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Original Article

COMPARISON OF METHOTREXATE GASTROINTESTINAL SIDE EFFECTS IN PATIENTS WITH RHEUMATOID ARTHRITIS AND PSORIATIC ARTHRITIS.

COMPARAÇÃO DOS EFEITOS COLATERAIS GASTROINTESTINAIS DO METOTREXATO EM PACIENTES COM ARTRITE PSORIÁSICA E PACIENTES COM ARTRITE REUMATOIDE

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RESUMO

Introdução: A artrite psoriásica (APSO) e a artrite reumatoide (AR) são doenças inflamatórias, crônicas e autoimunes. A artrite psoriásica é uma espondiloartrite relacionada à psoríase que acomete o sistema musculoesquelético e é negativa para o fator reumatoide, enquanto a artrite reumatoide afeta a membrana sinovial das articulações periféricas e se caracteriza por uma poliartrite, aditiva, simétrica em pequenas e grandes articulações. Ambas possuem como opção terapêutica o uso de metotrexato (MTX), um medicamento seguro, eficaz e de baixo custo, mas que possui alguns efeitos colaterais, sendo o mais frequente relacionado a alterações gastrointestinais.

Objetivo: Comparar os efeitos adversos gastrointestinais do metotrexato em pacientes com artrite psoriásica e artrite reumatoide.

Métodos: Este é um estudo observacional analítico transversal de pacientes com artrite psoriásica e artrite reumatoide em uso de metotrexato. A coleta de dados foi feita a partir da análise de prontuários e aplicação do questionário MISS (*Methotrexate Intolerance Severity Scor*e).

Resultados: Estudaram 112 pacientes, sendo 67 com AR e 45 com APSO. O grupo de pacientes com APSO demonstrou mais intolerância gastrointestinal quando comparado ao grupo da AR (p=0.007). Dos pacientes que não toleraram o MTX (37 pacientes com MISS≥ 6 pontos) 62% possuíam APSO. Os resultados também apontaram que indivíduos com MISS qualitativo positivo têm quase quatro vezes mais chances de não tolerar o MTX (p=0,0009). O índice de massa corporal (IMC) médio do grupo com intolerância gastrointestinal ao MTX foi maior do que o IMC dos que toleram o MTX (p=0,002). As variáveis que analisaram idade, sexo, fumo, uso de ácido fólico e via de administração de ácido fólico, e valor corpuscular médio (VCM) no hemograma não foram estatisticamente relevantes para a tolerabilidade gastrointestinal ao MTX.

Conclusão: Pacientes com APSO apresentaram mais intolerância ao MTX que pacientes com AR e valores mais elevados de IMC foram encontrados nos pacientes com mais efeitos gastrointestinais relacionados à medicação. Porém, não houve associação entre essas manifestações e os valores do VCM, a dose e via de administração do MTX e ao uso de ácido fólico.

Palavras chaves: Artrite Reumatoide, Artrite Psoriásica, Metotrexato.

ABSTRACT

Introduction: Psoriatic arthritis (PsA) and rheumatoid arthritis (RA) are chronic, inflammatory, autoimmune diseases. Psoriatic arthritis is a type of spondyloarthritis associated with psoriasis that affects the musculoskeletal system and is negative for rheumatoid factor, whereas rheumatoid arthritis affects the synovial membrane of peripheral joints and is characterized by an additive, symmetrical polyarthritis involving both small and large joints. Methotrexate (MTX) is a safe, effective, and low-cost treatment option for both conditions; however, it can lead to side effects, the most common of which are gastrointestinal disturbances.

Objective: To compare the gastrointestinal adverse effects of methotrexate in patients with psoriatic arthritis and rheumatoid arthritis.

Methods: This is a cross-sectional, observational analytical study of patients with psoriatic arthritis and rheumatoid arthritis who were undergoing methotrexate treatment. Data collection was carried out through medical chart reviews and administration of the MISS (Methotrexate Intolerance Severity Score) questionnaire.

Results: A total of 112 patients were studied, including 67 with RA and 45 with PsA. The PsA group demonstrated significantly greater gastrointestinal intolerance compared to the RA group ($p = 0.007$). Among the patients who did not tolerate MTX (37 patients with MISS ≥ 6 points), 62% had PsA. The results also indicated that individuals with a positive qualitative MISS score were nearly four times more likely to experience MTX intolerance ($p = 0.0009$). The average body mass index (BMI) of the group with gastrointestinal intolerance to MTX was higher than that of the group that tolerated MTX ($p = 0.002$). Variables such as age, sex, smoking status, folic acid use and route of administration, and mean corpuscular volume (MCV) in blood tests were not statistically significant in relation to gastrointestinal tolerability of MTX.

