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Artículo original

Tasa de retención de metotrexato en pacientes con artritis reumatoide y artritis psoriásica

Methotrexate retention rate in patients with rheumatoid arthritis and psoriatic arthritis

Amanda Collere Melara, Vitor Itiro Ishisak, Thelma Larocca Skare, Ana Paula Beckhauser, Bárbara Stadler Kahlow

Mackenzie Evangelic School of Medicine, PR, Brasil

Palabras clave: Sjögren primario; fenómeno de Raynaud; capilaroscopia; esclerosis sistémica muy temprana.

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RESUMEN

Introducción: el metotrexato (MTX) es una terapia de primera línea para la artritis reumatoide (AR) y la artritis psoriásica (APs). Se valora por su eficacia, bajo costo y facilidad de administración; sin embargo, los efectos adversos suelen llevar a la interrupción del tratamiento.

Objetivos: determinar las causas de suspensión del MTX en pacientes con AR y APs.

Materiales y métodos: se realizó un estudio retrospectivo que incluyó 148 pacientes (AR=102, APs=46) que recibieron MTX durante al menos un mes antes de su suspensión.

Resultados: las principales razones para la suspensión del MTX en pacientes con AR y APs fueron intolerancia gástrica: 71,5% (AR) vs. 45,6% (APs) (p=0,002); toxicidad hepática: 4,9% (AR) vs. 17,3% (APs) (p=0,02); falla del tratamiento: 8,8% (AR) vs. 15,2% (APs) (p=0,24). La mediana de uso del MTX fue de 60 meses en la AR y de 24 meses en la APs (p<0,0001). Ni la vía de administración, el índice de masa corporal, la edad ni el sexo influyeron en la duración del tratamiento.

Conclusiones: la intolerancia gástrica fue la principal causa de suspensión del MTX, especialmente en pacientes con AR. Además, la toxicidad hepática fue más frecuente en la APs. Aunque el uso de MTX fue más prolongado en la AR, los datos epidemiológicos y antropométricos no se asociaron con la suspensión del fármaco.

ABSTRACT

Introduction: *methotrexate (MTX) is a first-line therapy for rheumatoid arthritis (RA) and psoriatic arthritis (PsA). MTX is valued for its effectiveness, low cost, and ease of administration; however, side effects often lead to treatment discontinuation.*

Objectives: *to determine the causes for MTX discontinuation in patients with RA and PsA.*

Materials and methods: *retrospectively,148 patients (RA:102 and PsA: 46) who were under MTX administered for at least 1 month before withdrawal were analyzed.*

Contacto del autor: *Vitor Itiro Ishisaki*
E-mail: vitorishisaki@gmail.com
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Key words: *methotrexate; rheumatoid arthritis; psoriatic arthritis.*

Results: *the main reasons for discontinuing MTX in patients with RA and PsA were: gastric intolerance: 71.5% (RA) vs. 45.6% (PsA) (p=0.002); liver toxicity: 4.9% (RA) vs. 17.3% (PsA) (p = 0.02); treatment failure: 8.8% (RA) vs. 15.2% (PsA) (p=0.24). The median MTX use was 60 months in RA and 24 months in PsA (p<0.0001). Neither the route of administration, body mass index, age, nor sex influenced the duration of treatment.*

Conclusions: *gastrointestinal intolerance was the major cause of MTX withdrawal, especially in RA. However, hepatic toxicity was more commonly observed in patients with PsA. Although MTX was administered for longer periods for RA, epidemiological or anthropometric data were not associated with drug withdrawal.*

INTRODUCTION

Methotrexate (MTX) is a drug that is commonly used for the treatment of rheumatic diseases. Despite the development in the pharmacological field of immune-mediated diseases, MTX is still considered the gold standard treatment for rheumatoid arthritis (RA)[1]. MTX is also commonly used in several other rheumatic diseases instead of corticosteroids because it is safe, inexpensive, and easily available to the general population. MTX monotherapy has exhibited significant improvement in 23-40% of patients with RA[2].

