World Journal of Hepatology

Submit a Manuscript: https://www.f6publishing.com

World J Hepatol 2023 May 27; 15(5): 699-706

DOI: 10.4254/wjh.v15.i5.699

ISSN 1948-5182 (online)

ORIGINAL ARTICLE

Observational Study

Liver steatosis in patients with rheumatoid arthritis treated with methotrexate is associated with body mass index

Agustin Castiella, Luis Lopez-Dominguez, Maria J Sanchez-Iturri, Iratxe Urreta, Andrea De Diego, Joaquin Belzunegui, Eva Zapata

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Tanaka N, Japan; Zhang Y, China

Received: December 16, 2022
Peer-review started: December 16, 2022
First decision: December 31, 2022
Revised: January 7, 2023
Accepted: April 10, 2023
Article in press: April 10, 2023
Published online: May 27, 2023

Agustin Castiella, Department of Gastroenterology Service, Donostia University Hospital, Donostia 20014, Spain

Luis Lopez-Dominguez, Andrea De Diego, Joaquin Belzunegui, Department of Rheumatology, Donostia University Hospital, Donostia 20014, Spain

Maria J Sanchez-Iturri, Eva Zapata, Department of Gastroenterology, Donostia University Hospital, Donostia 20014, Spain

Iratxe Urreta, Department of Clinical Epidemiology, Donostia University Hospital, Donostia 20014, Spain

Corresponding author: Agustin Castiella, MD, PhD, Staff Physician, Department of Gastroenterology Service, Donostia University Hospital, Servicio Digestivo, Donostia 20014, Spain. agustincastiella@yahoo.es

Abstract

BACKGROUND

Methotrexate (MTX) is the usual first-line treatment for rheumatoid arthritis (RA). Long-term use of MTX has been associated with liver steatosis (LS) and liver fibrosis (LF).

AIM

To determine if LS in patients treated with MTX for RA is associated with MTX cumulative dose (MTX-CD), metabolic syndrome (MtS), body mass index (BMI), the male sex, or LF.

METHODS

A single-center, prospective study of patients receiving MTX for RA was performed from February 2019 to February 2020. The inclusion criteria were patients aged 18 years or older diagnosed with RA by a rheumatologist and being treated with MTX (without limitation on the duration of treatment). The exclusion criteria were previous diagnosis of liver disease (hepatitis B or C virus infection, known nonalcoholic fatty liver disease), alcohol consumption greater than 60 g/d in males or 40 g/d in females, human immunodeficiency virus infection on antiretroviral therapy, diabetes mellitus, chronic renal failure, congestive heart failure, or BMI greater than 30 kg/m^2. Patients receiving leflunomide in the 3 years prior to

the study were also excluded. Transient elastography (FibroScan, Echosens®, Paris, France) was used for fibrosis determination (LF > 7 KpA) and computer attenuation parameter (CAP) for LS (CAP > 248 dB/m). Demographic variables, laboratory data, MTX-CD (> 4000 mg), MtS criteria, BMI (> 25), transient elastography, and CAP scores were collected from all patients.

RESULTS

Fifty-nine patients were included. Forty-three were female (72.88%), and the mean age was 61.52 years (standard deviation: 11.73). When we compared MTX-CD ≤ 4000 mg (26 patients; 14 with LS and 12 without) with > 4000 mg (33 patients; 12 with LS and 21 without), no statistical differences were found (P = 0.179). We compared CAP scores stratified by MtS, BMI, sex, and LF. There were no significant differences in CAP scores based on the presence of MtS [CAP/MtS: 50 no MtS (84.75%); 9 MtS (15.25%); P = 0.138], the male sex (CAP/sex: 8 male/18 female LS; 8 male/25 female no LS; P = 0.576), or LF [CAP/fibrosis: 53 no LF (89.83%); 6 LF (10.17%); P = 0.239]. LS determined by CAP was significantly associated with BMI > 25 (CAP/BMI: 22 BMI ≤ 25 (37.29%); 37 BMI > 25 (62.71%); P = 0.002].

CONCLUSION

LS in patients with RA treated with MTX was not associated with MTX-CD, LF, the male sex, or MtS. However, BMI was significantly related to LS in these patients.

