Methotrexate-Related Liver Cirrhosis in Psoriatic Arthritis: A Case Report and Review of the Literature

Maria-Loukia Koutsompina¹, Maria Pappa², Stratigoula Sakellariou², Chrysoula G. Gialouri², George E. Fragoulis², Theodoros Androutsakos³

¹These authors contributed equally.

¹Department of Pathophysiology, “Laiko” Hospital, School of Medicine, National and Kapodistrian University of Greece, Athens, Greece, ²First Department of Internal Medicine, “Laiko” Hospital, School of Medicine, National and Kapodistrian University of Greece, Athens, Greece, ³Department of Pathology, School of Medicine, National and Kapodistrian University of Greece, Athens, Greece

ABSTRACT

Methotrexate is an anchor-drug for the treatment of inflammatory arthritides affecting peripheral joints, such as rheumatoid and psoriatic arthritis (PsA), but also for other immune-mediated diseases like psoriasis. Although it is generally a well-tolerated drug, adverse effects often occur. Reversible derangement of liver function test is the most common laboratory adverse event. However, in some cases, liver cirrhosis and/or fibrosis can occur. Besides, many of these diseases like PsA and psoriasis are closely linked with clinical conditions and risk factors that also contribute to liver damage/cirrhosis, such as increased body mass index, dyslipidaemia and diabetes mellitus (DM). It has been hypothesised that the aforementioned risk factors along with methotrexate usage can act synergistically, causing liver damage in these patients. Herein, we describe a PsA patient with DM who developed fatal liver cirrhosis after 10 years of treatment with MTX. We also review the literature about the liver toxicity of MTX in the context of PsA and psoriasis, describing concurring risk factors and histopathological findings. PubMed and Scopus were searched, without date limits. The keywords “methotrexate” AND “psoriatic arthritis” OR “psoriasis” AND “Liver damage” OR “liver fibrosis” OR “cirrhosis” were used. We found that although fibrosis/cirrhosis is present in about 10-25% of the patients, MTX can rarely cause liver damage itself. However, it can exert its effect when other factors, like increased alcohol consumption and obesity coexist. Prospective studies are needed, specifically examining the hepatotoxicity of MTX in individuals with immune-mediated diseases.

Mediterr J Rheumatol 2021;32(3):264-72
https://doi.org/10.31138/mjr.32.3.264

Keywords: Methotrexate, liver dysfunction, psoriatic arthritis, psoriasis

INTRODUCTION

Methotrexate (4-amino-10methylfolic acid, MTX), an antagonist of folic acid, is used widely in malignant and non-malignant diseases.¹² It is currently used as first-line disease modifying anti-rheumatic drug (DMARDs) in the treatment of rheumatoid and psoriatic arthritis (PsA) as well as in inflammatory bowel disease and in other non-rheumatic disorders.¹⁻⁴ MTX has a low cost and shows a good safety and efficacy profile. However, possible adverse events are always a concern.¹
Abnormal liver blood tests in patients treated with MTX has long been an issue. Most medical associations suggest a baseline assessment of liver function tests before the introduction, followed by transaminase measurement initially every 1 or 2 weeks for the first month, and every 2-3 months subsequently. MTX discontinuation is advised when transaminase levels are greater than 3 times of the upper limit of normal (ULN). The exact mechanism of MTX-induced hepatotoxicity is debatable. It seems that formation of polyglutamated MTX metabolite and its prolonged retention in the hepatic cells plays a pivotal role. It has also been shown that MTX promotes adenosine release from hepatocytes. This, stimulate further production of collagen by hepatic stellate cell adenosine A2a receptors, contributing thus to further production of collagen by hepatic stellate cell adenosine release from hepatocytes. This, stimulate further production of collagen by hepatic stellate cell adenosine A2a receptors, contributing thus to liver fibrosis.

MTX-induced hepatotoxicity has been regarded as a major side effect in the previous decades. However, recent meta-analyses have shown that despite increased incidence of transaminasaemia among patients with inflammatory arthritis who receive MTX, this is predominantly asymptomatic and rarely leads to liver injury/fibrosis, cirrhosis, and treatment discontinuation. It is estimated that the prevalence of cirrhosis is low in patients without comorbidities even after long-term use. The exact mechanism of MTX-induced hepatotoxicity is debatable. It seems that formation of polyglutamated MTX metabolite and its prolonged retention in the hepatic cells plays a pivotal role. It has also been shown that MTX promotes adenosine release from hepatocytes. This, stimulate further production of collagen by hepatic stellate cell adenosine A2a receptors, contributing thus to liver fibrosis.

