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ORIGINAL ARTICLES

Cumulative dose and length of methotrexate treatment were not shown to be predictors of hepatic fibrosis by elastography - a monocentric cohort study

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ABSTRACT

Objective: Methotrexate is used in several inflammatory diseases, such as rheumatoid arthritis (RA), spondyloarthritis (SpA) or inflammatory bowel disease (IBD). There has been some controversy regarding methotrexate liver toxicity, especially since the use of newer techniques. We aim to evaluate the prevalence of liver injury in methotrexate-treated patients with inflammatory diseases.

Methods: We performed a cross-sectional study where consecutive patients diagnosed with RA, SpA or IBD, treated with methotrexate, were submitted to liver elastography. The cutoff for fibrosis was ≥7.1 kPa. Comparisons between groups were evaluated using chi-square, t test and Mann-Whitney U test. Correlations were made between continuous variables using Spearman correlation. Logistic regression was performed to determine predictors of fibrosis.

Results: A total of 101 patients were included, 60 (59.4%) females, aged 46.2±12.6 years. Eleven patients (10.9%) had fibrosis, with a median score of 4.8 (4.1-5.9) kPa. Patients with fibrosis had higher rates of daily alcohol consumption (63.6% vs 31.1%, p=0.045). Methotrexate exposure time (OR 1.00, 95% CI 1.00-1.00, p=0.549) and cumulative dose (OR 1.00, 95% CI 1.00-1.00, p=0.629) were shown not to be predictors of fibrosis, unlike alcohol (OR 3.88, 95% CI 1.05-14.32, p=0.042). In multivariable logistic regression analysis, methotrexate cumulative and exposure times were not predictors of significant fibrosis, even when adjusted for alcohol consumption.

Conclusions: In this study, we found that fibrosis detected on hepatic elastography was not associated with methotrexate, unlike alcohol. Therefore, it is of paramount importance to redefine risk factors for liver toxicity in patients with inflammatory diseases under treatment with methotrexate.

Keywords: Spondylarthritis; Rheumatoid arthritis; Liver fibrosis; Methotrexate.

INTRODUCTION

Methotrexate (MTX) is a folate antagonist that inhibits dihydrofolate reductase and reduces intracellular stores of folic acid, affecting its role in the synthesis of purine and pyrimidine[1]. Due to its potent anti-inflammatory effect, it is one of the first-line treatments used for inflammatory diseases, such as rheumatoid arthritis (RA), psoriasis or inflammatory bowel disease (IBD)[2]. Although it has limited effect in the treatment of Crohn´s disease, it is recommended as first line therapy by both the European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR) in early and established rheumatoid arthritis, being the cornerstone of treatment[1] and it may be used in patients with peripheral articular involvement in spondyloarthritis[3, 4]. It has also a well-known side effect profile, ranging from mild effects such as stomatitis, fatigue, or diarrhea to more serious adverse effects, namely myelosuppression, pulmonary fibrosis, risk of lymphoma or hepatotoxicity[1, 5].

Hepatotoxicity has been one of the major drawbacks for the use of methotrexate. The first studies in treated psoriatic patients reported a rate of almost 50% of hepatotoxicity with fibrosis being the consequence of liver toxicity[6,7]. Some risk factors described were obesity, high alcohol intake, diabetes, and metabolic syndrome[8]. However, most recent literature reports significant lower rates of liver injury. A study in patients with IBD showed comparable incidence of liver toxicity with MTX and thiopurines[9]. Two studies in patients with RA reported a very low risk of fibrosis in patients treated with MTX and a more recent one showed no increased

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risk of liver fibrosis[10-12]. The first guidelines addressing liver toxicity of methotrexate were from Dermatology, suggesting liver biopsy after every 1500 mg of cumulative dose[13]. More recently, Rheumatology guidelines proposed liver function tests (LFT) and albumin screening every 1-3 months, recommending drug discontinuation when levels rise more than 3 times the upper limit of normal, thereby limiting liver biopsy to cases of persistently abnormal liver function tests after drug discontinuation[2, 14]. However, it is well known that liver fibrosis cannot be predicted by LFT, as patients with cirrhosis can have normal LFT[15], so other methods of identifying liver toxicity are needed.