Key Words: Methotrexate; Rheumatoid arthritis; Liver steatosis; Liver fibrosis; Transient elastography; Computed attenuation parameter

Core Tip: Methotrexate (MTX) is the cornerstone of treatment for rheumatoid arthritis and has been associated with the development of liver fibrosis (LF) and liver steatosis (LS). The objective of this work was to study if LS in patients with rheumatoid arthritis treated with MTX and determine the association with body mass index, MTX cumulative dose, sex, LF, and metabolic syndrome. We concluded that LS in patients with rheumatoid arthritis on MTX treatment was not related to MTX-cumulative dose, LF, the male sex, or metabolic syndrome. In our study, body mass index was significantly associated with LS in these patients.

Citation: Castiella A, Lopez-Dominguez L, Sanchez-Iturri MJ, Urreta I, De Diego A, Belzunegui J, Zapata E. Liver steatosis in patients with rheumatoid arthritis treated with methotrexate is associated with body mass index. *World J Hepatol* 2023; 15(5): 699-706

URL: https://www.wjgnet.com/1948-5182/full/v15/i5/699.htm

DOI: https://dx.doi.org/10.4254/wjh.v15.i5.699

INTRODUCTION

Methotrexate (MTX) has been used in the treatment of oncological and chronic inflammatory diseases. It is also the cornerstone of treatment for rheumatoid arthritis (RA). The most concerning long-term adverse effect of this treatment is the development of liver fibrosis (LF)[1-5]. Liver steatosis (LS) has been associated with RA and with MTX treatment[6]. Liver biopsy has been the gold standard for the study of LF and LS, but it has several limitations[3]. There is a disparity of fibrosis values between biopsy samples, and it is an invasive technique accompanied by risks[3].

Recent studies have been carried out on non-invasive measurements of LF. Transient elastography (TE) is a non-invasive method without side effects that also allows the sequential determination of liver fibrosis measurements over time, which makes it of great interest for the follow-up of these patients[2-4].

MTX, as a risk factor for secondary LS, has been studied recently. RA has been associated with moderate to severe LS; predisposing factors such as higher body mass index (BMI), the male sex, and MTX cumulative dose (MTX-CD) have been published[7]. However, there have been conflicting results, and the impact of MTX on nonalcoholic fatty liver disease (NAFLD) is still unclear[6-11].

The computer attenuation parameter (CAP) measures carried out at the time of TE correlates with the histological LS[12]. The CAP algorithm calculates the ultrasound signal attenuation[12]. LS has been evaluated recently using CAP in chronic MTX users and was common with moderate and severe LS predicting moderate to severe LF[13].

The objective of our work was to determine if LS in patients with RA treated with MTX is associated with BMI, MTX-CD, sex, LF, and metabolic syndrome (MtS).

MATERIALS AND METHODS

We performed a single-center, prospective study of patients receiving MTX for RA. The principle objective of this work was to study the presence of LF by TE and aspartate aminotransferase to platelet ratio index (APRI)[14] as well as the detection of LS by ultrasonography and CAP. Fibroscan® (FS) (Fibroscan®402, Echosens, France, www.echosens.com) was used for fibrosis determination (LF > 7 KpA). CAP was used for LS (CAP > 248 dB/m)[11]. Demographic variables, laboratory data, MTX-CD (> 4000 mg), MtS criteria, BMI (> 25), TE, and CAP scores were collected from all patients.

Patients were recruited between February 1, 2019 and January 31, 2020 from the Gastroenterology-Rheumatology clinics of our hospital. The inclusion criteria were patients aged 18 years or older diagnosed with RA by a rheumatologist, and being treatment with MTX (without limitation on the duration of treatment). The exclusion criteria were previous diagnosis of liver disease (hepatitis B or C virus infection, known NAFLD), alcohol consumption greater than 60 g/d for males or 40 g/d for females, HIV infection on antiretroviral therapy, diabetes mellitus, chronic renal failure, congestive heart failure, or BMI greater than 30 kg/m^2. Patients receiving leflunomide in the 3 years prior to the study were also excluded.

Demographic data analysis, treatment history, and MTX-CD were collected through computerized medical records. LF was defined by FS (measurement greater than 7 Kpa) and by APRI score (result greater than 0.7). The FS assessment was performed by a trained nurse. At the time of inclusion in the study, a blood test was performed to calculate the APRI score [aspartate aminotransferase level (upper limit of normal)/platelet level × 100]. High transaminase levels were defined as results above 33 U/L. Finally, disease activity was defined by a rheumatologist using the Disease Activity Score in 28 joints-c-reactive protein score. Data were collected by means of a questionnaire, a review of the computerized clinical history, and a visit to the gastroenterology clinic.