MTX can be used as both monotherapy or in combination with other drugs. It is administered at doses of 7.5 mg/week to 25 mg/week, as needed, to control the symptoms of the disease[2]. Several patients cannot tolerate this drug due to side effects. The most common side effects of MTX are gastrointestinal symptoms, hepatic dysfunction, mucocutaneous problems, and hematological toxicity[2]. In approximately one-third of the patients with RA and psoriatic arthritis (PsA), MTX is frequently discontinued because of poor tolerability[3].

Numerous studies have been conducted to identify factors that may favor or prevent the adverse events of MTX. Drug dosage, administration route, frequency of administration, and administration in combination with other drugs have been studied in this context[4-8]. However, the interpretation of the results of these studies has been challenging because genetic and epigenetic mechanisms are involved in MTX metabolism, yielding different results according to the geographic location[9-11]. Thus, herein, we studied patients from Southern Brazil to determine the causes for MTX discontinuation in patients with RA and PsA.

MATERIALS AND METHODS

This retrospective study of 148 patients (102 with RA and 46 with PsA) was approved by the Institutional Committee of Ethics in Research (No: 6.439.554; October 20, 2023). Using a consecutive convenience sampling patients who regularly visited a single public rheumatology outpatient clinic from 2000 to 2010 were enrolled in the study. The need for informed consent was waived due to the retrospective nature of the study. To be included, patients should have RA and PsA diagnoses, have used MTX for at least one month, and this medication should have been withdrawn for medical reasons. In the case of MTX withdrawal due to treatment failure, this drug should have been used for at least 8 weeks. The diagnosis of RA or PsA was made on the basis of the 2010 American College of Rheumatology (ACR)/European League against Rheumatism criteria or the Classification Criteria for Psoriatic Arthritis (CASPAR), respectively. Medical records with incomplete data or patients in whom the cause of MTX discontinuation was unclear were excluded from the study.

The following patient data were collected: sex, age, underlying diseases, period of MTX use, dose administered, administration route, comorbidities, drugs used concomitantly, height and weight for body mass index (BMI) calculation, hemoglobin level, transaminases level, and creatinine level. All data were collected on the date of MTX discontinuation. The participating outpatient clinic routinely prescribes oral folic acid (5 mg) twice a week in all patients being administered MTX.

Data were studied in frequency and contingency tables. Comparison of nominal data was done by Fisher and chi-squared tests, and of numerical data (months of MTX use accor-

ding to nominal variables: age, BMI, MTX dose) by the Mann-Whitney test. The Spearman test was used to perform correlation studies of the length of MTX retention with numerical variables. The adopted significance was <0.05. Statistical studies were conducted with the help of the software GraphPad Prism. 9.5.1.

RESULTS

Characteristics of the studied patients are shown in Table 1. A predominance of females was observed in the RA group. Furthermore, oral administration was more common than subcutaneous administration in both samples.

The main reasons for MTX discontinuation and a comparison of discontinuation causes between the RA and PsA groups are shown in Table 2. Gastrointestinal side effects were more common in the RA group, while hepatic dysfunction was more common in the PsA group.

MTX was administered for a median period of 60 (24-96) months and 24 (12-48) months in patients with RA and PsA, respectively (p<0.0001).

Table 3 shows the duration of drug administration according to the patients' sex and age, route of administration, dose of MTX, comorbidities, concomitant treatment, and BMI. This table highlights that RA female patients used the medication longer than males. No influence of other variables was noted.

Table 1: Description of studied sample.