Liver biopsy is considered the gold-standard for liver injury and liver fibrosis evaluation; however, it is an invasive procedure with inherent risks, and it is not practical as a monitoring tool for consecutive evaluations[2]. Therefore, non-invasive evaluation has recently merged as a very useful alternative, allowing serial evaluations for patients under MTX treatment for several years.

Some scores employed in clinical practice are very useful to calculate the risk of liver fibrosis and were mainly validated for hepatitis C and non-alcoholic fatty liver disease (NAFLD). Aspartate aminotransferase (AST) to Platelet Ratio Index (APRI) can be easily obtained using AST and platelet count but its ability to predict liver fibrosis is only moderate[16]. The Fibrosis-4 (FIB-4) index is another score validated in chronic liver disease as hepatitis C and NAFLD that is based on age, AST, alanine aminotransferase (ALT) and platelet count that has also been used to predict liver fibrosis, with a study revealing promising results in patients under methotrexate in RA[17].

Transient elastography (TE) is one of the main tools for liver fibrosis staging in patients with liver disease[18]. It was first described and validated in Hepatitis C patients but nowadays it is widespread used in liver disease. TE consists of a transducer which emits mild amplitude and low frequency vibrations, inducing a shear wave that propagates throughout the liver[19]. Several studies have already evaluated TE performance in liver fibrosis assessment in RA patients under MTX, and a more recent one showed better results when compared to APRI or FIB-4 score[1].

The aim of our study was to evaluate the prevalence and development of liver injury in methotrexate-treated patients with inflammatory diseases.

METHODS

Study design

We performed a cross-sectional, observational study where consecutive adult patients followed at the Rheumatology and Gastroenterology Departments of a tertiary center, with a clinical diagnosis of RA, SpA (both performed by Rheumatologists) or IBD (performed by Gastroenterologists), treated with methotrexate, were submitted to liver elastography and LFT. Patients were included if they had a clinical diagnosis of RA, SpA or IBD, in the absence of a previous liver disease. We collected demographic, clinical and laboratory data, including alcohol intake, body mass index (BMI), diabetes mellitus and dyslipidemia, ALT, AST, gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP), direct and indirect bilirubin (Brb), cholesterol and triglycerides, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), hemoglobin A1c (HbA1c), Homeostasis Model Assessment (HOMA), RA disease activity measured by Disease Activity Score 28 4 variables using C-reactive protein (DAS284V-CRP), length of treatment and methotrexate cumulative dose. We additionally evaluated concurrent therapies, namely non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, other conventional synthetic disease-modifying drugs (csDMARD) and biological DMARDs (bDMARDs). We calculated APRI and FIB-4. The protocol was approved by the Ethics Committee of our center. The study was run in accordance with the principles of the Declaration of Helsinki as amended in Fortaleza (2013). Written informed consent was obtained from each study participant.

Transient elastography

Liver stiffness measure (LSM) was performed on the patients in the supine position, with at least 6 hours of fasting, using FibroScan 502 (Echosens®) device, by the same certified Gastroenterologist. LSM was performed with M or XL probes in accordance with the thickness of subcutaneous fat (XL probe was used when subcutaneous thickness was > 2.5 cm). For each patient we performed 10 valid measures, and the average value was recorded. Quality criteria applied for LSM included a success rate ≥60% and an interquartile range <30% of the median. The cut-off considered for the presence of fibrosis was ≥7.1 kPa, found to be a reliable cut-off for fibrosis in the literature[20, 21].

