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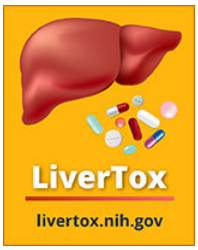


Methotrexate

Updated: February 19, 2020.

OVERVIEW

Introduction

Methotrexate is an antineoplastic and immunosuppressive agent widely used in the therapy of leukemia, lymphoma, solid tumors, psoriasis and rheumatoid arthritis. When given in high intravenous doses, methotrexate can cause acute elevations in serum enzymes, and long term methotrexate therapy has been associated with frequent but mild elevations in serum liver enzymes and, more importantly, with development of chronic liver injury, progressive fibrosis, cirrhosis and portal hypertension.

Background

Methotrexate (meth" oh trex' ate) is an antifolate and antimetabolite that is used extensively in the therapy of leukemia, lymphoma and several solid organ tumors. It also has potent immunomodulatory activity against psoriasis, inflammatory bowel disease and the inflammatory arthritidies. Methotrexate is considered a disease modifying antirheumatic drug (DMARD) and used widely in rheumatoid arthritis and other autoimmune diseases. Methotrexate acts by inhibition of folate metabolism, blocking dihydrofolic acid reductase, thereby inhibiting synthesis of purines and pyrimidines and decreasing DNA and RNA synthesis. Recent results suggest that methotrexate also leads to increase and release of adenosine, which may mediate its immunosuppressive activity. Folic acid antagonists (aminopterin) were developed in the late 1940s and introduced into clinical medicine shortly thereafter. Aminopterin was later replaced by methotrexate because of its better tolerance and lower rate of toxicity. Methotrexate was approved for use in cancer in the United States in 1955, for psoriasis in 1972 and rheumatoid arthritis in 1988 and is still widely used for these indications. Methotrexate is available in generic forms and under the brand names of Rheumatrex and Trexall in tablets of 2.5, 5, 7.5, 10 and 15 mg, and in both powdered and liquid-for-injection forms in vials of various strengths for intravenous, intramuscular or intrathecal injection. The dose regimen varies by indication; high, short term doses being used in treatment of cancer and chronic, lower doses for autoimmune conditions. The typical maintenance dose used to treat psoriasis and rheumatoid arthritis is 7.5 to 25 mg once weekly either orally or by injection. Side effects are mostly dose related and include stomatitis, oral ulcers, hair loss, fatigue, headache, gastrointestinal upset, nausea, diarrhea and bone marrow suppression. Severe adverse events include bone marrow suppression, severe infections, severe liver and lung disease, lymphomas, severe skin reactions, tumor lysis syndrome, fetal death and congenital abnormalities.

Hepatotoxicity

Methotrexate is well known to cause serum aminotransferase elevations and long term therapy has been linked to development of fatty liver disease, fibrosis and even cirrhosis. The literature on methotrexate is extensive, but

with great variability in rates of liver test and biopsy abnormalities at different doses, dose regimens and durations of therapy.

With high dose intravenous methotrexate, serum ALT levels can rise to 10 to 20 times the upper limit of normal (ULN) within 12 to 48 hours, but levels then fall rapidly to normal with only rare instances of jaundice or symptoms of liver injury. With long term, low-to-moderate dose methotrexate therapy, elevations in serum ALT or AST values occur in 15% to 50% of patients, but are usually mild and self-limiting. Approximately 5% of patients have elevations greater than twice normal and these abnormalities resolve rapidly with discontinuation or dose modification, but can resolve even with continuation at the same dose level. The reported rate of ALT elevations during therapy has varied considerably, perhaps because of differences in frequency of determinations (every month vs every 3, 6 or 12 months) and due to the timing of the blood sampling (whether just before or soon after the once weekly dose). Finally, coadministration of folic acid has been shown to decrease the frequency of serum enzyme elevations and now is commonly used.

Long term therapy with methotrexate has been associated with development of fatty liver and hepatic fibrosis and, in rare instances, portal hypertension and symptomatic cirrhosis. Symptoms are usually absent until cirrhosis is present, and liver tests are typically normal or minimally and transiently elevated. Routine monitoring of patients with regular liver biopsies done at 1 to 2 year intervals or with cumulative methotrexate doses of 1 to 10 grams demonstrates that approximately 30% of patients develop mild-to-moderate histological abnormalities (fat, cellular unrest, mild inflammation, nuclear atypical) and 2 to 20% of patients develop some degree of hepatic fibrosis. Well documented cases of cirrhosis arising during long term methotrexate therapy have been reported, but cirrhosis is rare in prospective series, even with routine histological monitoring. Patients who develop fibrosis on long term methotrexate therapy often have other risk factors for fatty liver disease, including excessive alcohol use, obesity, diabetes and concurrent administration of other potentially hepatotoxic agents. Use of high doses and daily methotrexate dosing is particularly associated with development of hepatic fibrosis and rates of cirrhosis of greater than 20% after 5 to 10 years of treatment. With more modern dose regimens (5 to 15 mg in one dose weekly with folate supplementation), fibrosis and clinically apparent liver disease are rare even with long term use. The hepatic fibrosis and cirrhosis due to methotrexate typically arise after 2 to 10 years of treatment and can present with ascites, variceal hemorrhage or hepatosplenomegaly. Some patients present with signs and symptoms of portal hypertension, yet have only moderate degrees of fibrosis, suggesting that methotrexate may also cause nodular regeneration. Patients who develop portal hypertension and cirrhosis usually have had minimal or no elevations in serum aminotransferase or alkaline phosphatase levels, and monitoring using serum enzymes appears to be poorly predictive of fibrosis development. Noninvasive markers of hepatic fibrosis, such as serial platelet counts, serum procollagen III aminoterminal peptide (PIIIP), serum bile acids, hepatic ultrasound, advanced imaging techniques and transient elastography may be more efficient in screening for fibrosis in patients on long term methotrexate, but the reliability and accuracy of these approaches has not been documented prospectively. Patients with cirrhosis due to methotrexate are often asymptomatic and the condition tends to be non-progressive, even in those who restart low dose therapy. Rare instances of hepatocellular carcinoma have been reported in patients with suspected methotrexate induced cirrhosis.

Low dose, long term methotrexate therapy has also been implicated in rare instances of reactivation of hepatitis B in patients with rheumatoid arthritis or psoriasis who were HBsAg carriers, without HBeAg and with normal ALT levels and no detectable or low levels of HBV DNA before starting methotrexate. The frequency of reactivation with methotrexate is unknown, but is probably low. Reactivation typically presents after years of therapy with methotrexate and most published cases were also receiving corticosteroids. The clinical presentation is characterized by insidious onset of fatigue, nausea and jaundice accompanied by marked elevations in serum ALT and HBV DNA levels. In some instances, the acute injury is severe and progressive resulting in liver failure. In many case reports, reactivation occurred when methotrexate was withdrawn, perhaps as a result of restoration of immune reactivity in those in whom HBV DNA levels have risen during

treatment. Reactivation has also been described in patients with antibodies to HBV without HBsAg (reverse seroconversion) treated with methotrexate and prednisone. The cases of reactivation of hepatitis B published in the literature have mostly resulted in death or emergency liver transplantation, perhaps reflecting publication bias for more severe cases. These cases have led to recommendations for routine screening for HBsAg before starting long term methotrexate therapy and prophylaxis with antiviral agents or careful monitoring for rises in HBV DNA levels if methotrexate is used. However, whether methotrexate on its own, without prednisone, can cause reactivation of hepatitis B is not clear.

Likelihood score: A (well known cause of chronic, clinically significant liver injury, portal hypertension and cirrhosis).

Mechanism of Injury

The mechanism of liver injury with methotrexate is believed to be direct toxicity, through inhibition of RNA and DNA synthesis in the liver and producing cellular arrest. Methotrexate therapy has been shown to increase hepatic stellate cell numbers, but the mechanism by which fibrosis is induced has not been clearly elucidated. Concurrent therapy with folate has been shown to reduce the rate of serum enzyme elevations during low dose methotrexate therapy.