		Total	RA	PsA
Female sex (n)		111/148 (75.0)	87/102 (85.2)	24/46 (52.1)
Age – years- mean (SD)		46.4 (12.8)	43.9 (12.1)	51.9 (12.8)
Tobacco exposure		66/148 (44.5)	47/102 (46.0)	19/46 (41.3)
Administration route n (%)				
	Oral	106/144 (73.6)	71/99 (71.7)	35/45 (77.7)
	Subcutaneous	38/144 (26.3)	28/99 (28.2)	10/45 (22.2)
BMI - kg/m^2 – median (IQR)		28.9 (25.0-32.3)	28.1 (24.7-32.1)	30.4 (26.4-33.4)
MTX mg/week - median (IQR)		25.0 (15.0-25.0)	25.0 (20.0-25.0)	20.0 (15.0-25.0)
Treatment duration – months- median (IQR)		48.0 (12.0-72.0)	60.0 (24.0-96.0)	24.0 (12.0-48.0)
Comorbidities – n (%)				
	Arterial hypertension	62/148 (41.8)	46/102 (45.0)	16/46 (34.7)
	Dyslipidemia	33/148 (22.2)	29/102 (28.4)	4/46 (8.6)
	Fibromyalgia	23/148 (15.5)	16/102 (15.6)	7/46 (15.2)
	Diabetes mellitus	13/148 (8.7)	7/102 (6.8)	6/46 (13.0)
	Depression	6/148 (4.0)	5/102 (4.9)	1/46 (2.1)
Other treatment – n (%)				
	Antimalarial	33/143 (23.0)	32/98 (32.6)	1/45 (2.2)
	Glucocorticoid	81/143 (56.6)	70/98 (71.4)	11/45 (24.4)
	Leflunomide	45/143 (31.4)	39/98 (39.7)	6/45 (13.3)
	Anti- TNF α	20/143 (13.9)	11/98 (11.1)	9/45 (20)
	Tocilizumab	5/143 (3.4)	5/98 (5.1)	0
	Rituximab	4/143 (2.7)	4/98 (4.0)	0
Laboratory results				
	Hemoglobin – g/dL – mean (SD)	13.6 (1.3)	13.3 (1.1)	14.2 (1.6)
	ALT – U/L – median (IQR)	24.0 (19.3-29.0)	23.0 (19.0-28.8)	25.5 (21.3-32.1)
	AST- U/L – median (IQR)	20.0 (16.0-28.0)	18.5 (15.0-24.0)	27.0 (20.0-37.0)
	Creatinine – mg/dL (IQR)	0.7 (0.6-0.9)	0.7 (0.6-0.8)	0.8 (0.7-1.0)

RA: rheumatoid arthritis; PsA: psoriatic arthritis; n: number; BMI: body mass index; SD: standard deviation; IQR: interquartile range; MTX: methotrexate; ALT: alanine aminotransferase; AST: aspartate transferase.

Table 2: Mainn causes of methotrexate dicontinuation in the studied sample.

	Total	RA	PsA	p*
Gastrointestinal intolerance - n (%)	94/148 (63.5)	73/102 (71.5)	21/46 (45.6)	**0.002**
Treatment failure - n (%)	16/148 (10.8)	9/102 (8.8)	7/46 (15.2)	0.24
Hepatic dysfunction - n (%)	13/148 (8.7)	5/102 (4.9)	8/46 (17.3)	**0.02**
Alopecia - n (%)	3/148 (2.0)	2/102 (1.9)	1/46 (2.1)	**
Cytopenias - n (%)	7/148 (4.7)	7/102 (6.8)	0	**
Mucositis - n (%)	3/148 (2.0)	3/102 (2.9)	0	**
Others - n (%)	14/148 (9.4)	3/102 (2.9)	11/46 (23.9)	

*- *p refers to comparison between RA and PsA;* ** *not studied due to small sample number.*
n: number; RA: rheumatoid arthritis; PsA: psoriatic arthritis.