Statistical Analysis

Statistical analysis was carried out by using SPSS version 25. We used Shapiro-Wilk test and histogram analysis for assessment of normality. Comparisons between groups (fibrosis versus non- fibrosis) were evaluated using chi-square, t test and Mann-Whitney U test. Spearman's correlation was used to assess associations between two or more continuous variables. Logistic regression was performed to determine predictors of fibrosis. Statistical analysis was performed at a significance level of 5%.

RESULTS

A total of 101 patients were included in this study. Patient demographic and clinical data are described in Table I. Sixty patients (59.4%) were female, 49 (48.5%) had RA, 17 (16.8%) SpA and 35 (34.7%) IBD, with median disease duration of 11.5 years, median MTX length of treatment 204 weeks and median MTX cumulative dose of 2385 mg. Thirty-five patients reported daily alcohol consumption. Of all the patients included, 11 (10.9%) had fibrosis, with a median score of 4.8 (4.1-5.9) kPa. Patients with fibrosis were comparable to patients without fibrosis concerning age, gender, disease and disease duration, diabetes mellitus, dyslipidemia, BMI, liver enzymes, HbA1c, HOMA, APRI, and FIB4 (Table II). However, patients with fibrosis revealed higher daily alcohol consumption rates (63.6% vs 31.1%, p=0.045). It should be noted that 25 patients (24.8%) had a daily alcohol intake lower than 30g/day, while the remainder 10 (9.9%) had an alcohol intake higher than 30g/day, with no differences in elastography scores. There were no statistically significant differences regarding MTX length of treatment or cumulative dose.

We performed a correlation analysis to assess the correlation between the MTX length of treatment and elastography results, as well as the correlation between MTX cumulative dose and elastography results; we found no significant correlations as well (Figure 1).

We assessed predictors of fibrosis by univariable logistic regression analysis. Alcohol intake (OR 3.88, 95% CI 1.05-14.32, p=0.042) was the only predictor of fibrosis; indeed, MTX length of treatment (OR 1.00, 95% CI 1.00-1.00, p=0.549) and MTX cumulative dose (OR 1.00, 95% CI 1.00-1.00, p=0.629) were shown not to be predictors of fibrosis (Table III). We then performed a multivariable logistic regression analysis including these 3 multivariable, in which MTX length of treatment and MTX cumulative dose were not predictors of significant fibrosis when adjusted for alcohol consumption; alcohol was found to be the only independent predictor of significant fibrosis, when adjusted for MTX length of treatment and MTX cumulative dose (OR 5.49, 95% CI 1.12-26.98, p=0.036).

Regarding the limited size of the fibrosis patients' group, we performed another analysis by splitting the groups at the median, in order to obtain groups with an equivalent number of patients – ≤4.8kPa (n=55) and >4.8 kPa (n=46). Both groups were similar regarding age, gender, disease and disease duration, diabetes mellitus, dyslipidemia, BMI, liver enzymes, HbA1c, HOMA, APRI and FIB4, while >4.8kPa patients had again higher rates of alcohol intake (45.7% vs 25.5%, p=0.034); again, no differences were found regarding MTX length