Outcome and Management

Methotrexate can lead to serious liver disease, portal hypertension, fibrosis and cirrhosis, usually with long term use particularly when given in daily regimens and in higher doses. Various guidelines have been developed and refined for monitoring of patients with psoriasis or rheumatic disorders during long term methotrexate use, although the effectiveness and necessity of these approaches are often debated. At present, both the American Academy of Dermatology and the American College of Rheumatology recommend careful evaluation of patients before initiating methotrexate therapy for evidence of liver disease and risk factors for developing fatty liver. While a pretreatment liver biopsy is no longer recommended for all patients, a biopsy is recommended in patients with any evidence of liver disease or significant risk factor (excessive alcohol use, chronic viral hepatitis, elevations in serum enzymes, and in selected patients with diabetes and obesity). Patients should be told to avoid alcohol use, and abstinence is often recommended. Concurrent administration of folic acid (~1 mg daily) has been shown to decrease the rate of liver test abnormalities on therapy without apparently affecting the efficacy of methotrexate. On-treatment monitoring of serum aminotransferase levels is recommended on a monthly basis for at least 6 months and then every 3 months, with more intensive monitoring and withdrawal of therapy if aminotransferase levels rise and stay above 3 times the ULN. Routine liver biopsy after a cumulative dose of 1, 3 and 8 grams of methotrexate is considered prudent, but guidelines from different societies vary on this issue. Alternatively, monthly aminotransferase levels can be monitored and patients with raised values at least 50% of the time might be candidates for surveillance liver biopsy. A system for grading of liver biopsies has been developed and widely used (Roenigk Scale). Patients with Roenigk IIIb (advanced fibrosis) or IV (cirrhosis) are advised to stop therapy. With improvement in noninvasive tests for liver fibrosis such as transient elastography and serum fibrosis markers, recommendations for surveillance liver biopsies will undoubtedly be relaxed. There does not appear to be cross reactivity in hepatic side effects between methotrexate and other disease modifying antirheumatic drugs (DMARDs) such as leflunomide, hydroxychloroquine, azathioprine, etanercept, or infliximab.

Drug Class: Antineoplastic Agents; Antirheumatic Agents; Dermatologic Agents; Gastrointestinal Agents

CASE REPORTS

Case 1. Cirrhosis and ascites after long term therapy with methotrexate. (1)

A 38 year old woman with rheumatoid arthritis who had been treated with prednisone, d-penicillamine and gold was switched to methotrexate (7.5 mg/week) and salicylate (3.9 g/day) because of poor response to the other agents. Her serum enzymes and bilirubin levels were normal and serum albumin 3.7 g/dL. Her arthritis symptoms improved on methotrexate therapy, and the dose was raised to 15 mg/week. After two years of methotrexate therapy, she underwent a routine surveillance liver biopsy which showed changes of steatosis and mild portal inflammation (Roenigk grade 1). Serum AST and alkaline phosphatase were still normal, but albumin levels had decreased to 3.2 g/dL. One year later, a repeat surveillance liver biopsy showed mild fibrosis and steatosis (Roenigk grade IIIA). A third liver biopsy done after 4 years of therapy (total dose 2.2 g) again showed moderate activity, steatosis and mild fibrosis. Serum aminotransferase and alkaline phosphatase levels were normal. One year later (year 5 of therapy), she presented with weight gain, peripheral edema and ascites. Serum ALT was 17 U/L, AST 35 U/L, bilirubin 0.2 mg/dL, albumin 2.4 g/dL and prothrombin time 18.4 seconds. She denied alcohol use or previous history of liver disease or exposures to viral hepatitis. Tests for hepatitis A and B were negative as were routine autoantibodies. A liver biopsy showed bridging fibrosis and moderate inflammation (Roenigk grade IIIB), but not frank cirrhosis. Methotrexate and salicylate were stopped and she improved clinically with resolution of the peripheral edema and ascites. Serum albumin levels rose and prothrombin time fell into the normal range. She was later maintained on salicylate alone.

Key Points

Medication:	Methotrexate (15 mg/week) for 5 years
Pattern:	Undefined (minimal or no serum enzyme elevation)
Severity:	4+ (ascites)
Latency:	5 years
Recovery:	Clinical improvements over the ensuing 4-6 months
Other medications:	Salicylate 3.9 g/day, prednisone 7.5 mg/day

Comment

Long term, low dose methotrexate is associated with insidious development of hepatic fibrosis in at least 5% of patients, which in some instances leads to cirrhosis and liver decompensation. The absence of serum enzyme elevations accompanying this progressive fibrosis makes it difficult to monitor patients short of performing routine surveillance liver biopsies at 1 to 2 year intervals. As shown in this example, even surveillance liver biopsies may not adequately reflect the severity of the liver injury and allow for stopping therapy before onset of serious fibrosis. Somewhat typical of fibrotic liver injury caused by methotrexate was the lack of accompanying clinical symptoms and the clinical improvement that occurred when methotrexate was stopped. The fact that the liver biopsy did not show frank cirrhosis, suggests that the portal hypertension may have been due in part to nodular regeneration. Salicylates decrease renal elimination of methotrexate and displace methotrexate from protein binding, and thus may increase the likelihood of toxicity.

Case 2. Cirrhosis after long term therapy with methotrexate.(2)

A 51 year old man with active rheumatoid arthritis was treated with methotrexate at an initial dose of 7.5 mg weekly, increasing to 15 mg weekly with daily folic acid and low doses of prednisone (5 mg daily) for four years with only partial control of his arthritis. He was then enrolled in an open label trial of the combination of

methotrexate and leflunomide (10 mg/day). He had significant improvement and continued on both drugs for a total of 3.5 years. During the first year of therapy, he had minor and transient serum ALT elevations, but none were more than 3 times the upper limit of normal (ULN) (Table). Six months into combination therapy, however, his platelet count began to fall, and it remained low despite a decrease in the dose of methotrexate to 5 mg weekly. After 3.5 years of combination therapy, an abdominal ultrasound showed mild hepatomegaly, splenomegaly with increased echogenicity of the liver suggestive of fatty infiltration. He denied alcohol use and any history or risk factors for liver disease. He had been treated with methotrexate for 7.5 years and received a cumulative dose of 4.5 g. Tests for hepatitis A, B and C were negative as were routine autoantibody tests. Liver tests including serum aminotransferase levels, alkaline phosphatase, bilirubin and albumin were normal and prothrombin time was not increased. A percutaneous liver biopsy showed marked fibrosis, early cirrhosis, mild steatosis and nuclear variability without inflammation or obvious necrosis.

Key Points

Medication:	Methotrexate (5-15 mg/week) for 7.5 years (total dose 4.5 g)
Pattern:	Undefined (no serum enzyme elevation)
Severity:	4+ (cirrhosis)
Latency:	~5 years
Recovery:	Not mentioned
Other medications:	Leflunomide (10 mg/day for 3 years), folic acid, prednisone (5 mg/day)

Laboratory Values

Years After Starting	ALT (U/L)	Alk P (U/L)	Platelets (per µL)	Other
4.0	38	101	181,000	Leflunomide started
4.2	39	119	206,000	
4.4	57	111	150,000	
4.6	28	105	129,000	
4.8	27	111	109,000	
5.0	38	106	105,000	Methotrexate dose reduced
5.5	37	117	98,000	
6.0	32	107	103,000	
6.5	28	101	96,000	
7.0	73	109	92,000	Bilirubin and albumin normal
7.5	21	115	148,000	Liver biopsy
Normal	**<44**	**<111**	**>160,000**	

Comment

This case demonstrates how significant hepatic fibrosis and portal hypertension can arise during methotrexate therapy without accompanying symptoms or significant elevations in serum aminotransferase levels. Also characteristic was the mild and nonprogressive nature of the cirrhosis despite continuation of methotrexate. A possible noninvasive marker for the development of significant fibrosis in this case was the decrease in platelet count, which fell from 181,000/µL at baseline to 105,000 µ/L one year later–a 47% decline and a “platelet slope” of -74,000/year. In analyses of serial platelet count determinations in patients who developed portal

hypertension, a platelet slope of -9,000/year was found to be indicative of the development of portal hypertension and hepatic dysfunction. Whether leflunomide contributed to the toxicity of methotrexate is not clear, but the findings are compatible with methotrexate toxicity based upon the duration and total dose received. The patient did not have typical risk factors for developing methotrexate related fibrosis such as excessive alcohol use, underlying viral hepatitis, renal insufficiency or diabetes (no mention is made of body weight or presence of obesity). While this patient did not qualify for undergoing surveillance liver biopsies (according to the criteria of the American College of Rheumatology), noninvasive tests such as PIIIP, hepatic imaging or elastography would have been appropriate and would likely have suggested the presence of significant fibrosis much earlier.