MTX-induced hepatotoxicity has been regarded as a major side effect in the previous decades. However, recent meta-analyses have shown that despite increased incidence of transaminasaemia among patients with inflammatory arthritis who receive MTX, this is predominantly asymptomatic and rarely leads to liver injury/fibrosis, cirrhosis, and treatment discontinuation. It is estimated that the prevalence of cirrhosis is low in patients without comorbidities even after long-term use. The exact mechanism of MTX-induced hepatotoxicity is debatable. It seems that formation of polyglutamated MTX metabolite and its prolonged retention in the hepatic cells plays a pivotal role. It has also been shown that MTX promotes adenosine release from hepatocytes. This, stimulate further production of collagen by hepatic stellate cell adenosine A2a receptors, contributing thus to liver fibrosis.

Herein, we present a patient with psoriatic arthritis (PsA) and type 2 diabetes mellitus who presented to our hospital with cirrhosis accompanied by severe ascitic fluid accumulation. After excessive work-up that included a liver biopsy, a diagnosis of MTX-related cirrhosis was made. A literature review about this matter is also presented.

CASE REPORT
A 65-year-old Caucasian male was admitted to our department due to large volume ascites. Three months before admission, the patient presented to another hospital with the same symptoms; a diagnosis of non-alcoholic steatohepatitis (NASH) induced cirrhosis was made and the patient was discharged with 40 mg furosemide and 75mg spironolactone daily. He had a medical history of PsA and type 2 diabetes mellitus, both diagnosed a decade ago, having normal levels of glycated haemoglobin (HbA1C) during the last five years. His medications included methotrexate once weekly being received for the last 6 years, with a cumulative dose of approximately 5gr, metformin and sitagliptin. Upon presentation, he was afebrile, with a blood pressure of 105/80 mmHg, heart rate of 92 beats per minute and an oxygen saturation of 94%, on air. He had large volume ascites, lower extremities oedema, palpable liver and spleen, as well as spider nevi in the torso and palmar erythema. The remainder of the physical examination was normal. His laboratory tests showed an elevated bilirubin concentration (2.52mg/dl, direct: 1.21mg/dl) with mild increase of gamma glutamyl-transferase (γGT) (143 U/L) and alkaline phosphatase (ALP) (131U/L), normal levels of alanine (ALT) and aspartate (AST) aminotransferases and cholesterol, while international normalised ratio (INR) was 1.17 and serum albumin 2.8g/dl (Table 1). Additionally, no abnormalities in liver function tests including AST/ALT/ALP/γGT/INR and albumin were noted in blood results available before the initiation of MTX. Testing for hepatitis A, B and C, for anti-nuclear antibodies, anti-smooth muscle antibodies, and anti-mitochondrial antibodies was negative, while serum ceruloplasmin and urine copper levels were also within normal levels (Table 1).

Ultrasonography of the abdomen revealed ascites, cirrhotic liver, splenomegaly, and a patent portal vein, while chest X-Ray showed right-sided pleural effusion. An ascites paracentesis was performed that revealed 383 cells, with 10% neutrophils and a serum albumin gradient (SAAG) of 2.5mg/dl, compatible with portal hypertension ascites (Table 1). Peritoneal fluid cytology and cultures were negative. Computed tomography (CT) of the abdomen revealed a cirrhotic liver with splenomegaly, portosystemic collaterals, and ascites. Magnetic Resonance Imaging (MRI) of the abdomen and Magnetic Resonance Cholangiopancreatography (MRCP) findings were in accordance with CTs’ findings; neither masses nor strictures in intra- or extrahepatic biliary ducts were identified. Upper gastrointestinal endoscopy was performed and revealed portal hypertensive gastropathy but no oesophageal or gastric varices. A transthoracic echocardiogram did not reveal heart failure, chronic compressive pericarditis, pathology of heart valves, or other heart disease that could lead to cirrhosis. Eventually, a liver biopsy was performed that revealed micronodular cirrhosis with lymphocytic infiltrates in fibrous septa and features of cholestasis at the periphery of cirrhotic nodules; no steatosis, ballooning, pericellular fibrosis, or interface hepatitis were noted (Figure 1). According to clinical history and histological examination, end-stage liver disease was diagnosed, and MTX was discontinued. High doses of furosemide and spironolactone were introduced to control the accumulation of ascites, however patient developed renal failure. Subsequently, diuretics were withdrawn, and frequent large volume paracentesis were initiated. Unfortunately, the patient died 8 months after the initial diagnosis, due to spontaneous bacterial peritonitis.