Statistical analysis

Initially, a descriptive analysis was performed by calculating the mean and standard deviation (SD) (or median and interquartile range) for quantitative variables. For qualitative variables, absolute and relative frequencies were calculated as percentages. To compare the distribution of qualitative variables, the χ^2 test or Fisher's exact test was used. Similarly, the Student's *t*-test or the Mann-Whitney *U* test was used to compare quantitative variables. STATA 16.1 software was used for all the analyses. Statistical review of the study was performed by a biomedical statistician (IU).

Ethics

The clinical research ethics committee of the Gipuzkoa health area (Código de Protocolo: ACLFSC-2018-01; Acta 01/2019) approved this study, and participants signed an informed consent form prior to inclusion.

RESULTS

We included 59 patients in the study. There were 43 females (72.88%), and 61.52 years (SD: 11.73) was the mean age. Clinical characteristics are presented in Table 1 and laboratory data in Table 2 (Supplementary materials). The mean duration of the MTX treatment was 82.4 mo (SD: 65.1). The mean MTX-CD of the patients was 5214.5 mg (SD: 4031.9). Twenty-six patients presented an MTX-CD ≤ to 4000 mg. Thirty-three had an MTX-CD > than 4000 mg.

Treatment duration and times of disease progression were longer in the MTX-CD > 4000 mg group. MTX monotherapy was used in 46 patients (77.90%). Only 7 patients (11.80%) were on nonsteroidal anti-inflammatory drug therapy in association with MTX.

Ultrasonography was performed in 56 patients, of whom 39 presented no LS (69.64%), and 17 (30.36%) had LS. CAP was determined in all 59 patients, categorizing 33 patients without LS and 26 patients with LS.

We then compared both methods (56 patients in total). Ultrasonography presented a positive predictive value of 88.2% [95% confidence interval (CI): 63.6%-98.5%] and a negative predictive value of 76.9% (95%CI: 60.7%-88.9%), with a sensitivity of 62.5% (95%CI: 40.6%-81.2%) and a specificity of 93.8% (95%CI: 79.2%-99.2%) compared to CAP. When comparing MTX-CD ≤ 4000 mg (26 patients, 14 with LS and 12 without) with > 4000 mg (33 patients; 12 with LS and 21 without), we found no statistical differences in LS between low and high MTX-CD (P = 0.179) (Figure 1A). CAP scores were compared stratified by BMI, sex, LF, or MtS. No significant differences were observed based on the the male sex (CAP/sex: 8 males/18 females LS; 8 males/25 females no LS; P = 0.576), LF [CAP/Fibrosis: 53 no LF

Table 1 Clinical characteristics

Clinical characteristics	Value
Female/male	43 (73%); 16 (27%)
Age in yr	61.52 (11.73)
Height in cm	162.02 (7.66)
Weight in kg	67.33 (10.52)
Waist circumference in cm	88.81 (10.92)
BMI in kg/m²	25.55 (3.05)
BMI < 25 score	22 (37.29%)
BMI > 25 score	37 (62.71%)
Metabolic syndrome	9 (15.25%)
Type 2 diabetes	2 (3.57%)
DAS28 score	2.36 (1.14)
Treatment duration MTX in mo	82.43 (65.08)
MTX-CD in mg	5214.5 (4031.9)
FibroScan in kPa	5.02 (2.24)
APRI in score	0.32 (0.15)
CAP in dB/m	251.33 (51.13)

Data are *n* (%) or mean ± SD. APRI: Aspartate aminotransferase to platelet ratio index; BMI: Body mass index; CAP: Computed attenuation parameter; DAS28: Disease Activity Score in 28 joints; MTX-CD: Methotrexate cumulative dose.