Conclusion: Patients with PsA showed greater intolerance to MTX than patients with RA, and higher BMI values were found in patients with more gastrointestinal side effects related to the medication. However, no association was found between these manifestations and MCV values, MTX dose or administration route, or folic acid use.

Keywords: Rheumatoid Arthritis, Psoriatic Arthritis, Methotrexate.

Introduction

Psoriatic arthritis (PsA) is an inflammatory joint disease associated with skin psoriasis that is negative for rheumatoid factor. [1] It has several classification systems, with the most commonly used currently being the CASPAR criteria. [2] The prevalence of PsA in the general population ranges from 0.1% to 1%, while among those with psoriasis, between 8% to 42%. It occurs in individuals of all ages, with a peak incidence in middle age, around 40–50 years, affecting similarly both sexes.[1-3] Although its etiology is not fully understood, it is known to be a multifactorial disease, in which the presence of genes such as HLA-B27, HLA-B38, HLA-B39, and HLA-B08, along with environmental factors, leads to the release of pro-inflammatory cytokines and, consequently, to the clinical manifestations of the disease.[3]

Rheumatoid arthritis (RA) is a systemic autoimmune disease that presents with symmetrical polyarthritis affecting both small and large joints, which can lead to periarticular damage and systemic inflammation with extra-articular manifestations.[4] Its prevalence varies according to ethnic characteristics; it is estimated to affect approximately 1% of the global population.[5] RA prevalence increases with aging, and this disease has a female-to-male ratio of approximately 3:1. Although its pathogenesis is not completely known, individuals with the “shared epitope,” including

HLA genotypes such as HLA-DR4 or HLA-DRB1, have a higher risk of having RA and of developing a more severe disease. The disease is also associated with environmental risk factors, including smoking and obesity. [4]

Both diseases have methotrexate (MTX) as the first-line treatment due to its safety, efficacy, and low cost.[6] MTX is an antimetabolite, antiproliferative, and anti-inflammatory agent that acts as an antagonist of dihydrofolate reductase, inhibiting folic acid synthesis.[7] Among its adverse effects, gastrointestinal symptoms are the most frequent, especially nausea, diarrhea, vomiting, and abdominal pain.[8] This intolerance can be assessed using the Methotrexate Intolerance Severity Score (MISS), in which a score equal to or greater than 6 is required for the patient to be considered intolerant to MTX.[6] Other factors may be associated with the presence of these adverse effects, such as folic acid supplementation and mean corpuscular volume (MCV).[9] Although gastrointestinal intolerance occurs in both PsA and RA, few studies have compared the prevalence and characteristics of these adverse effects between the diseases.

This study aimed to compare the gastrointestinal adverse effects of methotrexate in patients with psoriatic arthritis and rheumatoid arthritis; to analyze whether the dose and administration route influence the occurrence of gastrointestinal adverse effects; and to investigate whether elevated MCV is associated with MTX-related gastrointestinal side effects.

Methods

Study Design: This research is a cross-sectional, analytical, observational study.

Ethical Aspects: The study was approved by the Human Research Ethics Committee (CEP) of the Mackenzie Evangelical University Hospital (HUEM) – Mackenzie Evangelical College of Paraná (FEMPAR), under approval number 6.666.667. All participants signed an informed consent form.

Participants: The total sample consisted of 112 patients—45 with PsA and 67 with RA—attending to the Rheumatology outpatient clinic at HUEM. This was a convenience sample that included all patients using MTX for RA or PsA who met the inclusion and exclusion criteria, agreed to participate in the study, and attended the rheumatology clinic from March 2024 to March 2025.

Inclusion Criteria: Patients of both sexes, aged 18 years or older, diagnosed with psoriatic arthritis (based on CASPAR criteria) or rheumatoid arthritis (according to the 2010 classification criteria of the European League Against Rheumatism and the American College of Rheumatology) were included, provided they complied, signing the informed consent form.

Exclusion Criteria: Patients using non-steroidal anti-inflammatory drugs (NSAIDs) or other medications that could cause gastrointestinal adverse effects, as well as those diagnosed with inflammatory bowel disease, were excluded.