LITERATURE REVIEW
Search strategy
A literature search for relevant articles using PubMed and Scopus was performed. No date limits were ap-
plied, and last update was in June 2020. The keywords “methotrexate” AND “psoriatic arthritis” OR “psoriasis” AND “Liver damage” OR “liver fibrosis” OR “cirrhosis” were used. Search fields were restricted in the “Title/abstract” and in human species. In total, 301 studies were retrieved. After removal of the duplicates, studies describing paediatric patients and non-English literature, 217 studies were available for extraction. From those only 31 observational studies were found. Reference lists of relevant articles were also reviewed.17–47

Studies covering hepatotoxic effect of MTX. Data and pitfalls
Methotrexate has long been accused of severe hepatotoxicity, especially after long-term usage. However, the rising incidence of NASH-related cirrhosis and the association of psoriasis and PsA with the metabolic syndrome challenge the real hepatotoxic effect of methotrexate. As a matter of fact, a lot of studies have addressed this question in the literature, with the results being ambiguous. More precisely, most of the studies examining MTX-induced hepatotoxicity, yield a liver fibrosis ratio of 5.6 to 71 %, while cirrhosis ratio is even lower from 0 to 16.6% (Table 2). These studies have two major drawbacks; most of them were conducted 20 years ago, with 14 of them before 1990, and in only 5 of them liver biopsies (LB) before and after treatment are available.39–41,43 Thus, the net-effect of NASH in liver fibrosis cannot be safely assessed. Moreover, most of the studies include patients with psoriasis and only a few (n=6) patients with PsA.20,24,26,27,33,43

Table 1. Patient’s laboratory findings on admission.

|                                      | On admission | Reference Range |
|--------------------------------------|--------------|-----------------|
| Hgb (g/dl) / Hct (%)                 | 13 / 38.4    | 13.5 – 18 / 40-50 |
| WBC (K/μL)                           | 8.28         | 4.5-11.0        |
| Neutrophils/Lymphocytes/Monocytes (%)| 71.2 / 15.1 / 11.8 |             |
| PLTs (K/μL)                          | 172          | 140-440         |
| PT / APTT (sec) / INR                | 13.9 / 33.9 / 1.17 | 12.4/ 29-40 / 1 |
| Fibrinogen (mg/dL)                   | 545          | 180-400         |
| Glucose (mg/dL) / Glycosylated haemoglobin (%) | 102 / 7.8 | 72-106 / 4.8-6 |
| Urea / Creatinine (mg/dL)            | 42 / 1.1     | 40-60 / 0.7–1.2 |
| Potassium / Sodium (mmol/L)          | 5.3 / 140    | 3.7–4.9 / 136-143 |
| AST / ALT / GGT / ALP (U/L)          | 26 / 26/ 143/ 131 | < 35 / <35 / 8-61/ 135 -225 |
| Total Bilirubin / Direct Bilirubin (mg/dl) | 2.52 / 1.21 | 0.3–1.2 / 0.0–0.3 |
| Amylase (U/L)                        | 34           | 28-100          |
| Cholesterol / Triglyceride (mg/dl)   | 163 / 99     | 140-200 /50-150 |
| Lactate dehydrogenase (U/L)          | 341          | 135-225         |
| Total protein / Albumin (g/dl)       | 6.6 / 2.8    | 6.0–7.9 / 3.5–5.0 |
| Iron (μg/dL) / Ferritin (ng/dL)      | 108 / 325    | 38–190 / 30-400 |
| B12 (pg/mL) / Folic acid (mg/mL)     | 731 / 7.5    | 223-925 / 3.9–27 |
| CRP (mg/L)                           | 43.43        | 0-5             |
| TSH (mIU/L)                          | 2.34         | 0.5 – 8.9       |
| HBsAg / HBcAb / HCV Ab               | - / - / -    | - / - / -       |
| ANA / ASMA / AMA                     | - / - / -    | - / - / -       |

Abbreviations: Hgb: Haemoglobin; Hct: Haematocrit; WBC: White Blood Cells; PLTs: Platelets; PT: Prothrombin Time; APTT: activated partial thromboplastin time; INR: International Normalized Ratio; AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; GGT: Gamma-Glutamyl Transferase; ALP: Alkaline Phosphatase; CRP: C-reactive protein; TSH: Thyroid Stimulating Hormone; HBsAg: Hepatitis B surface Antigen; HBcAb: Hepatitis B core Antibodies; HCV Ab: Hepatitis C Virus Antibodies; ANA: Anti-nuclear Antibodies; ASMA: Anti-Smooth Muscle Antibodies; AMA: Anti-Mitochondrial Antibodies.
For psoriasis, in one of the largest studies by Zacharie et al. in 1980, 764 liver biopsies (LB) before and after MTX treatment were performed in 328 individuals with psoriasis; 25.6% of patients developed liver cirrhosis 5 years after methotrexate treatment. However, performing subsequent liver biopsies in some of these (n=14), the authors showed that cirrhosis did not progress in most cirrhotic patients, even though they continued methotrexate.41 It should be mentioned though that no data concerning diabetes mellitus (DM), hyperlipidaemia or body-mass index (BMI) were available. In another large study by Maybury et al. in 2019, that included 333 patients with psoriasis, 14.1% of them showed advanced fibrosis using transient elastography (TE). In this study central obesity, insulin resistance and active psoriasis but not MTX exposure were predisposing factors for advanced fibrosis.34