Table I. Clinical and laboratory data of the recruited patients

	Total (n=101)
Female gender – n (%)	60 (59.4)
Age, years – mean (SD)	53.9 (12.1)
Body mass index, kg/m2 – mean (SD)	25.9 (4.6)
Disease – n (%) Rheumatoid arthritis Inflammatory bowel disease Spondyloarthritis	 49 (48.5) 35 (34.7) 17 (16.8)
Disease duration, years – median (IQR)	11.5 (5-18)
Daily alcohol consumption – n (%)	35 (34.7)
Diabetes mellitus – n (%)	10 (9.9)
Dyslipidemia – n (%)	30 (29.7)
Current methotrexate dose, mg/week – median (IQR)	15 (11.3-25)
Duration of methotrexate treatment, weeks – median (IQR)	204 (72-416)
Cumulative methotrexate dose, mg – median (IQR)	2385 (940-5200)
NSAIDs – n (%)	36 (35.6)
Glucocorticoids – n (%)	33 (32.7)
Other csDMARDs – n (%)	6 (5.9)
bDMARD – n (%)	28 (27.7)
Erythrocyte sedimentation rate, mm/1st h – median (IQR)	12 (5.3-20)
C-reactive protein, mg/L – median (IQR)	4.15 (1.95-6.53)
DAS284V-CRP – mean (SD)	2.4 (1.2)
Albumin, g/L – mean (SD)	42.0 (2.4)
Aspartate transaminase (AST), UI/L – median (IQR)	25 (19.3-26.8)
Alanine transaminase (ALT), UI/L – median (IQR)	24.5 (16.8-30.8)
Glucose, mg/dL – median (IQR)	92 (86.3-96.8)
Hemoglobin A1C (HbA1c), % – mean (SD)	5.5 (0.6)
Homeostasis Model Assessment (HOMA) – median (IQR)	2.4 (2.0-3.9)
AST/ALT ratio – median (IQR)	1.0 (0.8-1.3)
AST to Platelet Ratio Index (APRI) – median (IQR)	0.3 (0.2-0.4)
Fibrosis-4 (FIB-4) Index for Liver Fibrosis – median (IQR)	1.1 (0.8-1.5)
Fibroscan score – median (IQR)	4.8 (4.1-5.9)
Significant fibrosis – n (%)	11 (10.9)

bDMARD – biological disease-modifying drugs; csDMARD – conventional synthetic disease-modifying drugs; DAS284V-CRP – Disease Activity Score 28 4 variables using C-reactive protein; IQR – Interquartile range; NSAIDS – Non-steroidal anti-inflammatory drugs; SD – Standard deviation.

Table II. Comparison between patients with and without fibrosis.

	No (n=90)	Fibrosis (n=11)	p
Female gender – n (%)	53 (58.9)	7 (63.3)	0.516
Age, years – mean (SD)	53.8 (11.6)	54.7 (16.1)	0.821
Body mass index, kg/m2 – mean (SD)	26.0 (4.6)	25.7 (5.2)	0.884
Disease – n (%) Rheumatoid arthritis Inflammatory bowel disease Spondyloarthritis	44 (48.9) 30 (33.3) 16 (17.8)	5 (45.5) 5 (45.5) 1 (9.1)	0.507
Disease duration, years – median (IQR)	10 (5-16.5)	18 (10-19)	0.052
Daily alcohol consumption – n (%)	28 (31.1)	7 (63.6)	**0.045**
Diabetes mellitus – n (%)	8 (8.9)	2 (18.2)	0.298
Dyslipidemia – n (%)	25 (27.8)	5 (45.5)	0.295
Current methotrexate dose, mg/week – median (IQR)	15 (12.5-20)	20 (15-25)	0.755
Duration of methotrexate treatment, weeks – median (IQR)	250 (187.5-566)	200 (87.5-668)	0.922
Cumulative methotrexate dose, mg – median (IQR)	3360 (1630-6770)	2225 (1697.5-10985)	0.794
NSAIDs – n (%)	33 (36.7)	3 (27.3)	0.742
Glucocorticoids – n (%)	29 (32.2)	4 (36.4)	0.746
Other csDMARDs – n (%)	5 (5.6)	1 (9.1)	0.509
bDMARD – n (%)	25 (27.8)	3 (27.3)	0.640
Erythrocyte sedimentation rate, mm/1st h – median (IQR)	14 (8-20)	16.5 (10.5-41)	0.380
C-reactive protein, mg/L – median (IQR)	5.55 (2.1-14.0)	2.50 (2.6-5.0)	0.930
Albumin, g/L – mean (SD)	41.5 (2.9)	41.8 (3.3)	0.483
Aspartate transaminase (AST), UI/L – median (IQR)	24 (20-27)	22.5 (16.3-46)	0.540
Alanine transaminase (ALT), UI/L – median (IQR)	23 (16-29)	28 (9.5-48)	0.125
Glucose, mg/dL – median (IQR)	91 (85-98.8)	84 (75-84)	0.331
Hemoglobin A1C (HbA1c), % – mean (SD)	5.5 (0.5)	5.6 (1.3)	0.551
Homeostasis Model Assessment (HOMA) – median (IQR)	2.4 (1.7-3.3)	2.5 (2.2-2.5)	0.555
AST/ALT ratio – median (IQR)	1.1 (0.9-1.3)	1.0 (0.8-1.7)	0.675
AST to Platelet Ratio Index (APRI) – median (IQR)	0.3 (0.2-0.4)	0.3 (0.2-0.5)	0.804
Fibrosis-4 (FIB-4) Index for Liver Fibrosis – median (IQR)	1.1 (0.8-1.5)	1.1 (0.7-2.0)	0.877