Table 3: Methotrexate treatment survival according to studied variables

MTX route, sex, comorbidities, concomitant treatment*						
	RA n=102			**PsA n=46**		
	With the variable (months)	**Without the variable (months)**	**p**	**With de variable (months)**	**Without the variable (months)**	**p**
Female sex	60.0 (36.0-96.0)	36.0 (11.0-60.0)	0.02	24.0 (11.5-56.0)	24.0 (12.0-52.0)	0.83
Tobacco exposure	60.0 (36.0 – 84.0)	60.0 (24.0-108.0)	0.60	24.0 (11.5-56.0)	12.0 (12.0-52.0)	0.98
Oral route	60.0 (24.0-96.0)	60.0 (36.0-81.0)	0.96	24.0 (12.0-56.0)	24.0 (12.0-56.0)	0.73
Hypertension	60.0 (24.0-96.0)	60.0 (24.0-84.0)	0.62	36.0 (12.0-63.0)	18.0 (12.0-54.0)	0.08
Dyslipidemia	72.0 (24.0-96.0)	60.0 (36.0-84.0)	0.70	40.0 (15.0-68.0)	24.0 (12.0-50.0)	0.28
Fibromyalgia	48.0 (30.0-102.0)	60.0 (24.0-96.0)	0.74	12.0 (12.0-24.0)	24.0 (12.0-56.0)	0.43
Diabetes	60.0 (24.0-96.0)	60.0 (24.0-96.0)	0.66	34.0 (9.7-60.0)	24.0 (12.0-48.0)	0.77
Depression	48.0 (30.0-198.0)	60.0 (24.0-96.0)	0.65	N too small		
Antimalarials	60.0 (36.0-96.0)	60.0 (24,0-84.0)	0.39	N too small		
Leflunomide	60.0 (24.0-90.0)	60.0 (30.0-102.0)	0.78	30.0 (21.0-66.0)	24.0 (12.0-56.0)	0.20
Glucocorticoid	60.0 (21.0-96.0)	60.0 (36.0-93.0)	0.45	12.0 (11.0-24.0)	24.0 (12.0-56.0)	0.18
Anti TNF-α	60.0 (36.0-108)	60.0 (24.0-96.0)	0.57	24.0 (12.0-30.0)	24.0 (12.0-56.0)	0.99
Tocilizumb	60.0 (17.2-81.0)	60.0 (24.0-96.0)	0.78	-		
Rituximab	48.0 (15.0-99.0)	60.0 (33.0-96.0)	0.76	-		
Correlations studies- Dose, patient's age and BMI						
	r	**95%CI**	**P**	**r**	**95%CI**	**p**
Age	-0.03	-0.22 to o.17	0.76	0.25	-0.05 to 0.51	0.09
Weekly dose	0.18	-0.02 to 0.37	0.07	0.16	-0.14 to o.44	0.28
BMI	0.17	-0.03 to 0.35	0.09	-0.23	-0.50 to 0.07	0.12

n: number; MTX: methotrexate; BMI: body mass index.
* *all values- median and interquartile range.*

DISCUSSION

In this study, we observed that the retention rate of MTX is higher in patients with RA than in patients with PsA. In a study by Loe et al., the retention rate of MTX over two years of treatment was similar between the RA and PsA groups. However, the authors noted a tendency for lesser improvement in the PsA group than in the RA group[11]. In a study by Nikiphorou et al. of 1,257 patients who were administered MTX, a similar rate of discontinuation was observed in the RA (34.1%) and PsA (36.8%) groups. Nevertheless, the study lacked data on the extent of treatment retention[3]. These differences, with our sample, may be due to the smaller number of subjects, the low percentage of PsA in our sample, and also to the lack of knowledge of the baseline inflammatory burden of our patients.

In the current study, gastrointestinal intolerance caused more treatment disruptions in the RA group, while hepatic dysfunction caused more treatment disruptions in the PsA group. The finding of cytopenia was equivalent in both the studied groups.