Studies for PsA
As far as PsA patients are concerned, in the largest cohort of them, including 70 PsA, 60 psoriasis patients and 39 controls, 18 of the 70 PsA patients (25.7%) had liver fibrosis or cirrhosis; however, no information about the severity of liver fibrosis or the number of cirrhotic patients is given.20 In the only study that includes almost exclusively PsA patients, with 47 PsA and only 7 patients with psoriasis and no articular involvement, 13% of the patients had early inflammation or fatty changes in LB, while 20% had liver fibrosis27; however, no grade 3 or 4 fibrosis was found. In both studies, no correlation between MTX use and liver fibrosis was noted.

Data from meta-analyses
A couple of meta-analyses have also been conducted, trying to clarify the association between MTX and hepatotoxicity.13 In one meta-analysis by O’Keefe et al in
1991, 15 studies including patients with RA or PsO were analyzed. According to this meta-analysis, progression of liver disease was associated with MTX cumulative dose. Also, psoriatic patients under MTX treatment, compared to those with RA, had a higher probability of developing liver damage. Importantly, alcohol abuse was identified as a risk factor for liver-damage severity and progression. In another meta-analysis by Maybury et al.

Table 2. Studies of methotrexate induced hepatotoxicity in psoriatic patients.

| First author, year (reference) | Number of patients | Disease | Type of study | Way of fibrosis assessment | Results |
|--------------------------------|--------------------|---------|---------------|----------------------------|---------|
| Roenigk HH, 1971¹⁷            | 37                 | PsO     | Prospective and Retrospective | LB      | 23 (62.1%) fibrosis, 6 (16%) cirrhosis |
| Dahl MG, 1971¹⁸               | 37                 | PsO     | Prospective   | LB      | 10 (27%) fibrosis, 7 (19%) cirrhosis  |
| Millward-Sadler GH, 1974²⁹    | 17                 | PsO     | Retrospective | LB      | 4 (23.5%) fibrosis, 3 (17.6%) cirrhosis |
| Zacharie H, 1975²⁹            | 56                 | PsO     | Prospective   | LB before and after treatment | 18 (32.1%) fibrosis, 3 (5.3%) cirrhosis |
| Nyfors A, 1976⁴⁰              | 88                 | PsO     | Retrospective | LB before and after treatment | 5 (5.6%) fibrosis, 6 (6.8%) cirrhosis after treatment |
| Zacharie H, 1980⁴¹            | 328 (764 LB)       | PsO     | Prospective   | LB before and after treatment | 19/183 (10.3%) cirrhosis in patients treated with methotrexate (25.6%) cirrhosis after 5-years of treatment with MTX |
| Ashton R, 1981⁴²               | 38                 | PsO     | Retrospective | LB      | 7 (18.5%) fibrosis, 2 (5%) cirrhosis  |
| Lanse S, 1985⁴³               | 30                 | PsO, PsA (n=18) | Prospective | LB before and after treatment | No worsening of LB when baseline LB normal 1/11 with fatty infiltration worsened after treatment |
| Van de Kerkhof PC, 1985⁴⁴     | 44                 | PsO     | Prospective   | LB after treatment         | 9 (20.4%) fibrosis, 2 (4.5%) cirrhosis  |
| Pestana A, 1985⁴⁵             | 32                 | PsO     | Retrospective | LB      | 15 (46.8%) fibrosis, 5 (15.6%) cirrhosis |
| Risteli J, 1988⁴⁶             | 24                 | PsO     | Prospective   | LB      | 11 (45.8%) fibrosis, 4 (16.6%) cirrhosis |
| O’Connor G, 1989³⁷            | 78 (95 LB)         | PsO     | Retrospective | LB      | 40/95 (42%) fibrosis                  |
| Newman M, 1989⁴⁷              | 168 (364 LB)       | PsO     | Retrospective | LB (31 patients before and after, 86 only after, 51 only before treatment) | 8/31 (25.8%) fibrosis, 3/31 (9.6%) cirrhosis |
| Zachariae H, 1991²⁰           | 132                | PsO (62), PsA (70) | Retrospective | LB      | 42 (31.8%) fibrosis or cirrhosis    |
| Themido R, 1992³⁸             | 30                 | PsO     | Retrospective | LB (before and after treatment) | 15 (50%) fibrosis, 3 (10%) cirrhosis  |
| Nohlgård C, 1993²¹            | 26 (43 LB)         | PsO     | Prospective (??) | LB      | 25 (58%) fibrosis 4 (9.3%) cirrhosis |
made in 2014,46 eight observational studies and a total population of 429 patients with PsO were included. MTX treatment appeared to contribute to any liver fibrosis and cirrhosis with a pooled risk difference of 0.22 (95% CI 0.04-0.41) and 0.04 (95% CI 0.02-0.07) respectively. No other risk factors like DM, high BMI value or alcohol abuse were found to contribute to liver fibrosis. However, the quality of the included studies was deemed to be weak by the authors. Collectively, one could say that fibrosis and/or fibrosis...
is present in about 15-25% of patients with psoriasis or PsA. MTX, along with other risk factors, like alcohol abuse, DM, and obesity seem to act synergistically promoting liver damage. It is impossible to speculate though to which extent each factor contributes.