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Methotrexate – Generic, Trexall®

DRUG CLASS

Antineoplastic Agents

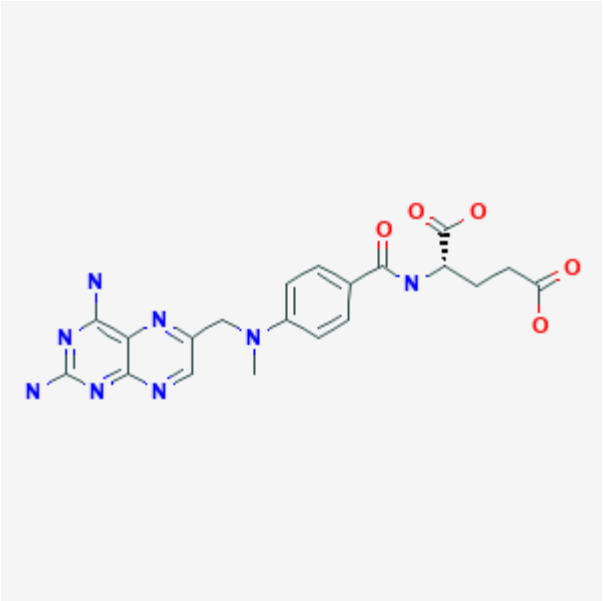
Antirheumatic Agents

Dermatologic Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Methotrexate	59-05-2	C20-H22-N8-O5	

CITED REFERENCES

1. Clegg DO, Furst DE, Tolman KG, Pogue R. Acute, reversible hepatic failure associated with methotrexate treatment of rheumatoid arthritis. J Rheumatol. 1989;16:1123–6. PubMed PMID: 2585411.

2. Weinblatt ME, Dixon JA, Falchuk KR. Serious liver disease in a patient receiving methotrexate and leflunomide. Arthritis Rheum. 2000;43:2609–11. PubMed PMID: 11083289.

ANNOTATED BIBLIOGRAPHY

References updated: 19 February 2020

Zimmerman HJ. Methotrexate. Oncotherapeutic and immunosuppressive agents. In, Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999, pp. 681-7.

(Expert review of hepatotoxicity of methotrexate published in 1999).

Aithal GP. Hepatotoxicity related to methotrexate. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013, pp. 593-604.

(Review of clinical features, course and outcome of methotrexate hepatotoxicity with discussion and comparison of guidelines for monitoring).

Wellstein A, Giaccone G, Atkins MB, Sausville EA. Antimetabolites. Cytotoxic agents. In, Brunton LL, Hilal-Dandan R, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 13th ed. New York: McGraw-Hill, 2018, pp. 1177-80.

(Textbook of pharmacology and therapeutics).

Colsky J, Greenspan EM, Warren TN. Hepatic fibrosis in children with acute leukemia after therapy with folic acid antagonists. AMA Arch Pathol. 1955;59:198–206. PubMed PMID: 13227717.

(Five children with acute leukemia who had remission with aminopterin or methotrexate therapy developed cirrhosis within 8 months to 1.5 years of starting therapy).

Hutter RVP, Shipkey FH, Tan CTC, Murphy ML, Chowdhury M. Hepatic fibrosis in children with acute leukaemia: a complication of therapy. Cancer. 1960;13:288–307. PubMed PMID: 14405648.

(Review of liver histology from autopsies on 273 children with leukemia; rate of fibrosis increased with introduction of chemotherapy, including antifolates aminopterin and methotrexate from 31% [usually mild] to 84% [29% moderate and 1% severe]).

Ryan TJ, Vickers HR, Salem SN, Callender ST, Badenoch J. The treatment of psoriasis with folic acid antagonists. Br J Dermatol. 1964;76:555–64. PubMed PMID: 14242178.

(Among 14 patients with psoriasis treated with aminopterin or methotrexate using a daily schedule and rest periods, 4 had elevations in ALT [62-122 U/L], rapidly returning to normal upon stopping; liver biopsy in one patient showed steatosis).

O'Rourke RA, Eckert GE. Methotrexate-induced hepatic injury in an adult. A case report. Arch Intern Med. 1964;113:191–4. PubMed PMID: 14090383.

(62 year old with psoriasis treated with methotrexate for 2 years [25-50 mg/week] had AST 66 U/L, Alk P 1.5 times ULN, bilirubin 0.6 mg/dL, and liver biopsy showing mild fatty change and periportal fibrosis).

Taft LI. Methotrexate induced hepatitis in childhood leukemia. Isr J Med Sci. 1965;1:823–7. PubMed PMID: 5856123.

(Among 32 Australian children with acute leukemia treated with methotrexate for more than a month, 7 developed evidence of cirrhosis [ascites in 6, jaundice in 1] which was documented by liver biopsy in 3; after only 3-10 months of therapy, improving clinically with stopping therapy).

Hersh EM, Wong VG, Henderson ES, Freireich EJ. Hepatotoxic effects of methotrexate. Cancer. 1966;19:600–6. PubMed PMID: 5933584.

(Analysis of 22 patients given high doses of methotrexate [2-4 five-day courses at 10-22 mg/m^2], ALT levels rose in ~90% of patients, peak levels of 37-1100 U/L, resolving with stopping therapy; biopsies in 12 patients showed portal inflammation in 6, fatty change in 5, fibrosis in 1).

Talerman A, Thompson RB. Hepatic fibrosis in a child possibly due to prolonged methotrexate. J Clin Pathol. 1966;19:81–2. PubMed PMID: 5907470.

(11 year old child with leukemia treated with methotrexate for 3 years [total dose 2.5 g] died of leukemic relapse and had hepatomegaly with extensive hepatic fibrosis and steatosis on autopsy).

Fry L. The treatment of psoriasis with parenteral methotrexate. Br J Dermatol. 1966;78:282–8. PubMed PMID: 5937350.

(Among 15 patients treated for psoriasis with weekly parenteral methotrexate doses of 25-100 mg for 1-6 months, 9 developed raised AST levels [58-208 U/L], usually lasting for less than 7 days after an injection, all resolving with stopping).

Coe RO, Bull FE. Cirrhosis associated with methotrexate treatment of psoriasis. JAMA. 1968;206:1515–20. PubMed PMID: 5695945.

(Three patients developed cirrhosis during methotrexate therapy for psoriasis with insidious onset after 1, 2 and 5.5 years with minimal elevations in ALT [peak 53-132 U/L], Alk P [1.2-2 times ULN], and bilirubin [0.9-1.9 mg/dL], presenting with peripheral edema, ascites and hepatomegaly).

Auerbach R. Cirrhosis and methotrexate treatment of psoriasis. JAMA. 1969;208:155. PubMed PMID: 5818508.

(Letter in response to Coe and Bull questioning relationship of liver injury and methotrexate).

Roenigk HH Jr, Fowler-Bergfeld W, Curtis GH. Methotrexate for psoriasis in weekly oral doses. Arch Dermatol. 1969;99:86–93. PubMed PMID: 5761810.

(Among 204 patients with psoriasis treated with oral methotrexate [25 mg weekly], AST elevations occurred in 6.8%, but liver biopsies done on patients with abnormal liver tests found "no significant pathologic changes").

Dahl MG. Methotrexate and the liver. Br J Dermatol. 1969;81:465–7. PubMed PMID: 4891127.

(Description of 3 patients who developed hepatic fibrosis on oral methotrexate for psoriasis for up to 2.5 years).

Dubin HV, Harrell ER. Absorption of methotrexate and hepatotoxicity. JAMA. 1969;210:1104. PubMed PMID: 5394437.

(Letter in response to Baker and Dahl raising issue of variability in absorption of methotrexate as basis for variability in rates of hepatotoxicity).

Epstein EH Jr, Croft JD Jr. Cirrhosis following methotrexate administration for psoriasis. Arch Dermatol. 1969;100:531–4. PubMed PMID: 5350403.

(46 year old man with psoriasis developed cirrhosis after 5 years of methotrexate therapy [10-80 mg/week] with jaundice, [bilirubin 7.4 mg/dL, ALT 35 U/L, Alk P 1.5 times ULN], ascites and hepatomegaly, dying 4 months later of end stage liver disease and autopsy showing small nodular liver with diffuse fibrosis and fatty change).

McDonald CJ, Bertino JR. Parenteral methotrexate in psoriasis. A report on the efficacy and toxicity of long-term intermittent treatment. Arch Dermatol. 1969;100:655–68. PubMed PMID: 4243752.

(Results of methotrexate therapy in 36 patients with psoriasis; side effects included elevations in AST in 4 patients, 2 of whom had cirrhosis, but both were alcoholic and improved with stopping alcohol intake).

Muller SA, Farrow GM, Martalock DL. Cirrhosis caused by methotrexate in the treatment of psoriasis. Arch Dermatol. 1969;100:523–30. PubMed PMID: 5350402.

(Two cases of cirrhosis arising in patients with psoriasis on methotrexate; 37 and 52 year old men treated for 7 and 5 years with normal AST levels and improvement on stopping therapy).

Sharp H, Nesbit M, White J, Krivit W. Methotrexate liver toxicity. J Pediatr. 1969;74:818–9. PubMed PMID: 5778839.