Data collection: The following data were collected from medical records or through patient interviews:

(a) Demographic and anthropometric data: age, age at disease onset, sex, race, smoking status, weight and height for body mass index (BMI) calculation.

(b) Laboratory data: white blood cell count, mean corpuscular volume (MCV), hematocrit, and platelet count.

(c) Clinical data: gastrointestinal manifestations and concurrent medication use, including folic acid.

(d) Application of the MISS questionnaire to assess intolerance and gastrointestinal adverse effects related to methotrexate in PsA and RA patients [6]. This questionnaire has 12 questions. In the absence of symptoms, a score of 0 is assigned, and in the presence of symptoms, scores range from 1 (mild) to 3 (severe). The maximum score is 36 (indicating severe gastrointestinal intolerance to MTX), and the minimum is 0 (no GI adverse effects). A score ≥6 indicates MTX intolerance.

Statistical Analysis: Data were collected and stored in a Microsoft Excel spreadsheet. Statistical analyses were performed using GraphPad Prism version 8.0.0 for Windows (GraphPad Software, San Diego, California, USA). Results were expressed as means, medians, minimum and maximum values, and standard deviations (quantitative variables), or as frequencies and percentages (qualitative variables). Inferential analysis used Chi-square and Fisher's exact tests for categorical data, and Student's t-test or Mann–Whitney test for numerical data. A p-value <0.05 was considered statistically significant.

Results

Sample Analysis: The total sample consisted of 112 patients: 45 with psoriatic arthritis and 67 with rheumatoid arthritis. In both disease groups; the majority were female and of Caucasian ethnicity. Regarding BMI, both groups had a mean value above the ideal weight range: RA patients were classified as overweight, while PsA patients had class I obesity.

Table 1 – Description of the Studied Sample

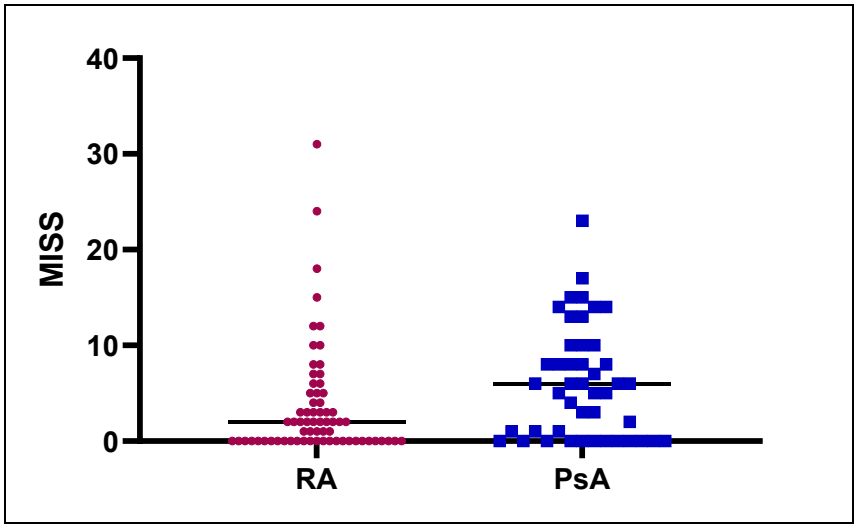
	TOTAL	Rheumatoid arthritis	Psoriatic arthritis
Number	112	67	45
Female gender	82/112	57/67	20/45
Ethnic background			
Caucasians	99/112	59/67	40/45
Afrodescendent	12/112	7/67	5/45
Asian	1/112	1/67	0
Age- years - mean (SD)	57.6(11.5)	58.9 (12.3)	55.5(10.2)
Age at diagnosis –years -mean (SD)	46.8 (11.7)	46.5 (12.2)	47.4 (11.2)
Tobacco exposure – n	7/112	7/67	0
BMI- mean (SD) – Kg/m^2	29.2(5.7)	27.9 (5.3)	31.0 (5.8)
Leucocytes– n/mm3 – median (IQR)	6.960 (5575-8515)	6240 (5350-8280)	7250 (5985-9070)
MCV – fl - median - (IQR)	89.4 (86.0-93.0)	90.1 (87.0-93.0)	88.4 (84.2-92.7)
Hematocrite – % - median (IQR)	40.5 (38.1-43.6)	40.0 (38.1-41.6)	42.9 (38.5-45.9)
Platelets - n/mm3 – median (IQR)	231.950 (194.375-279.375	226.200 (184.000-291.000)	234.000 (197.500-262.900)
Not using folic acid– (n)	9/110	3/65	6/45