DISCUSSION
We present a patient with PsA under long-term MTX treatment and diabetes mellitus that was admitted to our department with decompensated liver cirrhosis. PsA is a chronic inflammatory arthritis associated with psoriasis accompanied by a variety of other clinical manifestations. Psoriasis and PsA are strongly associated with clinical features of metabolic syndrome (MetS), including insulin resistance, central obesity, elevated blood pressure, athrogenic dyslipidaemia, and non-alcoholic fatty liver disease. The prevalence of MetS and its individual components is higher in PsA patients compared to general population and patients with other rheumatic diseases.

For instance, strong epidemiological data from cross-sectional studies correlate total cholesterol levels and body mass index (BMI) with joint and skin disease activity, thus implying a negative impact of MetS in achieving low disease activity and good clinical response in PsA patients. PsA and MetS share common pathophysiological pathways; endothelial dysfunction, dysregulation of innate immunity and increased pro-inflammatory cytokine production are a few of the mechanisms implicated.

Adipokines are also increasingly recognized as important players in the interplay between PsA and MetS; they also play a role in the development of liver fibrosis/cirrhosis. In our patient, both NASH and MTX-induced cirrhosis could explain the clinical course. Histologically, MTX hepatotoxicity includes macrovesicular steatosis, ballooning degeneration and fibrosis, features also characteristic of non-alcoholic steatohepatitis. A MTX-related autoimmune hepatitis-like pattern showing portal and periportal interface inflammation has also been reported. Hepatocyte nuclear pleomorphism, hyperchromasia, and vacuolation are considered MTX-specific findings; however, they are not invariably present. In our case, the combination of histology findings with the clinical features make the diagnosis of MTX-related cirrhosis likely. In fact, we and other investigators believe that drugs work synergistically with other risk factors like diabetes, contributing to development and progression of liver injury. In our patient, despite the fact that glycemic control was adequate for the last 5 years, diabetes mellitus most probably acted as an aggravating factor of MTX-related liver injury with the final outcome being cirrhosis.

We acknowledge that our case-based review has certain limitations. First, we cannot exclude the possibility that a degree of liver damage pre-existed in our patient, nor that NASH could be the major cause of his liver damage. Besides, as mentioned, there is a degree of overlap between NASH and MTX-related liver injury, at a histological level. The point of our study was to highlight and discuss the possible aggravating role of MTX in liver damage, especially when other risk factors concur. Furthermore, our review was not systematic; therefore, it was registered. Also, only two major databases were searched. In this context, some studies might have been missed. We expect however, that most of them would have been published in PubMed or Scopus.

It is unfortunate that only limited data exist, examining the level, prevalence, and contributing risk factors for liver damage in PsA. This possibly owes to the heterogeneity of the disease as well as to the availability of different techniques used for liver damage assessment (eg, liver biopsies, elastography). Apparently, more studies, of prospective nature and specifically designed for this purpose are needed.

In conclusion, most researchers agree that MTX by itself seldom leads to significant liver fibrosis, however one should consider methotrexate-induced cirrhosis when a patient has comorbidities, especially chronic hepatitis, diabetes mellitus, alcohol overconsumption or hypertriglyceridemia. It is of question, how often and with which tools these patients should be followed-up.

CONFLICT OF INTEREST
The authors declare no conflict of interest.

FUNDING
No specific funding was received.