(Prospective study of 10 children receiving methotrexate [7 on daily and 4 on intermittent therapy for leukemia] found hepatic fibrosis and fat even without liver test abnormalities, often improving after stopping therapy).

Psoriasis, methotrexate, and cirrhosis. JAMA. 1970;212:314–5. PubMed PMID: 5467236.

(Editorial recommending caution in using methotrexate particularly because "results of liver-function tests may be deceiving because transient abnormalities frequently occur in the absence of significant hepatotoxicity, while irreversible liver damage may exist despite normal results").

Bender AS. Hazards of prolonged low-dose methotrexate therapy. Va Med Mon. 1970;97:218–9. PubMed PMID: 5317468.

Dubin HV, Harrell ER. Liver disease associated with methotrexate treatment of psoriatic patients. Arch Dermatol. 1970;102:498–503. PubMed PMID: 5474111.

(Three men with psoriasis, ages 23, 41 and 51 years, treated with methotrexate for 2-8 years had liver biopsies showing fibrosis, ballooning degeneration and inflammation, with poor correlation to AST elevations which were intermittent and mild).

Holst R, Mobacken H. Nord Med. 1970;84:1193–6. [Liver damage during methotrexate treatment of psoriasis]. Swedish. PubMed PMID: 5469272.

(Three patients with psoriasis on methotrexate had abnormal liver biopsy findings of inflammation and steatosis).

Weinstein GD, Cox JW, Suringa DW, Millard MM, Kalser M, Frost P. Evaluation of possible chronic hepatotoxicity from methotrexate for psoriasis. Arch Dermatol. 1970;102:613–8. PubMed PMID: 5501902.

(Analysis of liver biopsies done on 29 patients with psoriasis; among 21 on methotrexate, 16 had steatosis, 2 had fibrosis and 1 cirrhosis [78 year old woman treated for 2 years]; among 8 on no therapy 4 had steatosis but none had fibrosis and all had normal ALT and AST levels).

Almeyda J, Baker H, Levene GM, Barnardo D, Landells JW. Methotrexate, alcohol, and liver damage. Br Med J. 1971;2:167. PubMed PMID: 5581500.

(Among 39 patients with psoriasis on methotrexate undergoing liver biopsy, 12 had fibrosis and 3 cirrhosis [all 3 were heavy drinkers]; among 20 patients not on methotrexate, 3 had fibrosis).

Almeyda J, Barnardo D, Baker H. Drug reactions XV. Methotrexate, psoriasis and the liver. Br J Dermatol. 1971;85:302–5. PubMed PMID: 4939241.

(Review of hepatotoxicity of methotrexate in psoriasis based upon 7 publications; among 130 biopsies done before therapy 29% were normal, 57% had mild or nonspecific changes, 5% fibrosis and 1.5% cirrhosis often corresponding to alcohol history; among 193 biopsies done during methotrexate therapy, 21% were normal, 23% had fibrosis and 11% cirrhosis, with marked variability in rates of cirrhosis [5-16%]; alcohol could not explain all hepatic fibrosis associated with methotrexate therapy).

Baker H. Liver damage and methotrexate. Br Med J. 1971;2:776. PubMed PMID: 5090795.

(Comments on drug levels with daily versus weekly dosing of methotrexate).

Dahl MG, Gregory MM, Scheuer PJ. Liver damage due to methotrexate in patients with psoriasis. Br Med J. 1971;1:625–30. PubMed PMID: 5548839.

(Among 37 patients with psoriasis treated with methotrexate who were not heavy drinkers, cirrhosis was present in 7 [19%], fibrosis in 10 [27%] and minor abnormalities in 17 [46%] including fat, ballooning degeneration and inflammation; fibrosis appeared only after 10 months and correlated with duration of therapy; nonspecific findings of fat and inflammation can be seen in pretreatment biopsies; AST elevations occurred in almost all patients, but were mild and transient and did not predict the severity of biopsy changes).

Filip DJ, Logue GL, Harle TS, Farrar WH. Pulmonary and hepatic complications of methotrexate therapy of psoriasis. JAMA. 1971;216:881–2. PubMed PMID: 5108291.

(49 year old man with psoriasis developed pulmonary toxicity and liver disease [biopsy showing fat and fibrosis] after 5 years of methotrexate therapy, improving on withdrawal).

Price LA. Liver damage and methotrexate. Br Med J. 1971;2:464. PubMed PMID: 5576011.

(Letter arguing for use of folinic acid when using methotrexate even in oral low dose therapy).

Roenigk HH Jr, Bergfeld WF, St Jacques R, Owens FJ, Hawk WA. Hepatotoxicity of methotrexate in the treatment of psoriasis. Arch Dermatol. 1971;103:250–61. PubMed PMID: 5548272.

(Liver biopsies in 50 patients with psoriasis; 7 of 13 had abnormal histology before therapy which correlated with alcohol history; 28 of 37 taken during methotrexate therapy were abnormal including 6 with cirrhosis; initial scoring system proposed with 1=normal; 2=minor steatosis; 3=moderate-to-severe steatosis and inflammation; 4=fibrosis; 5=cirrhosis).

Tashima CK. Methotrexate and hepatic disease. JAMA. 1971;216:2018. PubMed PMID: 5108642.

(70 year old woman with psoriasis presented with cirrhosis and end stage liver disease after being treated with methotrexate for 4 years; alcohol history unclear).

Vogler WR, Jacobs J. Toxic and therapeutic effects of methotrexate-folinic acid(Leucovorin) in advanced cancer and leukemia. Cancer. 1971;28:894–901. PubMed PMID: 5315548.

(Toxicity of high dose methotrexate followed by leucovorin rescue in patients with cancer and leukemia; little on hepatotoxicity).

Zachariae H, Schiodt T. Liver biopsy in methotrexate treatment. Acta Derm Venereol. 1971;51:215–20. PubMed PMID: 4103033.

(Analysis of 57 liver biopsies from 36 patients with psoriasis on methotrexate therapy showed high rate of findings in pretreatment biopsies and no significant change except for increase in steatosis on treatment; ALT elevations occurred but liver biopsies often showed no abnormalities; no mention of fibrosis).

Almeyda J, Barnardo D, Baker H, Levene GM, Landells JW. Structural and functional abnormalities of the liver in psoriasis before and during methotrexate therapy. Br J Dermatol. 1972;87:623–31. PubMed PMID: 4648805.

(Liver biopsies on 67 patients with psoriasis comparing 25 not on therapy to 42 on methotrexate [for 0.3-7 years]: 56% vs 40% were normal, 28% vs 24% had nonspecific, mild changes, 16% vs 29% had fibrosis and 0% vs 7% had cirrhosis; fibrosis more common with daily dose regimens and in alcoholics).

Dahl MG, Gregory MM, Scheuer PJ. Methotrexate hepatotoxicity in psoriasis--comparison of different dose regimens. Br Med J. 1972;1:654–6. PubMed PMID: 5015292.

(Analysis of liver biopsies from 44 patients with psoriasis treated with methotrexate, found 6 with cirrhosis [13%] and 11 fibrosis [25%]; presence of fibrosis correlating with duration of therapy and with daily [12 of 22] rather than weekly [2 of 14] dosing).

Griesman FA, Hammer CJ, Fenster LF. Methotrexate-associated liver disease in psoriatic patients. Northwest Med. 1972;71:609–12. PubMed PMID: 5053597.

Ryan TJ, Sadler GH, Guerrier C, Vickers HR. Methotrexate hepatotoxicity in psoriasis. Br Med J. 1972;2:296. PubMed PMID: 5022031.

(Among 4 patients with psoriasis on methotrexate for more than 10 years using daily regimens, 2 had cirrhosis, but 2 had no fibrosis on biopsy).

Robeson JA, Spenney J, Hirschowitz BI. Cirrhosis following prolonged treatment of psoriasis with methotrexate orally. South Med J. 1972;65:453–6. PubMed PMID: 5028402.

(60 year old non-drinking woman with psoriasis on methotrexate for 9 years presented with cirrhosis and ascites [bilirubin 1.0 mg/dL, AST 25, Alk P 2.5 times ULN, albumin 2.7, prothrombin index 63]; patient improved clinically on withdrawal).

Roenigk HH Jr, Maibach HI, Weinstein GD. Use of methotrexate in psoriasis. Arch Dermatol. 1972;105:363–5. PubMed PMID: 5012144.

(Recommended liver biopsy before starting methotrexate and repeat liver biopsy based upon abnormal liver tests and proposed a five-point grading system from normal [Grade I] to cirrhosis [Grade 5]).