Table 2 Laboratory data

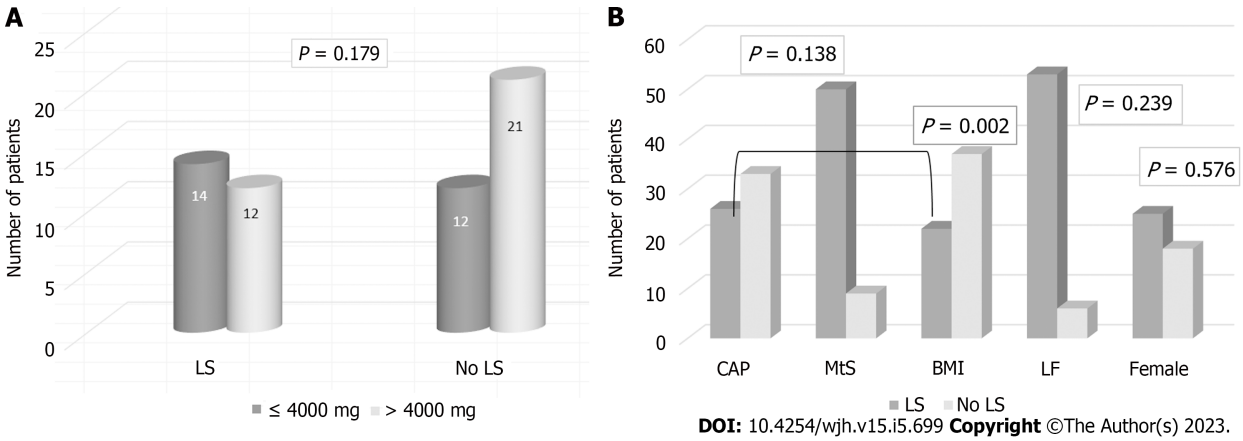
Classification	Value
AST in U/L	24.52 (12.56)
ALT in U/L	22.23 (12.15)
GGTP in U/L	23.42 (13.43)
AP in U/L	76.05 (23.72)
Bilirubin in mg/dL	0.50 (0.25)
Albumin in g/dL	4.39 (0.29)
Glucose in mg/dL	101.50 (16.08)
Triglycerides in mg/dL	99.43 (45.87)
Cholesterol in mg/dL	205.42 (43.57)
HDL-cholesterol in mg/dL	62.85 (14.74)

Data are mean ± SD. ALT: Alanine aminotransferase; AP: Alkaline phosphatase; AST: Aspartate aminotransferase; GGTP: Gamma glutamyl transpeptidase; HDL: High-density lipoprotein.

(89.83%); 6 LF (10.17%); $P = 0.239$], or MtS [CAP/MtS: 50 no MtS (84.75%); 9 MtS (15.25%); $P = 0.138$]. Nonetheless, LS measured by CAP was significantly related with BMI > 25 [CAP/BMI: 22 BMI ≤ 25 (37.29%); 37 BMI > 25 (62.71%); $P = 0.002$] (Figure 1B).

DISCUSSION

MTX is the gold standard of RA treatment, both in monotherapy and associated with biological therapies[15]. LF has been associated with chronic MTX use in this disease. There is increasing evidence



DOI: 10.4254/wjh.v15.i5.699

Figure 1 Liver steatosis. A: Liver steatosis by methotrexate cumulative dose; B: Liver steatosis by computer attenuation parameter compared with metabolic syndrome, body mass index, liver fibrosis, and sex. CAP: Computer attenuation parameter; MtS: Metabolic syndrome; BMI: Body mass index; LF: Liver fibrosis; LS: Liver steatosis.

that LF is broadly affected by other factors: Alcohol, other associated drugs, and MtS are directly related with the development of LF[16-19].

Drugs can affect LS development. The possible effect of MTX in the presence of LS in patients with RA is currently being studied. According to laboratory research, folate deficiency produced by chronic MTX treatment could promote liver fat accumulation[20], but folic acid supplementation has been recommended and is currently being used in treatment regimens. Studies have shown conflicting results, and the impact of MTX on LS is still unclear[6].

Choi *et al*[6] investigated whether MTX-CD in 368 RA patients led to LS determined by ultrasound, but they did not detect a significant association between LS development and MTX administration, suggesting that to adjust for individualized risk factors for NAFLD may be more efficient than MTX discontinuation in LS detection/management. Hypertriglyceridemia and higher BMI were associated with an increased risk of LS.

Erre *et al*[7] recently studied the independent association of LS and RA. In 223 patients with RA, they found that RA is independently associated with LS (moderate to severe), scored by ultrasound, and male sex, higher BMI, and MTX-CD are independent risk factors for the development of LS[7].

Mori *et al*[8] studied the association between NAFLD and liver injury during MTX treatment in 846 patients with RA. They did not observe a significant impact of MTX dose and duration on histological severity. On the other hand, Sakthiswary *et al*[9] concluded, in a retrospective study, that the MTX-CD was the only independent predictor of MTX-associated LS with transaminitis in a cohort of 978 patients with RA.