REFERENCES
1. Bedoui Y, Guillet X, Sélambarom J, Guiraud P, Giry C, Jaffar-Bandjee MC, et al. Methotrexate an old drug with new tricks. Int J Mol Sci 2019;20(20).
2. Cutolo M, Sulli A, Pizzorni C, Seriolo B, Straub RH. Anti-inflammatory mechanisms of methotrexate in rheumatoid arthritis. Ann Rheum Dis 2001;60(8):729-35.
3. Brown PM, Pratt AG, Isaacs JD. Mechanism of action of methotrexate in rheumatoid arthritis, and the search for biomarkers. Nat Rev Rheumatol 2016;12(12):731-42.
4. Chan ESL, Cronstein BN. Methotrexate how does it really work? Nat Rev Rheumatol 2010;6(3):175-8.
5. Kalb RE, Strober B, Weinstein G, Labwohl M. Methotrexate and psoriasis: 2009 National Psoriasis Foundation Consensus Conference. J Am Acad Dermatol 2009;60(5):824-37.
6. Ledingham J, Gullick N, Irving K, Gorodkin R, Aris M, Burke J, et al. BSR and BHPR guideline for the prescription and monitoring of non-biologic disease-modifying anti-rheumatic drugs. Rheumatol (United Kingdom) 2017;56(6):865-8.
7. Saag KG, Gim GT, Patkar NM, Anuntiyo J, Finney C, Curtis J, et al. American College of Rheumatology 2008 recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis. Arthritis Care Res 2008;59(6):762-84.
of polyglutamates, Arthritis Rheum 1986;20(7):832-35.
9. Chan ESL, Montesinos MC, Fernandez P, Desai A, Delano D, Yee H, et al. Adenosine A2A receptors play a role in the pathogenesis of hepatic cirrhosis. Br J Pharmacol 2006;148(9):1144-55.
10. Curtis JR, Beukelman T, Onofrei A, Greenberg JD, Kavanaugh A, Reed G, et al. Elevated liver enzyme tests among rheumatoid arthritis and psoriatic arthritis patients treated with methotrexate and/or leflunomide. Ann Rheum Dis 2011;69(1):43-7.
11. Drensen L, Klaarbeek NS, van den Broek M, van Groenendaal JH, de Sonnaville PB, Kerstens PJ, et al. Risk of alamine transferase (ALT) elevation in patients with rheumatoid arthritis treated with methotrexate in a DAS-steered strategy. Clin Rheumatol 2013;32(5):585-90.
12. Saltic 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(7):1100-4.
13. Whiting-O’Keefe QE, Fye KH, Sack KD, Strom BL. Methotrexate for methotrexate-induced liver fibrosis: A 10-year follow-up. Br J Gastroenterol 1996;10(6):369-75.
14. Wilke WS, Biro JA, Segal AM. Methotrexate in the treatment of arthritis and connective tissue diseases. Cleve Clin J Med 1987;54(4):327-38.
15. Fuhrbrigg RC, Özen S, Dedeoğlu F. Arthritis Care & Research. This pagination and proofreading process which may lead to differences between this version and the, Published online 2016.
16. Visser K, Van Der Heijde DMFM. Risk and management of liver toxicity during methotrexate treatment in rheumatoid and psoriatic arthritis: A systematic review of the literature. Clin Exp Rheumatol 2009;27(6):1017-25.
17. Roeing Jr. HH, Bergfeld WF, Jacques R St., Owens FJ, Hawk WA, Weinstein GD, et al. Evaluation of Possible Chronic Hepatotoxicity From Methotrexate for Psoriasis. Arch Dermatol 1971;102(6):250-61.
18. Dahl MGC, Gregory MM, Scheuer PJ. Liver Damage due to Methotrexate in Patients with Psoriasis. Br Med J 1971;1(5750):625-30.
19. Rietel J, Segoard H, Oikarinen A, Rietel L, Karvonon J, Zachariae H. Aminoterminal propeptide of type III procollagen in methotrexate-induced liver fibrosis and cirrhosis. Br J Dermatol 1988 Sep;119(3):321-5.
20. ariae H, Aslam HM, Bjerring P, Segoar H, Zachariae E, Heickendorff L. Serum aminoterminal propeptide of type III procollagen in psoriasis and psoriatic arthritis: relation to liver fibrosis and arthritis. J Am Acad Dermatol 1991;25(1 Pt 1):50-3.
21. Nohlgård C, Arnold GL, Gowans JDC, Kaplan MM. Low incidence of arthritis and connective tissue diseases. Cleve Clin J Med 1995;63(5):774-8.
22. Boffa MJ, Chalmers RJG, Haboubi NY, Shomaf M, Mitchell DM. Sequential liver biopsies during long-term methotrexate treatment for psoriasis: A reappraisal. Br J Dermatol 1995;133(5):774-8.
23. Mataltjian DA, Ross JB, Williams CN, Colwell SJ, Eastwood BJ. Methotrexate hepatotoxicity in psoriatics: Report of 104 patients from Nova Scotia, with analysis of risks from obesity, diabetes and alcohol consumption during long term follow-up. Can J Gastroenterol 1996;10(6):399-75.
24. Grimmer LE, Gill SA, Harris MD. Liver biopsy in psoriatic arthritis to detect methotrexate hepatotoxicity. J Clin Rheumatol 2001;7(4):224-7.