Roenigk HH Jr, Maibach HI, Weinstein GP. Methotrexate therapy for psoriasis. Guideline revisions. Arch Dermatol. 1973;108:35. PubMed PMID: 4716739.

(Change in grading system to: Grade I=normal or mild fatty infiltration, nuclear variability and portal inflammation; II=moderate changes; III=fibrosis [with septa]; IV=cirrhosis; with recommendations not to use or continue methotrexate in patients with Grade III changes and to perform a liver biopsy before starting therapy).

Weinstein G, Roenigk H, Maibach H, Cosmides J, Halprin K, Millard M, et al. Psoriasis-liver-methotrexate interactions. Arch Dermatol. 1973;108:36–42. PubMed PMID: 4716740.

(Cooperative study with analysis of 742 biopsies from 550 patients with psoriasis on methotrexate from 10 clinical centers; ALT levels elevated in 12% before and 13% after methotrexate; moderate-severe fibrosis in 7% vs 13%, cirrhosis in 1.5% vs 2.6%, fibrosis correlating with duration and cumulative dose, daily dosing, alcohol intake, obesity and diabetes).

Coughlin GP, Henderson DW, Reid JG, Grant AK. Cirrhosis following methotrexate administration for psoriasis. Med J Aust. 1973;2:499–501. PubMed PMID: 4750546.

(52 year old with psoriasis [non-drinker] treated with methotrexate [daily regimens] for 3 years presented with large liver, AST 50 U/L, Alk P 1.5 times ULN, albumin 30 gm/dL, platelets 37,000/μL, and biopsy showing cirrhosis; improved clinically upon withdrawal).

Horvath E, Kovacs K, Ross RC. Liver ultrastructure in methotrexate treatment of psoriasis. Arch Dermatol. 1973;108:427–8. PubMed PMID: 4729773.

(Analysis of 9 biopsies from patients with psoriasis on methotrexate which had only mild, nonspecific changes on light microscopy but showed increase in Ito cells by electron microscopy).

Kraus Z, Vortel V, Fixa B, Komárková O. Cesk Dermatol. 1973;48:255–62. [Liver of psoriatic patients treated with methotrexate]. Czech. PubMed PMID: 4727832.

Moldenhauer E, Dabels J, Diwok K, Leithäer W, Nowotny P. Dermatol Monatsschr. 1973;159:242–8. [Incidence of liver diseases in psoriatic patients with special reference to methotrexate therapy]. German. PubMed PMID: 4704945.

Pai SH, Werthamer S, Zak FG. Severe liver damage caused by treatment of psoriasis with methotrexate. N Y State J Med. 1973;73:2585–7. PubMed PMID: 4518596.

(32 year old with psoriasis treated with methotrexate for 3 years [0.5 g] presented with fever, coma and acidosis; autopsy showed advanced fibrosis; no liver tests or alcohol history provided).

Palmer HM. Hepatotoxicity of methotrexate in the treatment of psoriasis. Practitioner. 1973;211:324–8. PubMed PMID: 4759241.

(Analysis of 37 patients with psoriasis on long term methotrexate, usually 5 days a week for 2 months to 6 years; 4 of 23 biopsies showed fibrosis and 3 cirrhosis [after 1.8-2.8 g total dose]).

Podurgiel BJ, McGill DB, Ludwig J, Taylor WF, Muller SA. Liver injury associated with methotrexate therapy for psoriasis. Mayo Clin Proc. 1973;48:787–92. PubMed PMID: 4758150.

(Among 35 patients with psoriasis treated with methotrexate for 1 to 8 years, liver biopsies showed fibrosis in 5 [14%] and cirrhosis in 4 [11%]; presence of fibrosis correlated with AST elevations, >2 years of therapy, and daily administration).

Tobias H, Auerbach R. Hepatotoxicity of long-term methotrexate therapy for psoriasis. Arch Intern Med. 1973;132:391–6. PubMed PMID: 4783020.

(Liver biopsy results on 88 patients with psoriasis treated with methotrexate found increase in fibrosis and cirrhosis after cumulative dose of 2 g; rates higher in alcoholics; fat was present in 64% of 14 untreated versus 61% of 41 treated non-users of alcohol; nuclear changes found in most treated patients; ALT and AST usually normal).

Millward-Sadler GH, Ryan TJ. Methotrexate induced liver disease in psoriasis. Br J Dermatol. 1974;90:661–7. PubMed PMID: 4853200.

(Among 19 patients with psoriasis treated with methotrexate for 1-10 years, 2 had fibrosis and 3 cirrhosis; fibrosis correlated with duration of therapy and was more common with daily vs weekly regimens; serum liver tests were not helpful in identifying patients with fibrosis).

Reese LT, Grisham JW, Aach RD, Eisen AZ. Effects of methotrexate on the liver in psoriasis. J Invest Dermatol. 1974;62:597–602. PubMed PMID: 4835782.

(Among 102 liver biopsies done in 70 patients with psoriasis, fibrosis was present in 1 of 35 [3%] untreated versus 3 of 35 [9%] on methotrexate [1 with cirrhosis], but nonspecific changes were found equally in the two groups, and serum enzyme elevations did not correlate with histological findings).

Ruszczak Z, Prószynska-Kuczynska W, Krajewski C. Wiad Lek. 1974;27:1083–6. [Side effects of methotrexate in the treatment of skin diseases]. Polish. PubMed PMID: 4600611.

Shapiro HA, Trowbridge JO, Lee JC, Maibach HI. Liver disease in psoriatics - an effect of methotrexate therapy? Arch Dermatol. 1974;110:547–51. PubMed PMID: 4414499.

(Among 67 patients with psoriasis, liver fibrosis and fat did not correspond with methotrexate therapy; cirrhosis present in 4 of 20 [20%] before therapy and 5 of 46 [12%] on methotrexate; amount of fat and liver tests abnormalities were also similar in untreated and treated patients).

Delbrück H, Schaison G, Chelloul N, Bernard J. Dtsch Med Wochenschr. 1975;100:1792–7. [Carcinoma of the liver in a child after seven-year complete remission of acute lymphoblastic leukaemia(author's transl)]. PubMed PMID: 169114.

(12 year old girl on maintenance methotrexate and mercaptopurine for 7 years after remission in acute leukemia presented with hepatocellular carcinoma).

Warin AP, Landells JW, Levene GM, Baker H. A prospective study of the effects of weekly oral methotrexate on liver biopsy. Br J Dermatol. 1975;93:321–7. PubMed PMID: 1103936.

(25 patients with psoriasis underwent 192 liver biopsies before and after 1-5 years of weekly oral methotrexate therapy showed no increase in fibrosis or inflammation; pretreatment liver biopsies in 66 patients were normal in 67%, had nonspecific changes in 26%, fibrosis in 6% and cirrhosis in 1 alcoholic patient).

Nyfors A, Svejgaard A. The relation of HL-A antigens to liver histology in methotrexate-treated psoriatics. Acta Derm Venereol. 1976;56:235–8. PubMed PMID: 59509.

(In 45 patients with psoriasis on methotrexate therapy [14 with cirrhosis or fibrosis], no association was found between HLA-A and liver histological findings).

Hopwood D, Nyfors A. Effect of methotrexate therapy in psoriatics on the Ito cells in liver biopsies, assessed by point-counting. J Clin Pathol. 1976;29:698–703. PubMed PMID: 956451.

(Among 24 patients with psoriasis treated with methotrexate, light and electron microscopy of liver tissue showed increase in hepatic stellate cells [mean volume density rising from 0.25% to 0.66%] with methotrexate therapy, not correlating with dose and decreasing rapidly with stopping; morphology of stellate cells did not change).

Nyfors A, Poulsen H. Liver biopsies from psoriatics related to methotrexate therapy. 1. Findings in 123 consecutive non-methotrexate treated patients. Acta Pathol Microbiol Scand A. 1976;84:253–61. PubMed PMID: 1274590.

(Among 123 liver biopsies in patients with psoriasis not on methotrexate, 49% were normal, 37% had fatty change, 12% had nonspecific findings, 1% fibrosis and 1% cirrhosis; abnormalities correlating with raised AST [high specificity, low sensitivity], alcohol history, age and obesity).

Nyfors A, Poulsen H. Liver biopsies from psoriatics related to methotrexate therapy. 2. Findings before and after methotrexate therapy in 88 patients. A blind study. Acta Pathol Microbiol Scand A. 1976;84:262–70. PubMed PMID: 1274591.

(Among 88 patients with psoriasis undergoing liver biopsy before and after 2-72 months [175-4590 mg] of weekly doses of methotrexate, 6 [7%] developed cirrhosis and 5 [6%] fibrosis with little correlation with dose, alcohol history, AST elevations or pretreatment liver histology).

