia García M. Adherence to disease-modifying treatments in patients with multiple sclerosis in Spain. Patient Prefer Adherence. 2019 Feb 13;13:261-72. https://doi.org/10.2147/PPA.S187983

29. Spessotto CV, Cavalli H, Eboni ACB, Machado RB, Mousquer AM, Palazzo LB, et al. Patients' satisfaction with and views about treatment with disease-modifying drugs in multiple sclerosis. Arq Neuropsiquiatr. 2016 Aug;74(8):617-20. https://doi.org/10.1590/0004-282X20160091

30. Hirt PA, Castillo DE, Yosipovitch G, Keri JE. Skin changes in the obese patient. J Am Acad Dermatol. 2019 Nov;81(5):1037-57. https://doi.org/10.1016/j.jaad.2018.12.070

31. Gil-González I, Martín-Rodríguez A, Conrad R, Pérez-San-Gregorio MA. Quality of life in adults with multiple sclerosis: a systematic review. BMJ Open. 2020 Nov 30;10(11):e041249. https://doi.org/10.1136/bmjopen-2020-041249

32. Milstein-Moscati I, Persano S, Castro LLC. Aspectos metodológicos e comportamentais da adesão à terapêutica. In: Castro LLC, org. Fundamentos de farmacoepidemiologia. São Paulo: AG Editora; 2000. p. 171-9.

33. Klauer T, Zettl UK. Compliance, adherence, and the treatment of multiple sclerosis. J Neurol. 2008 Dec;255(suppl 6):87-92. https://doi.org/10.1007/s00415-008-6016-8

34. Devonshire V, Lapierre Y, Macdonell R, Ramo-Tello C, Patti F, Fontoura P, et al. The Global Adherence Project (GAP): a multicenter observational study on adherence to disease-modifying therapies in patients with relapsing-remitting multiple sclerosis. Eur J Neurol. 2011 Jan;18(1):69-77. https://doi.org/10.1111/j.1468-1331.2010.03110.x

35. Treadaway K, Cutter G, Salter A, Lynch S, Simsarian J, Corboy J, et al. Factors that influence adherence with disease-modifying therapy in MS. J Neurol. 2009 Apr;256(4):568-76. https://doi.org/10.1007/s00415-009-0096-y
36. Celius EG, Thompson H, Pontaga M, Langdon D, Laroni A, Potra S, et al. Disease progression in multiple sclerosis: a literature review exploring patient perspectives. PatientPreferAdherence.2021Jan8;15:15-27.https://doi.org/10.2147/PPA.S268829
37. Yalçın GY, Beser A, Kürtüncü M. Evaluation of the relationship between socio-demographic characteristics and social support with adherence to treatment in patient with multiple sclerosis. Int J Disabil Sports Health Sci. 2022 Dec 20;5(2):75-82. https://doi.org/10.33438/ijdshs.1105516
38. Machado M, Goulart A, Teich V. Adesão ao tratamento para esclerose múltipla com terapias de primeira linha: análise longitudinal retrospectiva. J Assist Farmac Farmacoecon. 2016 Dec;1(3):10-9. https://doi.org/10.22563/2525-7323.2016.%20v1.n3.p.10-19
39. Mah J, Thannhauser JE. Management of multiple sclerosis in adolescents - current treatment options and related adherence issues. Adolesc Health Med Ther. 2010 Jun 17;1:31-43. https://doi.org/10.2147/AHMT.S7594
40. Manso LN. Reações cutâneas provocadas por imunomoduladores injetáveis associadas ao tratamento de esclerose múltipla [dissertation]. Botucatu: Universidade Estadual Paulista Júlio de Mesquita Filho; 2016.

Author contributions - CRediT

LNMO: conceptualization; data curation; formal analysis; investigation; resources; writing - original draft; and writing – review and editing.
HAM: formal analysis; software; validation; visualization and writing – revision and editing.
TLS: visualization; writing - original draft; and writing – revision and editing.
LPFA: conceptualization; methodology; project administration; supervision; visualization; and writing – revision and editing.

Funding

This research received no funding.

Conflict of Interest

None.