The prevalence of gastrointestinal intolerance as a side effect of MTX ranges from 11.9% to 62.3%[2,6]. However, its pathophysiology is poorly understood. Mucositis in the gastrointestinal tract has been documented in MTX users for cancer treatment, which may cause loss of mucosal integrity and barrier dysfunction[12]. Moreover, apoptotic enteropathy secondary to gut mucosal permeability modifications and damage to the enterocyte's mitochondria has been associated with high cellular concentrations of MTX[13]. Folic acid administration reportedly ameliorates the gastrointestinal symptoms, and this may be attributed to the large amounts of folic acid required by gastrointestinal mucosal cells due to its high turnover[14,15]. Variations in MTX transport genes and miRNAs have been linked to this form of toxicity. Methylene tetrahydro folate reductase enzyme (MTHFR), folylpolyglutamate synthase mitochondrial enzyme (FPGS), and gamma-glutamyl hydrolase (which removes gamma-linked glutamate from MTX) are some of the genes identified in MTX toxicity[16,17].

Obesity, which is commonly seen in patients with psoriasis, the presence of alcoholic liver disease, and metabolic dysfunction-associated steatotic liver disease are commonly associated with an increased risk of hepatic dysfunction in patients being administered MTX[18]. These side effects may also have a genetic influence. Polymorphisms associated with high intracellular levels of MTX polyglutamate or diminished levels of the target enzyme increase the susceptibility of the patient to hepatic injury[19]. Although the mechanism by which MTX adversely affects the liver remains unclear,it may be a result of direct damage to the hepatocytes[20].

In the present study, the administration route did not impact drug retention in either the RA or PsA group. Similarly, in a double-blinded study by Braun et al., there was no difference in tolerability according to the administration route[7]. However, Branco et al. determined that subcutaneous administration was better tolerated than oral administration[21], while the opposite finding was noted in other studies[6].

The weekly dosage of MTX did not correlate with the treatment duration in the current study. This may be attributed to the fact that the MTX dose was relatively high (median of 25 mg/week for RA and 20 mg/week for PsA), which did not allow for an appropriate comparison with patients using a lower dose. Furthermore, MTX may not have been discontinued in patients using a lower dose of MTX. Similarly, in a retrospective study of 815 patients with rheumatic disease who were treated for 6 months, the MTX dose did not significantly affect the rate of adverse events[1].In another study on MTX dose escalation, there was no statistically significant association between dosage and side effects[22]. In the study by Schnabel et al., a tendency toward increased gastrointestinal toxicity in the higher-dose group was observed. However, the retention rate was 74%in the group using 15 mg/week for 12 months 73% in the group using 25 mg/week[23].

In the current study, no data indicated that the MTX association with other antirheumatic drugs enhanced MTX discontinuation. This is particularly relevant in patients using the combination of MTX and leflunomide, which has been associated with a significantly increased risk of leucopenia and liver damage[24].

Finally, the current study determined that the patients' BMI and age did not affect the duration of drug treatment in both the RA and PsA groups. Females used MTX for a longer period than males in the RA group only. This finding is consistent with that of the study by Perrotta et al.[25], and

Albrecht et al.[26], where men more frequently discontinued MTX due to adverse effects.

This study is limited by its retrospective nature and the small sample size (mainly in the PsA group). Another limitation is that no data on disease activity was collected, but the number of patients withdrawing for lack of effectiveness was similar in both groups. Also, it is worthwhile to note that, on this sample, patients with RA made greater use of corticosteroids than those with PsA, which is understandable since there is a risk of psoriasis flare during its withdrawal; this may have had some influence on the results[27]. Furthermore, genetic analyses were not conducted. Prospective designs with larger samples and genetic studies should be conducted in future studies to provide further enlightenment.

CONCLUSIONS

In conclusion, gastric intolerance is the major cause of MTX withdrawal, and it is more frequently observed in patients with RA. Furthermore, hepatic toxicity is more common in PsA than in RA. Patients with RA used MTX for a longer period than patients with PsA. However, the drug dosage, administration route, and epidemiological or anthropometric data are not associated with drug retention.

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