Recently, detection of LS by CAP in chronic MTX users was published for the first time. Tomaszewski *et al*[13] studied 172 patients on MTX (45 with RA). Diabetes mellitus, hypertension, and BMI ≥ 30 were predictors of LS. LS determined by CAP was frequent. Moderate and severe LS in this study predicted moderate to severe fibrosis of the liver.

Our prospective study was designed to determine in patients with RA treated with MTX if LS, as measured by CAP, was associated with BMI, sex, LF, or MTX-CD. When we compared MTX-CD ≤ 4000 mg with > 4000 mg, no statistical differences were found. There were no significant differences between the presence and absence of MtS, the male sex, or LF, but LS determined by CAP was significatively associated with BMI > 25 ($P = 0.002$).

Our study had limitations. The sample size was relatively small, and we included all the patients with RA on MTX treatment, without a treatment duration limitation. More females than males were included in this study, and given the limited sample size, it is difficult to conclude that there is no relationship between sex and LS. The strengths of the study were that it was a prospective study and that LS was determined as measured by the CAP.

CONCLUSION

We concluded that in our series of patients treated with MTX for RA, LS is not associated with MTX-CD, LF, the male sex, or MtS. In our study, BMI is significantly associated with LS. It seems that other factors, apart from MTX-CD or treatment duration, are more important for the development of LS in these patients.

ARTICLE HIGHLIGHTS

Research background

Methotrexate (MTX) remains the cornerstone of treatment for rheumatoid arthritis (RA), both in monotherapy and in association with other treatments. The most concerning adverse effect of this treatment, in the long term, is liver fibrosis (LF). Liver steatosis (LS) has been associated with RA and with MTX.

Research motivation

MTX, as a risk factor for secondary LS, has been studied recently. RA has been independently associated with moderate to severe LS. Sex, higher body mass index (BMI), and MTX cumulative dose (MTX-CD) are predisposing factors. However, the studies have shown conflicting results, and the impact of MTX on LS is still unclear.

Research objectives

The objective of our work was to study if LS in RA patients treated with MTX was related to BMI, MTX-CD, metabolic syndrome (MtS), sex, or LF.

Research methods

We performed a prospective study of RA patients treated with MTX. The principal objective of this work was to study the presence of LF by transient elastography and aspartate aminotransferase to platelet ratio index as well as the detection of LS by ultrasonography and computer attenuation parameter (CAP).

Research results

Fifty-nine patients were included in the study. When comparing MTX-CD ≤ 4000 mg with > 4000 mg, we found no statistical differences in LS between low and high MTX-CD. We compared CAP scores with MtS, BMI, sex, and LF. There were no significant differences based on the presence or absence of MtS, the male sex, or LF. LS determined by CAP was significantly associated with BMI > 25.

Research conclusions

We concluded that, in our series, LS in RA patients treated with MTX is not related to sex, MTX-CD, MtS, or LF. BMI > 25 is significatively associated with LS in our study. Other factors, apart from MTX-CD or time in treatment, are more important for the development of LS in these patients.

Research perspectives

The routine incorporation of FS for the study of LF and LS in RA patients with MTX treatment is critical and will aid in understanding the real impact of MTX on LS. More studies (larger and multicentric) are recommended to validate these results.

FOOTNOTES

Author contributions: Castiella A and Lopez-Dominguez L were the guarantors and designed the study; Castiella A, Lopez-Dominguez L, Sanchez-Iturri MJ, Urreta I, De Diego A, Belzunegui J, and Zapata E participated in the acquisition, analysis, and interpretation of the data and drafted the initial manuscript; Castiella A, Lopez-Dominguez L, and Zapata E revised the article critically for important intellectual content.

Institutional review board statement: Institutional review board statement statement: The study was reviewed and approved by the clinical research ethics committee of the Gipuzkoa health area (Código de Protocolo: ACLFSC-2018-01; Acta 01/2019).

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: All authors report having no relevant conflicts of interest for this article.

Data sharing statement: No additional data are available.

STROBE statement: The authors have read the STROBE Statement checklist of items, and the manuscript was prepared and revised according to the STROBE Statement checklist of items.