bDMARD – biological disease-modifying drugs; csDMARD – conventional synthetic disease-modifying drugs; IQR – Interquartile range; NSAIDS – Non-steroidal anti-inflammatory drugs; SD – Standard deviation.

of treatment and cumulative dose (Figure 2).

Univariable logistic regression analysis revealed that MTX length of treatment (OR 1.00, 95% CI 1.00-1.00, p=0.607) and MTX cumulative dose (OR 1.00, 95% CI 1.00-1.00, p=0.376) were not predictors of elastography score >4.8kPa as well.

Since patients with RA represent the majority of patients included (n=49), and objective data on disease activity were not found in a very significant percentage of the other diseases studied, we performed a sub analysis to try to find an association between disease activity and elastography scores. Patients with RA presented with a mean DAS284V-CRP disease activity of 2.4±1.2, and we found no differences between disease activity assessed by DAS284V-CRP and the presence of liver fibrosis, regardless of the cutoff used (4.8 or 7.1 kPa).

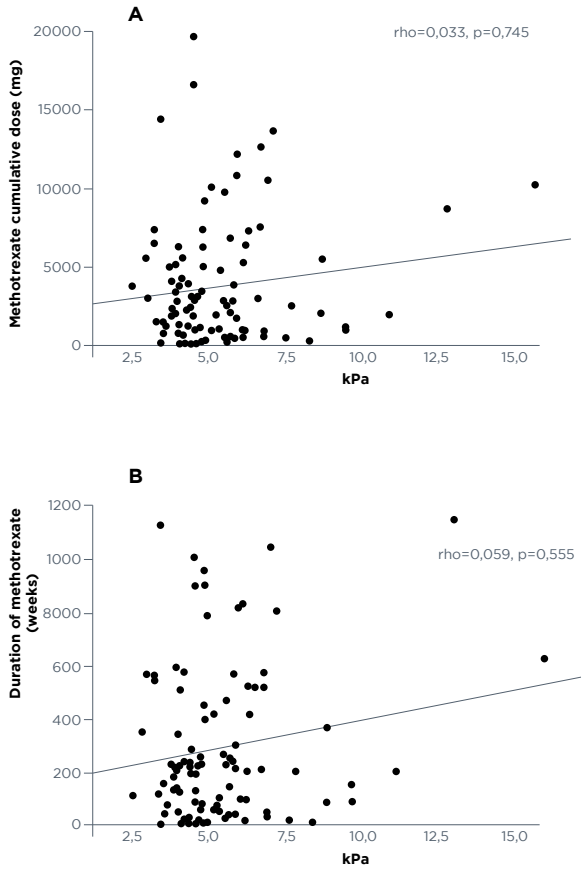

Figure 1. Correlation between elastography scores and (A) methotrexate cumulative dose; (B) duration of methotrexate.