Nyfors A. Liver biopsies from psoriatics related to methotrexate therapy. 3. Findings in post-methotrexate liver biopsies from 160 psoriatics. Acta Pathol Microbiol Scand A. 1977;85:511–8. PubMed PMID: 899789.

(Among 160 patients with psoriasis treated with methotrexate, 92 had a single liver biopsy on therapy of whom 1% had cirrhosis and 7% fibrosis [correlated with alcohol intake and age but not total dose]; among 68 with two liver biopsies on therapy [total dose 175-5568 mg], 21% had cirrhosis and 24% fibrosis, fibrosis correlating with alcohol intake during therapy, obesity and older age, but cirrhosis found almost only in patients with >2 g methotrexate exposure).

Nyfors A, Hopwood D. Liver ultrastructure in psoriatics related to methotrexate therapy. 1. A prospective study of findings in hepatocytes from 24 patients before and after methotrexate treatment. Acta Pathol Microbiol Scand A. 1977;85:787–800. PubMed PMID: 602766.

(Liver biopsies taken before and during methotrexate therapy in 24 patients with psoriasis showed increase in hepatocyte membrane whorls and vacuoles and increase in autophagic vacuoles, but no correlation with duration of therapy or total dose).

Hopwood D, Nyfors A. Liver ultrastructure in psoriatics related to methotrexate therapy. 2. Findings in bile ducts from 11 methotrexate treated psoriatics and 2 controls. Acta Pathol Microbiol Scand A. 1977;85:801–11. PubMed PMID: 602767.

(Bile duct histology was studied by light and electron microscopy in 11 patients with psoriasis on methotrexate and 2 controls showed increase in autophagic vacuoles in biliary epithelial cells and nonspecific findings of mitochondrial damage and membrane whorls and particulate debris in lumen).

Horvath E, Kovacs K, Ross RC, Saibil F, Kerenyi NA. Desmosomal abnormalities in the liver of methotrexate-treated psoriatics. Experientia. 1977;33:1202–4. PubMed PMID: 560985.

(Among 50 liver biopsies from patients with psoriasis on methotrexate for 0.1 to 15 years, detachment of desmosomes was found in half of cases along with microfilaments anchored to mitochondria).

Nyfors A, Poulsen H. Morphogenesis of fibrosis and cirrhosis in methotrexate-treated patients with psoriasis. Am J Surg Pathol. 1977;1:235–43. PubMed PMID: 920871.

(Analysis of progression of fibrosis using 31 liver biopsies from 8 patients with psoriasis treated with methotrexate [4 developed fibrosis, 4 cirrhosis]; early changes were focal interface hepatitis, followed by entry of fibrous septa, that then linked portal areas, that could lead to micronodular cirrhosis).

McIntosh S, Davidson DL, O'Brien RT, Pearson HA. Methotrexate hepatotoxicity in children with leukemia. J Pediatr. 1977;90:1019–21. PubMed PMID: 870655.

(8 children treated with methotrexate [1-11 g/m^2] for leukemia underwent liver biopsy, and 5 had fibrosis; all had at least transient AST elevations [peak 49-400 U/L]).

Ruymann FB, Mosijczuk AD, Sayers RJ. Hepatoma in a child with methotrexate-induced hepatic fibrosis. JAMA. 1977;238:2631–3. PubMed PMID: 200767.

(11 year old girl with acute leukemia treated with methotrexate for 6 years died of recurrence; found on autopsy to have hepatic steatosis, fibrosis, nodular liver and a small hepatocellular carcinoma).

Chan H, Evans WE, Pratt CB. Recovery from toxicity with high-dose methotrexate: prognostic factors. Cancer Treat Rep. 1977;61:797–804. PubMed PMID: 19151.

(Among 65 patients with cancer given high dose methotrexate with leucovorin rescue, 6 had severe toxicity marked by neutropenia and infections and 3 died with multiorgan failure and sepsis with jaundice and ALT elevations).

Horvath E, Saibil FG, Kovacs K, Kerenyi NA, Ross RC. Fine structural changes in the liver of methotrexate-treated psoriatics. Digestion. 1978;17:488–502. PubMed PMID: 710735.

(Electron microscopy was done on 55 liver biopsies from 52 patients with psoriasis, 47 on methotrexate therapy; most common findings were diverse mitochondrial abnormalities, detachment of desmosomal plaques and hyperplasia of stellate cells, but these changes did not correlate with duration of therapy or hepatic injury as shown by light microscopy).

Perez C, Sutow WW, Wang YM, Herson J. Evaluation of overall toxicity of high-dosage methotrexate regimens. Med Pediatr Oncol. 1979;6:219–28. PubMed PMID: 314042.

(Among 349 courses of high dose methotrexate with leucovorin rescue, AST elevations occurred after 59% with values >3 times ULN in 16%; however, all resolved).

Plomteux G, Closon MT. Med Chir Dig. 1979;8:385–7. [Hepatic tolerance of methotrexate]. French. PubMed PMID: 534014.

Vaughan WP, Wilcox PM, Alderson PO, Ettinger DS, Abeloff MD. Hepatic toxicity of adjuvant chemotherapy for carcinoma of the breast. Med Pediatr Oncol. 1979;7:351–9. PubMed PMID: 547161.

(Four patients being treated with cyclophosphamide, methotrexate and 5-fluouracil developed focal defects on liver scans which were thought to be metastases, but later presumed due to hepatotoxicity with only minor elevations in AST and Alk P, injury being attributed to methotrexate).

Nyfors A. Methotrexate therapy of psoriasis. Effect and side effects with particular reference to hepatic changes. A survey. Dan Med Bull. 1980;27:74–96. PubMed PMID: 7000451.

(Extensive review of history of development of methotrexate, changes in dosing schedules and evolution of understanding of hepatotoxicity with detailed analysis of liver histology).

Parker D, Bate CM, Craft AW, Graham-Pole J, Malpas JS, Stansfeld AG. Liver damage in children with acute leukaemia and non-Hodgkin's lymphoma on oral maintenance chemotherapy. Cancer Chemother Pharmacol. 1980;4:121–7. PubMed PMID: 6930333.

(36 children on maintenance chemotherapy for leukemia or lymphoma with methotrexate [25-30 mg/m^2] and mercaptopurine had frequent AST and Alk P elevations; 8 had liver biopsy which were abnormal in 6 with cirrhosis in 1, no anti-HCV testing available).

Robinson JK, Baughman RD, Auerbach R, Cimis RJ. Methotrexate hepatotoxicity in psoriasis. Consideration of liver biopsies at regular intervals. Arch Dermatol. 1980;116:413–5. PubMed PMID: 7369769.

(Among 131 liver biopsies done in 43 patients with psoriasis on methotrexate, fibrosis [grade IIIA or B changes] found in 11 after 1-6 years of therapy [total dose 0.6-2.7 g], not predicted by ALT or AST values, but did correlate with older age and total duration of treatment).

Zachariae H, Kragballe K, Søgaard H. Methotrexate induced liver cirrhosis. Studies including serial liver biopsies during continued treatment. Br J Dermatol. 1980;102:407–12. PubMed PMID: 7387883.

(Analysis of 764 liver biopsies done on 328 patients with psoriasis; 2 had cirrhosis before therapy [0.6%], rising to 13.5% after 2 years and 26% after 5 years; often nonprogressive and patients tolerated continuation of therapy).

Zachariae H, Kragballe K, Thestrup-Pedersen K, Kissmeyer-Nielsen F. HLA antigens in methotrexate-induced liver cirrhosis. Acta Derm Venereol. 1980;60:165–6. PubMed PMID: 6155028.

(HLA-typing done on 20 patients with psoriasis and methotrexate related cirrhosis was compared to 44 treated patients without cirrhosis and 1291 controls; found a slight increase in HLA-A1+B8 [25% vs 7% vs 15%]).

Willkens RF, Watson MA, Paxson CS. Low dose pulse methotrexate therapy in rheumatoid arthritis. J Rheumatol. 1980;7:501–5. PubMed PMID: 7420331.

(32 patients with rheumatoid arthritis were treated with methotrexate [7.5-15 mg/week] for 0.3-5 years; 4 had liver biopsies after 2 years of treatment; in those with liver test abnormalities, mild fatty change in 1).

Eschenbach C, Schmitz-Moormann P, Gutjahr P. Helv Paediatr Acta. 1980;35:577–84. [Liver cell carcinoma following juvenile acute lymphoblastic leukemia. Case contribution]. German. PubMed PMID: 6259092.

(Child with chronic hepatitis B died of hepatocellular carcinoma 5 years after chemotherapy for acute leukemia using methotrexate).