Country/Territory of origin: Spain

ORCID number: Agustin Castiella 0000-0003-3179-9233; Luis Lopez-Dominguez 0000-0001-9097-4164; Maria J Sanchez-Iturri 0000-0001-6018-1569; Iratxe Urreta 0000-0003-0498-6033; Andrea De Diego 0000-0001-6092-9776; Joaquin Belzunegui 0000-0002-8955-6130; Eva Zapata 0000-0002-5412-619X.

S-Editor: Fan JR
L-Editor: Filipodia
P-Editor: Fan JR

REFERENCES

1 **Wade SD**, Yoshida EM, Carruthers MN, Weinblatt ME. Transient Elastography for Monitoring for Hepatotoxicity in Rheumatoid Arthritis Patients on Long-term Methotrexate. *J Clin Rheumatol* 2021; **27**: e131-e134 [PMID: 30106792 DOI: 10.1097/RHU.0000000000000885]

2 **Arena U**, Stasi C, Mannoni A, Benucci M, Maddali-Bongi S, Cammelli D, Assarat A, Marra F, Pinzani M. Liver stiffness correlates with methotrexate cumulative dose in patients with rheumatoid arthritis. *Dig Liver Dis* 2012; **44**: 149-153 [PMID: 21930442 DOI: 10.1016/j.dld.2011.08.013]

3 **Barbero-Villares A**, Mendoza J, Trapero-Marugan M, Gonzalez-Alvaro I, Daudén E, Gisbert JP, Moreno-Otero R. Evaluation of liver fibrosis by transient elastography in methotrexate treated patients. *Med Clin (Barc)* 2011; **137**: 637-639 [PMID: 21719043 DOI: 10.1016/j.medcli.2010.12.024]

4 **Park SH**, Choe JY, Kim SK. Assessment of liver fibrosis by transient elastography in rheumatoid arthritis patients treated with methotrexate. *Joint Bone Spine* 2010; **77**: 588-592 [PMID: 20471892 DOI: 10.1016/j.jbspin.2010.02.024]

5 **Olsson-White DA**, Olynyk JK, Ayonrinde OT, Paramalingam S, Keen HI. Assessment of liver fibrosis markers in people with rheumatoid arthritis on methotrexate. *Intern Med J* 2022; **52**: 566-573 [PMID: 33135387 DOI: 10.1111/imj.15125]

6 **Choi Y**, Lee CH, Kim IH, Park EH, Park S, Yoo WH. Methotrexate use does not increase the prevalence of hepatic steatosis: a real-world retrospective nested case-control study. *Clin Rheumatol* 2021; **40**: 2037-2045 [PMID: 33078254 DOI: 10.1007/s10067-020-05456-y]

7 **Erre GL**, Castagna F, Sauchella A, Meloni P, Mangoni AA, Farina G, Woodman R, Dore MP, Vidili G. Prevalence and risk factors of moderate to severe hepatic steatosis in patients with rheumatoid arthritis: an ultrasonography cross-sectional case-control study. *Ther Adv Musculoskelet Dis* 2021; **13**: 1759720X211042739 [PMID: 34819999 DOI: 10.1177/1759720X211042739]

8 **Mori S**, Arima N, Ito M, Fujiyama S, Kamo Y, Ueki Y. Non-alcoholic steatohepatitis-like pattern in liver biopsy of rheumatoid arthritis patients with persistent transaminitis during low-dose methotrexate treatment. *PLoS One* 2018; **13**: e0203084 [PMID: 30142184 DOI: 10.1371/journal.pone.0203084]

9 **Sakthiswary R**, Chan GY, Koh ET, Leong KP, Thong BY. Methotrexate-associated nonalcoholic fatty liver disease with transaminitis in rheumatoid arthritis. *ScientificWorldJournal* 2014; **2014**: 823763 [PMID: 24971392 DOI: 10.1155/2014/823763]

10 **García DS**, Saturansky EI, Poncino D, Martínez-Artola Y, Rosenberg S, Abritta G, Ascimani-Peña C, Cravero A. "Hepatic toxicity by methotrexate with weekly single doses associated with folic acid in rheumatoid and psoriatic arthritis. What is its real frequency? *Ann Hepatol* 2019; **18**: 765-769 [PMID: 31105018 DOI: 10.1016/j.aohep.2019.01.011]