25. Zachariae H, Heickendorff L, Segoard H. The value of aminoterminal propeptide of type III procollagen in routine screening for methotrexate-induced liver fibrosis: A 10-year follow-up. Br J Dermatol 2001;144(1):100-3.
26. Wollina U, Ständer K, Barta U. Toxicity of methotrexate treatment in psoriasis arthritis: short- and long-term toxicity in 104 patients. Clin Rheumatol 2001;20(6):406-10.
27. Lindsay K, Fraser AD, Layton A, Goodfield M, Gruss H, Gough A. Liver fibrosis in patients with psoriasis and psoriatic arthritis on long-term, high cumulative dose methotrexate therapy. Rheumatology 2009;48(5):659-72.
28. Laharie D, Seneschal J, Scheaverbeke T, Doutre MS, Longy-Boursier M, Pellegren JL, Chabrun E, et al. Assessment of liver fibrosis with transient elastography and FibroTest in patients treated with methotrexate for chronic inflammatory diseases: A case-control study. J Hepatol 2010;53(6):1035-40.
29. Millward-Sadler GH, Ryan TJ, Mj, Methotrexate induced liver disease in psoriasis. Br J Dermatol 1974 Jun;90(6):687-90.
30. Barbo-Visnises A, Mendoza J, Traperio-Manugan M, Gonzalez-Alvaro I, Dauden E, Gisbert J, et al. Evaluation of liver fibrosis by transient elastography in methotrexate treated patients. Med Clin (Barc) 2011;137(14):637-9.
31. Vandervoort EAM, Koehler EM, Nijstens T, Stricker BH, Hofman A, Janssens HLA, et al. Increased prevalence of advanced liver fibrosis in patients with psoriasis: A cross-sectional analysis from the rotterdam study. Acta Derm Venereol 2016;96(2):213-7.
32. Talmi T, Nikamo P, Rosenberg P, Stähle M. Transient elastography may improve detection of liver fibrosis in psoriasis patients treated with methotrexate. Acta Derm Venereol 2017;97(8):952-4.
33. Garcia DS, Saturansky EI, Poncino D, Martinz-Artoya Y, Rosenberg S, Abritta G, et al. “Hepatic toxicity with weekly single doses associated with folic acid in rheumatoid and psoriatic arthritis. What is its real frequency?” Ann Hepatol 2019;18(5):765-9.
34. Maybury CM, Porter HF, Kloozko E, Dutchworth M, Cotton A, Thornsberry K, et al. Prevalence of Advanced Liver Fibrosis in Patients with Severe Psoriasis. JAMA Dermatology 2019;155(9):1026-32.
35. Neema S, Banerjee D, Radhakrishnan S, Vasudevan B, Sinha P, Oberoi B. Use of Transient Elastography in Detection of Liver Fibrosis in Psoriasis Patients - A Cross- Sectional Study. Indian Dermatol Online J 2020;11(3):387-90.
36. Honda H, Ikejima K, Hirose M, Yoshikawa M, Lang T, Enomoto N, et al. Leptin is required for fibrogenic responses induced by thioacetamide in the murine liver. Hepatology 2002;36(1):12-21.
37. O’Connor GT, Olmstead EM, Zug K, Baughman R, Beck J, Dunn J, et al. Detection of hepatotoxicity associated with methotrexate therapy for psoriasis. Arch Dermatol 1989;125(9):1209-17.
38. Themido R, Loureiro M, Peacqueiro M, Brandio M, Campos MC. Methotrexate hepatotoxicity in psoriatic patients submitted to long-term therapy. Acta Derm Venereol 1992;72(5):361-4.
39. Zachariae H, Grunnet E, Sogoard H (1975) Liver biopsy in methotrexate treated psoriasis: a reevaluation. Acta Derm Venereol 1975;55(4):291-6.
40. Nyfors A, Poulsen H. LIVER BIOPSY FROM PSORIATICS RELATED TO METHOTREXATE THERAPY. 2. Findings before and after Methotrexate Therapy in 88 Patients. A Blind Study. Acta Pathol Microbiol Scand Sect A Pathol 1976;84 (A3):262-70.
41. Zachariae H, Kragballe K, Sogoard H. Methotrexate induced liver cirrhosis: STUDIES INCLUDING SERIAL LIVER BIOPSY DURING CONTINUED TREATMENT. Br J Dermatol 1980;102(4):407-12.
42. Ashton RE, Millward-Sadler GH, White JE. Complications in methotrexate treatment of psoriasis with particular reference to liver fibrosis. J Invest Dermatol 1982;78(4):223-29.
43. Lanse SB, Arnold GL, Gowans JDC, Kaplan MM. Low incidence of hepatotoxicity associated with long-term, low-dose oral methotrexate in treatment of refractory psoriasis, psoriatic arthritis, and rheumatoid arthritis - An acceptable risk/benefit ratio. Dig Dis Sci 1985;30(2):104-9.
44. Van De Kerkhof PCM, Hoefnagels WHL, Van Haelst UJGM, Mali JWH. Methotrexate maintenance therapy and liver damage in psoriasis. Clin Exp Dermatol 1985;10(3):194-200.
45. Pestana A, Halprin KM, Taylor JR, Schiff ER, Esquenazi V, Comerford A, Reed G, et al. Adenosine A2A receptors play a role in the pathogenesis of hepatitis C. J Hepatol 2003;39(1):157-64.
47. an M, Auerbach R, Feiner H, Holzman RS, Shupack J, Migdal P, et al. Evaluation of Possible Chronic Hepatotoxicity From Methotrexate for Psoriasis. Arch Dermatol 1989;125(9):613-8.