Kamen BA, Nylen PA, Camitta BM, Bertino JR. Methotrexate accumulation and folate depletion in cells as a possible mechanism of chronic toxicity to the drug. Br J Haematol. 1981;49:355–60. PubMed PMID: 6170307.

(Red cell folate was decreased in 9 of 12 children on methotrexate and in 3 of 5 liver samples from patients on long term methotrexate).

Roenigk HH Jr, Auerbach R, Maibach HI, Weinstein GD. Methotrexate guidelines - revised. J Am Acad Dermatol. 1982;6:145–55. PubMed PMID: 7037877.

(Expert review of methotrexate and recommendations for use and monitoring; recommended liver biopsy before starting therapy, ALT testing at 3-4 month intervals and repeat liver biopsy after 1.5 g total dose and based upon relative risk, risk factors being alcohol use, previous arsenic exposure, diabetes, obesity, renal impairment and pretreatment liver pathology).

Ashton RE, Millward-Sadler GH, White JE. Complications in methotrexate treatment of psoriasis with particular reference to liver fibrosis. J Invest Dermatol. 1982;79:229–32. PubMed PMID: 7130740.

(Among 38 patients with psoriasis undergoing liver biopsy before and during methotrexate therapy, 7 [18%] developed fibrosis and 2 [5%] cirrhosis after 16-38 months [1-3.4 g], of whom 3 had moderate alcohol intake).

Lenler-Petersen P, Søgaard H, Thestrup-Pedersen K, Zachariae H. Galactose tolerance test and methotrexate-induced liver fibrosis and cirrhosis in patients with psoriasis. Acta Derm Venereol. 1982;62:448–9. PubMed PMID: 6183903.

(A total of 151 galactose elimination tests were done on 45 patients with psoriasis and fibrosis undergoing liver biopsies during methotrexate therapy; abnormal results were found in 6% of 46 patients with normal biopsy, 14% of 105 with fibrosis and 20% of 41 with cirrhosis).

Zachariae H, Bjerring P. Methotrexate in psoriasis with and without leucovorin: effect of different dosage schedules on acute liver toxicity. Acta Derm Venereol. 1982;62:446–8. PubMed PMID: 6183902.

(Comparison of patients with psoriasis given varying regimens of methotrexate [5 mg over 3 days vs 25 mg once weekly, orally vs intramuscularly, with and without leucovorin] found no difference in AST increase during week after dosing [110-187% increase compared to baseline]).

Geronemus RG, Auerbach R, Tobias H. Liver biopsies upsilon liver scans in methotrexate-treated patients with psoriasis. Arch Dermatol. 1982;118:649–51. PubMed PMID: 7114866.

(Technetium 99m sulfur-colloid scans were not accurate in detecting fibrosis in patients with psoriasis on methotrexate, being abnormal in 6 of 17 patients with normal liver histology and 2 of 5 with fibrosis).

Lawrence CM, Strange RC, Summerly RA, Scriven AJ, Elmahallowy M, Wood A, Fletcher PJ, et al. Assessment of liver function using fasting bile salt concentrations in psoriasis prior to and during methotrexate therapy. Clin Chim Acta. 1983;129:341–51. PubMed PMID: 6851172.

(Fasting bile acid levels were measured in 18 patients with psoriasis before therapy and 21 receiving long term methotrexate; elevations in bile acids were more accurate than routine liver tests in predicting severe histological abnormalities, but were not sufficiently reliable to detect moderate or severe histological changes).

Beck HI, Foged EK. Toxic hepatitis due to combination therapy with methotrexate and etretinate in psoriasis. Dermatologica. 1983;167:94–6. PubMed PMID: 6628806.

(47 year old with psoriasis who had been on oral weekly methotrexate for 10 years with normal liver tests, developed fever, jaundice and ascites 4 months after adding 25-75 mg/day etretinate [AST 460 U/L, Alk P 1.5 times ULN, bilirubin 17 mg/dL, prothrombin index 27%], with resolution 2 months after stopping both agents; liver biopsy later showed cirrhosis).

Breithaupt H, Küenzlen E. High-dose methotrexate for osteosarcoma: toxicity and clinical results. Oncology. 1983;40:85–9. PubMed PMID: 6600827.

(9 patients with osteosarcoma received 122 infusions of high dose methotrexate with leucovorin rescue; "Mild to moderate elevations of serum transaminases have been recorded in nearly each course, usually returning to normal values within 1 week." One patient developed nausea with ALT 1090 U/L and normal bilirubin and with recurrence on re-infusion).

Groff GD, Shenberger KN, Wilke WS, Taylor TH. Low dose oral methotrexate in rheumatoid arthritis: an uncontrolled trial and review of the literature. Semin Arthritis Rheum. 1983;12:333–47. PubMed PMID: 6348949.

(Retrospective analysis of 28 patients with rheumatoid arthritis treated with methotrexate for 4-30 months; 3 had liver biopsies for elevated serum enzymes and all 3 were normal).

Hoffmeister RT. Methotrexate therapy in rheumatoid arthritis: 15 years experience. Am J Med. 1983;75:69–73. PubMed PMID: 6660241.

(Retrospective analysis of 78 patients with rheumatoid arthritis treated with methotrexate for up to 15 years; 34 patients underwent 67 liver biopsies, 50 biopsies were normal and 17 showed mild abnormalities with fat and inflammation, 7 with portal fibrosis but none with cirrhosis).

Hilgers RD, Alberts DS, Standefer JC, Skipper BE, Miles NJ, Borst J. Phase II and pharmacokinetics study of high-dose methotrexate in the treatment of advanced gynecologic malignancy. Gynecol Oncol. 1984;18:62–70. PubMed PMID: 6609105.

(Among 15 patients with gynecological malignancies given several courses of high dose intravenous methotrexate [0.5-8 g/m^2] with leucovorin rescue, AST elevations occurred during 6% of courses, but all were asymptomatic and resolved).

Haim N, Kedar A, Robinson E. Methotrexate-related deaths in patients previously treated with cis-diamminedichloride platinum. Cancer Chemother Pharmacol. 1984;13:223–5. PubMed PMID: 6541532.

(6 patients with cancer receiving high dose methotrexate [40 mg/m^2] and cis-diamminedichloride platinum [CDDP] died with severe stomatitis, fever and leucopenia followed by renal and hepatic failure; the CDDP perhaps causing excessive methotrexate toxicity because of its nephrotoxicity).

Birnie GG, Fitzsimons CP, Czarnecki D, Cooke A, Scobie G, Brodie MJ. Hepatic metabolic function in patients receiving long-term methotrexate therapy: comparison with topically treated psoriatics, patient controls and cirrhotics. Hepatogastroenterology. 1985;32:163–7. PubMed PMID: 2865199.

(Indocyanine green and antipyrine clearance were measured in 11 patients with psoriasis on long term methotrexate [iv every 2 weeks for 1-16 years] and 14 patients not on therapy and compared to routine liver tests; patients on methotrexate had lower clearances, but there was complete overlap with normal subjects).

Hendel J, Poulsen H, Nyfors B, Nyfors A. Changes in liver histology during methotrexate therapy of psoriasis correlated to the concentration of methotrexate and folate in erythrocytes. Acta Pharmacol Toxicol (Copenh). 1985;56:321–6. PubMed PMID: 4024960.

(Among 31 patients with psoriasis on methotrexate therapy, liver biopsies showed mild to moderate fatty change and none had progression of fibrosis, but abnormalities that did occur correlated with lower red cell folate and higher methotrexate levels).

Weinblatt ME, Coblyn JS, Fox DA, Fraser PA, Holdsworth DE, Glass DN, Trentham DE. Efficacy of low dose methotrexate in rheumatoid arthritis. N Engl J Med. 1985;312:818–22. PubMed PMID: 3883172.

(Placebo controlled crossover trial of methotrexate [7.5-15 mg/week] for 24 weeks in 33 patients with severe rheumatoid arthritis; abnormal ALT or AST occurred in 21% on drug and 3% on placebo, all episodes resolving rapidly with holding the dose).

van de Kerkhof PC, Hoefnagels WH, van Haelst UJ, Mali JW. Methotrexate maintenance therapy and liver damage in psoriasis. Clin Exp Dermatol. 1985;10:194–200. PubMed PMID: 4006282.

(Among 44 patients with psoriasis treated with methotrexate for 3 to 15 years, 7 [16%] had fibrosis and 2 [4.5%] cirrhosis, no correlation with ALT or AST elevations and poor correlation with total dose; more common in elderly; all received >2 g total dose).

Williams HJ, Willkens RF, Samuelson CO Jr, Alarcon GS, Guttadauria M, Yarboro C, Polisson RP, et al. Comparison of low-dose oral pulse methotrexate and placebo in the treatment of rheumatoid arthritis: a controlled clinical trial. Arthritis Rheum. 1985;28:721–30. PubMed PMID: 3893441.