Likewise, there was no statistically significant correlation between elastography scores, and RA disease activity measured by DAS284V-CRP (rho 0.235, p=0.145).

Regarding the tools we used to estimate the presence of liver fibrosis, we performed another correlation analysis with elastography scores, however, we found that there were not any significant correlations with those indices and elastography scores – APRI (rho -0.049, p=0.626), and FIB-4 (rho 0.033, p=0.817).

DISCUSSION

Methotrexate is frequently used therapy, effective in patients with RA, SpA and IBD, but it has been linked to the development of liver fibrosis. The aim of this study was to provide a comprehensive assessment of methotrexate-induced hepatotoxicity in patients with chronic inflammatory diseases. The main finding of this study is that, apparently, there is no association between the methotrexate dose and the presence of hepatic fibrosis in patients with inflammatory rheumatic diseases (RA and SpA) and inflammatory bowel disease. Other studies have evaluated methotrexate-related hepatotoxicity through elevation of liver enzymes[9] as well as, more recently, liver elastography[10-12] and even liver biopsy[13]. This study used hepatic elastography and evaluated other comorbidities, hepatic enzyme levels, and tools that may allow the assessment of fibrosis.

Our patients were on methotrexate at a median cumulative dose of 2385 mg, for a median treatment period of 204 weeks. This is in line with other studies published on this topic, with cumulative doses between 1200 and 4900mg[22,23]. As previously described, despite being a frequently reported problem, more recent studies have shown lower rates of hepatotoxicity in relation with methotrexate dosing. Liver fibrosis detected by transient elastography has been described in a recent systematic literature review as ranging from 10.9-40%, using the same cutoff (7.1kPa)[18]. Other studies have reported higher presence of fibrosis ≥7.1kPa using similar methods (43.9%)[24]. The authors reported higher BMI and metabolic syndrome prevalence as a possible explanation for those results[25]. We performed multiple statistical evaluations, based on the fibrosis score, with different cut offs, having observed a trend towards the presence of higher fibrosis scores in patients with longer length of treatment and/or cumulative dose of methotrexate, although with no statistical and clinical significance. The results obtained in the regression models make it quite clear that there is no significant association between the cumulative dose and the time of exposure to methotrexate and the presence of hepatic fibrosis, while we identified alcohol consumption as a determining factor in this process.

Previous studies have reported obesity, high alcohol intake, diabetes and metabolic syndrome as factors that increase the risk of hepatotoxicity[8,18,26]. In this study, the only significant association was obtained with alcohol consumption. In fact, this association is a very

Table III. Univariable logistic regression analysis for significant fibrosis.

	P-value	Odds ratio (95% confidence interval)
Alcohol intake	0.042	3.88 (1.05-14.32)
Duration of methotrexate treatment	0.549	1.00 (1.00-1.00)
Cumulative methotrexate dose	0.629	1.00 (1.00-1.00)