MTX dose - mg/week – median (IQR)		20.0 (15.0-25.0)	20.0 (15.0-25.0)	15.0 (15.0-25.0)
Administration route				
	Oral	99/112	60/67	39/45
	Subcutaneous	13/112	7/67	6/45
Treatment				
	Anti TNF	22/112	10/67	12/45
	Secuquinumab	16/112	0	16/45
	Risanquizumab	2/112	0	2/45
	iJak	7/112	7/67	0
	Leflunomide	28/112	22/67	6/45
	Hidroxicloroquin	5/112	5/67	0
	Sulfassalazin	2/112	2/67	0
	Tocilizumab	2/112	2/67	0
	Rituximab	5/112	5/67	0
	Prednisone	22/112	20/67	2/45

N= number; BMI= body mass index, VCM=mean corpuscular volume; TNF= tumoral necrosis factorl; iJAK-JAK inhibitor; SD= standard deviation; IQR= interquartile range.

MISS Score Comparison: Comparison of MISS scores between RA and PsA patients revealed a statistically significant difference between the two groups. See **figure 1.**

Figure 1 – Comparison of MISS values between rheumatoid arthritis (RA) and psoriatic arthritis (PsA) patients



RA: median MISS = 2.0 (0.0–5.0); PsA: median MISS = 6.0 (0.0–23.0); p = 0.007

In the RA group, 14/67 (20.8%) patients were intolerant to MTX, while in the PsA group, 23/45 (51.1%) were intolerant (p = 0.0009).

Comparison of MTX tolerant and intolerant patients with RA and PsA: The comparison between the two groups is shown in **Table 2**. The only observed significant difference was in BM; higher BMI was associated with greater intolerance.

Table 2 – Comparison Between MTX-Tolerant and Intolerant Patients

	MISS<6	MISS ≥ 6	P
N	75	37	
Age (years)	59.8 (10.9)	55.1 ((12.5)	0.11
Females (n)	27/37	20/75	0.96
Caucasian ethnic background- (n)	3/37	9/74	0.74
Smokers– (n)	1/37	6/75	0.42
BMI– Kg/m2 – mean ±SD	27.7(24.2-30.8)	30.8 (28.3-34.8)	**0.002**
Not using folic acid (n)	4/37	5/74	0.47
Dose -mg/semana	15 (15-21.2)	20 (15-25)	0.32
Subcutaneous administration (n)	5/37	8/75	0.65
Hematocrit (%)	40.6 (39.1-43.1)	40.3 (37.3-43.8)	0.38
Leukocytes – n/mL – median (IQR)	7060 (5540-8836)	6900 (5620-8250)	0.72
Platelets – n/mL-median (IQR)	237.400 (195.700-289.800)	228.900 (193.200-275.000)	0.36
MCV – fl – median (IQR)	88.5 (84.7-92.5)	89.4 (86.8-93.0)	0.26

MCV=median corpuscular volume; MISS= Methotrexate intolerance severity score; n=number; BMI= body mass index; SD= standard deviation; IQR= interquartile range; n= number .

Discussion

This study demonstrated that patients with PsA, female sex, and higher BMI were more likely to be intolerant to MTX. Almalag et al., in a study with 117 RA patients, showed that among the 55 classified as intolerant to MTX, 94.5% were women.[10] Additionally, Bulatović Calasan et al., in a study of 291 patients (249 with RA and 42 with PsA) also found that female patients had lower MTX tolerability (75%) compared to male patients (25%).[11] Almalag et al. suggested that this could be due to MTX being primarily excreted by the kidneys, and since glomerular filtration rate is lower in women, serum levels may be higher.[10]

Regarding the higher MTX intolerance observed in the current study, the literature remains controversial. In the study by Bulatović Calasan et al., a similar prevalence of gastrointestinal intolerance was observed between groups, although slightly higher in PsA patients (14.3%) compared to RA patients (10.4%).[12] Conversely, Dalkilic et al., in a study of 420 patients (346 with RA and 74 with PsA), concluded that patients in both groups tolerated MTX similarly.[13]