48. An M, Auerbach R, Feiner H, Holzman RS, Shupack J, Migdal P, et al. Evaluation of Possible Chronic Hepatotoxicity From Methotrexate for Psoriasis. Arch Dermatol 1989;125(9):613-8.

49. Gisondi P, Fostini AC, Fossati I, Girolomoni G, Targher G. Psoriasis and the metabolic syndrome. Clin Dermatol 2018;36(1):21-8.

50. Dal Bello G, Gisondi P, Idolazzi L, Girolomoni G. Psoriatic Arthritis and Diabetes Mellitus: A Narrative Review. Rheumatol Ther 2020;7(2):271-85.

51. Gelfand JM, Yeung H. Metabolic syndrome in patients with psoriatic disease. J Rheumatol 2012;39(SUPPL. 89):24-8.

52. Gottlieb AB, Dann F. Comorbidities in Patients with Psoriasis. Am J Med 2009;122(12):1-9.

53. Labitigan M, Bahçe-Altuntas A, Kremer JM, Reed G, Greenberg J, Jordan N, et al. Higher rates and clustering of abnormal lipids, obesity, and diabetes mellitus in psoriatic arthritis compared with rheumatoid arthritis. Arthritis Care Res 2014;66(4):600-7.

54. Puig L. Cardiometabolic comorbidities in psoriasis and psoriatic arthritis. Int J Mol Sci 2018;19(1).

55. Di Minno MND, Peluso R, Iervolino S, Lupoli R, Russolillo A, Scarpà R, et al. Obesity and the prediction of minimal disease activity: A prospective study in psoriatic arthritis. Arthritis Care Res 2013;65(1):141-7.

56. Leite BF, Morimoto MA, Gomes C, Klemz B, Genaro P, Damasceno N, et al. Higher bodily adiposity, fat intake, and cholesterol serum levels are associated with higher disease activity in psoriatic arthritis patients: Is there a link among fat and skin and joint involvement? Lipids Health Dis 2020;19(1):1-10.

57. Russolillo A, Iervolino S, Peluso R, Lupoli R, Di Minno A, Pappone N, et al. Obesity and psoriatic arthritis: From pathogenesis to clinical outcome and management. Rheumatol (United Kingdom) 2013;52(1):62-7.

58. Nestle F, Kaplan D, Barker J. Review Article: Mechanisms of Disease Psoriasis. N Engl J Med 2009;361(5):496-509.

59. Nikiforou E, Fragoulis GE. Inflammation, obesity and rheumatic disease: common mechanistic links. A narrative review. Ther Adv Musculoskelet Dis 2018 Aug;10(8):157-67.

60. Leclercq IA, Farrell GC, Schriemer R, Robertson GR. Leptin is essential for the hepatic fibrogenic response to chronic liver injury. J Hepatol 2002;37:206-13.

61. Buechler C, Haberl EM, Rein-Fischboeck L, Aslanidis C. Adipokines in liver cirrhosis. Int J Mol Sci 2017;18(7):1392.

62. Ataseven H, Bahcecioglu IH, Kuzu N, Yalınüz M, Celebi S, Erensoy A, et al. The levels of ghrelin, leptin, TNF-α, and IL-6 in liver cirrhosis and hepatocellular carcinoma due to HBV and HDV infection. Mediators Inflamm 2006;2006:1-6.

63. Bolukbas FF, Bolukbas C, Horoz M, Gurnus M, Erdogan M, Zeyrek F, et al. Child-Pugh classification dependent alterations in serum leptin levels among cirrhotic patients: A case controlled study. BMC Gastroenterol 2004;4:1-6.

64. McCullough AJ, Bugianesi E, Marchesini G, Kalhan SC. Gender-dependent alterations in serum leptin in alcoholic cirrhosis. Gastroenterology 1998;115(4):947-53.

65. Onodera K, Kato A, Suzuki K. Serum leptin concentrations in liver cirrhosis: Relationship to the severity of liver dysfunction and their characteristic diurnal profiles. Hepatol Res 2001;21(3):205-12.

66. Quintin E, Scoazec JY, Marotte H, Miossec P. Rare incidence of methotrexate-specific lesions in liver biopsy of patients with arthritis and elevated liver enzymes. Arthritis Res Ther 2010;12(4).