11 **Shetty A**, Cho W, Alazawi W, Syn WK. Methotrexate Hepatotoxicity and the Impact of Nonalcoholic Fatty Liver Disease. *Am J Med Sci* 2017; **354**: 172-181 [PMID: 28864376 DOI: 10.1016/j.amjms.2017.03.014]

12 **Karlas T**, Petroff D, Sasso M, Fan JG, Mi YQ, de Lédinghen V, Kumar M, Lupsor-Platon M, Han KH, Cardoso AC, Ferraioli G, Chan WK, Wong VW, Myers RP, Chayama K, Friedrich-Rust M, Beaugrand M, Shen F, Hiriart JB, Sarin SK, Badea R, Jung KS, Marcellin P, Filice C, Mahadeva S, Wong GL, Crotty P, Masaki K, Bojunga J, Bedossa P, Keim V, Wiegand J. Individual patient data meta-analysis of controlled attenuation parameter (CAP) technology for assessing steatosis. *J Hepatol* 2017; **66**: 1022-1030 [PMID: 28039099 DOI: 10.1016/j.jhep.2016.12.022]

13 **Tomaszewski M**, Dahiya M, Mohajerani SA, Punja H, Ko HH, Sun M, Ramji A. Hepatic steatosis as measured by the computed attenuation parameter predicts fibrosis in long-term methotrexate use. *Can Liver J* 2021; **4**: 370-380 [PMID: 35989896 DOI: 10.3138/canlivj-2020-0040]

14 **Castiella Eguzkiza A**, de Diego A, Lopez Dominguez L, Sanchez Iturri MJ, Urreta I, Vaamonde M, Belzunegui J, Zapata E. Evaluation of liver fibrosis in patients with rheumatoid arthritis treated with methotrexate. Utility of fibroscan and biomarkers in clinical practice. *UEG Journal* 2021; **9** (suppl): 655-656

15 **Fraenkel L**, Bathon JM, England BR, St Clair EW, Arayssi T, Carandang K, Deane KD, Genovese M, Huston KK, Kerr G, Kremer J, Nakamura MC, Russell LA, Singh JA, Smith BJ, Sparks JA, Venkatachalam S, Weinblatt ME, Al-Gibbawi M, Baker JF, Barbour KE, Barton JL, Cappelli L, Chamseddine F, George M, Johnson SR, Kahale L, Karam BS, Khamis AM, Navarro-Millán I, Mirza R, Schwab P, Singh N, Turgunbaev M, Turner AS, Yaacoub S, Akl EA. 2021 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. *Arthritis Care Res (Hoboken)* 2021; **73**: 924-939 [PMID: 34101387 DOI: 10.1002/acr.24596]

16 **Salliot C**, van der Heijde D. Long-term safety of methotrexate monotherapy in patients with rheumatoid arthritis: a systematic literature research. *Ann Rheum Dis* 2009; **68**: 1100-1104 [PMID: 19060002 DOI: 10.1136/ard.2008.093690]

17 **Park JS**, Park MC, Park YB, Lee SK, Lee SW. Concurrent use of methotrexate and celecoxib increases risk of silent liver fibrosis in rheumatoid arthritis patients with subclinical reduced kidney function. *Clin Rheumatol* 2014; **33**: 1415-1423 [PMID: 24941927 DOI: 10.1007/s10067-014-2719-7]

18 **Lee SW**, Park HJ, Kim BK, Han KH, Lee SK, Kim SU, Park YB. Leflunomide increases the risk of silent liver fibrosis in patients with rheumatoid arthritis receiving methotrexate. *Arthritis Res Ther* 2012; **14**: R232 [PMID: 23107811 DOI: 10.1186/ar4075]

19 **Cervoni JP**, Alby-Lepresle B, Weil D, Zhong P, Aubin F, Wendling D, Toussirot E, Vuitton L, Carbonnel F, Blondet R, Thévenot T, Calès P, Monnet E, Di Martino V. A pragmatic non-invasive assessment of liver fibrosis in patients with psoriasis, rheumatoid arthritis or Crohn's disease receiving methotrexate therapy. *Clin Res Hepatol Gastroenterol* 2020; **44S**: 100003 [PMID: 33602481 DOI: 10.1016/j.clirex.2020.100003]

20 **Sid V**, Siow YL, O K. Role of folate in nonalcoholic fatty liver disease. *Can J Physiol Pharmacol* 2017; **95**: 1141-1148 [PMID: 28460180 DOI: 10.1139/cjpp-2016-0681]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com