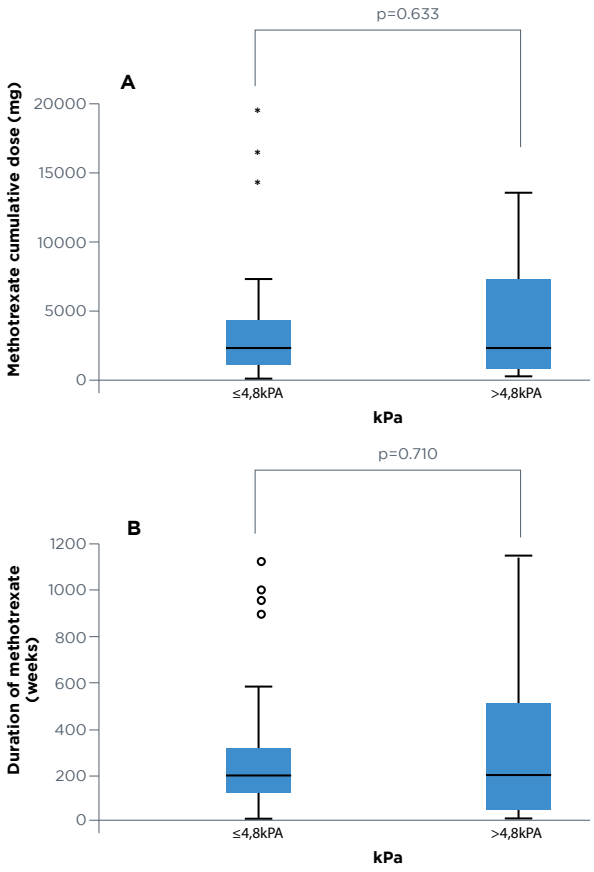

Figure 2. Distribution of methotrexate cumulative dose (A) and duration (B) according to the presence of elastography scores with 4.8 kPa cutoff.

relevant conclusion of this study, since it was obtained even after adjusting for the variables studied, such as the cumulative dose and the time of exposure to methotrexate.

This study is almost unique, to our knowledge, due to the inclusion of patients with three different pathologies in terms of pathophysiology, in a collaboration between Rheumatology and Gastroenterology, in which methotrexate use is done in a different way. Others have reported no significant incidence of MTX-induced hepatotoxicity in patients with RA[10, 12] and only one study has reported the use of elastography to evaluate hepatotoxicity in psoriasis, RA and IBD, where patients under MTX treatment and patients not treated with methotrexate were included[11]. We analyzed patients with RA, which was the group with higher number of patients, and we found that the presence of higher disease activity was also not associated with the presence of hepatic fibrosis.

In our study, unlike other studies, in addition to elastography, we additionally decided to include markers used to estimate the risk of liver fibrosis, such as APRI and FIB-4[16,17] which were evaluated in all patients, regardless of the diagnosis. In our study, however, it is interesting to verify that the APRI and FIB-4 values were not different in the groups with and without significant fibrosis, and overall, there were no significant correlations between those measures and elastography scores. Therefore, in our evaluation, those were not good predictors of liver fibrosis.

In this study, liver biopsy, the most reliable test to assess the presence of fibrosis, was not used. However, the results seem to contradict the idea that liver biopsy is necessary in patients under methotrexate therapy if we only consider the cumulative dose of the drug, as recommended, for example, by Dermatology[13].

There are several limitations of this study. First, it is a retrospective study, so compliance cannot be accurately guaranteed and there may have been some discrepancy related to the calculated cumulative dose of methotrexate values; similarly, there is insufficient information about how liver function test changed the management of patients specifically regarding the methotrexate dose. The non-inclusion of a control group (patients not exposed to methotrexate) prevented us from performing another type of evaluation, namely the comparison between taking methotrexate and not taking it, in patients with chronic inflammatory diseases. Despite being something original in this study, the sub analysis in patients with rheumatoid arthritis alone is limited, since disease activity was only evaluated on the date of the global assessment for the study, not allowing us to know how disease activity had been in the previous months and/or years. Since the patients did not have to be escalated to other immunosuppressive therapies, we believe that we have obtained a more homogeneous group in terms of global disease activity, nonetheless this is still a limitation. Another possible limitation in the interpretation of these results is the fact that the patients were on MTX for a median duration of only 204 weeks, with a median dose of 2385mg. Although, in general, the results do not differ much from what we observed in our population, the authors believe that further studies, with the inclusion of a larger sample and containing patients under treatment with methotrexate for a longer time, may be very important, so that more robust conclusions can be reached on this relevant topic.

In conclusion, the authors highlight that, in this study, no association was identified between fibrosis detected on elastography and cumulative dose or methotrexate exposure time. We found an association, however, with alcohol consumption. As such, it is crucial to redefine risk factors for liver toxicity in patients with inflammatory diseases under methotrexate therapy.

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