In this sample, PsA patients had a mean BMI of 31 Kg/m^2 (class I obesity), which was higher than that found in RA patients. Supporting this, Wibetoe et al., in a study of 3,517 individuals—1,961 with RA, 835 with spondyloarthritis, and 721 with PsA—found obesity to be more prevalent in PsA than in other forms of arthritis.[14] Similarly, Zohar et al. reported a higher obesity prevalence among PsA patients (34.5%) compared to the general population (23.6%).[15] One hypothesis for this finding is the increased number of adipokines in PsA patients. The literature also suggests that obesity affects both disease activity and therapeutic decisions, as it contributes to a chronic low-grade inflammatory state. [16,17]

With respect to the influence of obesity on MTX treatment, in this study, patients with MISS ≥ 6 had a significantly higher average BMI (30.8 kg/m²) compared to MTX-tolerant patients (27.7 kg/m²; p = 0.0021). Thus, the majority of MTX-intolerant patients had PsA and higher BMI. One possible hypothesis is that since obesity is associated with hepatic steatosis—and the liver is the main site of MTX metabolism—this hepatic alteration may reduce MTX degradation and elimination. Consequently, MTX may

remain biologically active for a longer period, increasing the risk of adverse effects, including gastrointestinal symptoms. Furthermore, PsA itself has been linked to an increased risk of liver diseases such as cirrhosis and non-alcoholic fatty liver disease, conditions that may be exacerbated by obesity.[16,17] Hoekstra et al. found that higher BMI was associated with increased hepatotoxicity and MTX discontinuation, although they did not establish a relationship between BMI and gastrointestinal adverse effects.[12]

As in the studies by Bulatović Calasan et al. and Almalag et al., smoking status was not associated with gastrointestinal intolerance to MTX in the present study. However, a limitation here is that only current smoking was considered; past exposure was not evaluated. [10,11]

Regarding the route of administration, 86.48% of patients in this study used oral MTX. Islam et al., in a study of 92 RA patients (half receiving oral and half subcutaneous MTX), found fewer adverse effects in the subcutaneous group. Notably, nausea (63% vs. 37%), vomiting (30% vs. 11%), and dyspepsia (48% vs. 29%) were reduced.[18] Similarly, Tanaka et al., in a study of 102 RA patients (52 subcutaneous, 50 oral), found fewer adverse effects, particularly gastrointestinal, in those using the subcutaneous route.[19] However, Bulatović Calasan et al., when comparing MISS scores between parenteral and oral MTX users, found higher gastrointestinal intolerance in the oral group, which was attributed to a greater prevalence of behavioral symptoms.[11] In the present study, no significant difference in MTX tolerability was observed according to the route of administration.

The median weekly MTX dose in the MISS ≥ 6 group was 20 mg, compared to 15 mg in the tolerant group; however, this difference was not statistically significant. Although MTX dose is generally considered a risk factor for intolerance, both Bulatović Calasan et al. and Almalag et al. found no dose differences between tolerant and intolerant patients, supporting the present findings.[10,11] Conversely, Fatimah et al., in a study of 150 RA patients, found that gastrointestinal intolerance was more common in those taking 20 mg MTX (46.2%) versus 7.5 mg (20%).[20]

Regarding folic acid supplementation, most patients were using it concurrently with MTX, as it is known to reduce MTX side effects such as nausea, indigestion, and diarrhea.[21] Among the 37 patients with gastrointestinal intolerance in this study, only 4 were not taking folic acid. Likewise, Hoekstra et al., in a study of 411 RA patients randomized to receive either folic acid or placebo, found no association between folic acid use and MTX-related GI side effects.[12] In the present study, the number of patients not using folic acid was too small to draw any conclusions.

The mean MCV in patients with MISS ≥ 6 was 88.5 fl, which is within the reference range. The literature suggests that elevated MCV may be associated with increased MTX toxicity.[22] However, this association was not observed in the present study.

Conclusions

This study showed that patients with PsA experienced more gastrointestinal side effects related to MTX compared to those with RA.

Additionally, patients with MTX intolerance in both groups had higher BMI values, especially in the PsA group, which had a mean BMI consistent with class I obesity.

No differences in MTX tolerability were observed between oral and subcutaneous administration routes. Regarding MTX dose, no statistically significant relationship was found between weekly dose and gastrointestinal side effects.

Although the literature suggests that elevated MCV may indicate increased MTX toxicity, this association was not observed in the present study, and the average MCV values were within normal limits. Likewise, the influence of folic acid on gastrointestinal intolerance could not be evaluated due to the low number of non-users in the sample.

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