(Controlled trial of methotrexate [7.5-15 mg/week] vs placebo for 18 weeks in 189 patients with rheumatoid arthritis; ALT elevations >2 times ULN occurred in 19% of 95 patients on methotrexate vs 3% of 94 on placebo; most common cause of drug withdrawal).

Lanse SB, Arnold GL, Gowans JD, 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;30:104–9. PubMed PMID: 3967557.

(Serial liver biopsies among 30 patients with psoriasis or rheumatoid arthritis treated with oral methotrexate weekly showed normal results in 50% and all remained normal on repeat biopsy 1-10 years later; among 11 with fat and 4 with mild fibrosis initially, 4 worsened, 8 were unchanged and 3 were better in follow up and none developed cirrhosis).

Mackenzie AH. Hepatotoxicity of prolonged methotrexate therapy for rheumatoid arthritis. Cleve Clin Q. 1985;52:129–35. PubMed PMID: 4028418.

(Among 60 patients with rheumatoid arthritis being treated with methotrexate who underwent liver biopsy, none had fibrosis; and rates of steatosis [50% vs 44%] and portal inflammation [18% vs 20%] were not increased compared to controls).

Pestana A, Halprin KM, Taylor JR, Schiff ER, Esquenazi V, Comerford M, Gomez C. Predictive value of HLA antigen for methotrexate-induced liver damage in patients with psoriasis. J Am Acad Dermatol. 1985;12(1 Pt 1):26–9. PubMed PMID: 3980800.

(Among 32 patients with psoriasis treated with methotrexate for at least 4 years who had variable degrees of hepatic fibrosis, HLA typing showed no association with degree of fibrosis or cirrhosis).

Tolman KG, Clegg DO, Lee RG, Ward JR. Methotrexate and the liver. J Rheumatol Suppl. 1985;12 Suppl 12:29–34. PubMed PMID: 3831362.

(Analysis of liver biopsies in 29 patients with rheumatoid arthritis on weekly methotrexate for at least 2 years, found 24% normal, 41% with mild changes, 34% with fibrosis and none with cirrhosis; ALT levels did not predict more severe histologic changes; hypoalbuminemia and persistent ALT elevations were somewhat predictive and significant abnormalities found only after 1.5 g total dose).

Weinstein A, Marlowe S, Korn J, Farouhar F. Low-dose methotrexate treatment of rheumatoid arthritis. Long-term observations. Am J Med. 1985;79:331–7. PubMed PMID: 4036984.

(Among 25 patients with rheumatoid arthritis treated with methotrexate for 0.5 to 5 years, ALT elevations found in 48% at least once; 6 of 17 [35%] had fibrosis on liver biopsy but none had cirrhosis; histology having a poor correlation with ALT elevations).

Miller JA, Dodd H, Rustin MHA, Lees WR, Levene GM, Kirby JD, Munro DD. Ultrasound as a screening procedure for methotrexate-induced hepatic damage in severe psoriasis. Br J Dermatol. 1985;113:699–705. PubMed PMID: 3913457.

(Among 82 patients with psoriasis on methotrexate, abnormal ultrasound findings [moderate-severe fat or fibrosis] found in 22% of those with normal [n=49], 73% of those with abnormal liver biopsies without fibrosis [n=30] and all with fibrosis [n=8]).

Jones SK, Aherne GW, Campbell MJ, White JE. Methotrexate pharmacokinetics in psoriatic patients developing hepatic fibrosis. Arch Dermatol. 1986;122:666–9. PubMed PMID: 3717976.

(Pharmacokinetic studies on 7 patients with psoriasis with fibrosis due to methotrexate and 12 without fibrosis showed no differences in peak levels of methotrexate or rates of clearance).

Kremer JM, Lee JK. The safety and efficacy of the use of methotrexate in long-term therapy for rheumatoid arthritis. Arthritis Rheum. 1986;29:822–31. PubMed PMID: 3741499.

(Among 29 patients with rheumatoid arthritis treated with methotrexate for 7-54 months, 69% had at least one AST elevation, occurring randomly and not requiring dose change; comparison of 29 baseline and 31 follow up liver biopsies showed minimal worsening and no correlation with AST elevations).

Kremer JM, Galivan J, Streckfuss A, Kamen B. Methotrexate metabolism analysis in blood and liver of rheumatoid arthritis patients: association with hepatic folate deficiency and formation of polyglutamates. Arthritis Rheum. 1986;29:832–5. PubMed PMID: 2427090.

(Among 29 patients with rheumatoid arthritis, measurement of folate metabolites in liver tissue showed evidence of folate deficiency in all patients on methotrexate which was restored by oral folate therapy).

Reynolds FS, Lee WM. Hepatotoxicity after long-term methotrexate therapy. South Med J. 1986;79:536–9. PubMed PMID: 3704718.

(Among 14 patients with psoriasis who underwent liver biopsy, 4 [27%] had fibrosis all of whom had been treated for more than 5 years).

Berkowitz RS, Goldstein DP, Bernstein MR. Ten years' experience with methotrexate and folinic acid as primary therapy for gestational trophoblastic disease. Gynecol Oncol. 1986;23:111–8. PubMed PMID: 3002916.

(Among 185 patients with gestational trophoblastic disease treated with methotrexate and leucovorin rescue, sustained remission in 82% with one course; hepatotoxicity occurred in 14% but abnormalities returned to normal within 2 weeks).

Rademaker M, Webb JA, Lowe DG, Meyrick-Thomas RH, Kirby JD, Munro DD. Magnetic resonance imaging as a screening procedure for methotrexate induced liver damage. Br J Dermatol. 1987;117:311–6. PubMed PMID: 3676081.

(Among 51 patients with psoriasis on methotrexate therapy, magnetic resonance imaging liver parameters did not correlate with either steatosis or fibrosis on liver biopsy).

Gispen JG, Alarcón GS, Johnson JJ, Acton RT, Barger BO, Koopman WJ. Toxicity of methotrexate in rheumatoid arthritis. J Rheumatol. 1987;14:74–9. PubMed PMID: 3572937.

(Among 72 patients with rheumatoid arthritis treated with oral methotrexate weekly, 55% had benefit and 74% had side effects, usually minor, but 7 were serious and 2 patients died both related to leukopenia and infection and not to liver injury).

Leonard PA, Clegg DO, Carson CC, Cannon GW, Egger MJ, Ward JR. Low dose pulse methotrexate in rheumatoid arthritis: an 8-year experience with hepatotoxicity. Clin Rheumatol. 1987;6:575–82. PubMed PMID: 3449308.

(Among 163 patients with rheumatoid arthritis treated with methotrexate for 0.3-7 years [total dose 0.1-3.1 g], serum enzyme elevations occurred at least once in 58% but led to discontinuation in only 5%; elevations did not correlate with alcohol use, age, dose or days relative to methotrexate dose).

Williams CN, McCauley D, Malatjalian DO, Turnbull GK, Ross JB. The aminopyrine breath test, an inadequate early indicator of methotrexate-induced liver disease in patients with psoriasis. Clin Invest Med. 1987;10:54–8. PubMed PMID: 3581546.

(Among 32 patients with psoriasis on methotrexate therapy, aminopyrine breath tests were abnormal [<7%] in none of 24 without fibrosis and 3 of 8 with fibrosis and, thus, were not accurate enough to replace liver biopsy in assessing progressive injury).

Shepard KV, Levin B, Faintuch J, Doria MI, DuBrow RA, Riddell RH. Hepatitis in patients receiving intraarterial chemotherapy for metastatic colorectal carcinoma. Am J Clin Oncol. 1987;10:36–40. PubMed PMID: 2950752.

(Among 51 patients with metastatic colon cancer treated with hepatic intra-arterial floxuridine [FUDR] and dichloromethotrexate or mitomycin, 47% developed liver injury and 25% were jaundiced, usually within 1-8 weeks of the first cycle [ALT 26-710 U/L, bilirubin 3-12.5 mg/dL], resolving in 1 week to 3 months, but two developed biliary stricture, cause likely to be FUDR).

Fried M, Kalra J, Ilardi CF, Sawitsky A. Hepatocellular carcinoma in a long-term survivor of acute lymphocytic leukemia. Cancer. 1987;60:2548–52. PubMed PMID: 2444327.

(28 year old woman presented with hepatocellular carcinoma and cirrhosis 22 years after diagnosis of acute leukemia treated successfully with mercaptopurine and methotrexate [6 years: total dose 4 g], with ALT 90 U/L, Alk P 538 U/L, bilirubin 1.3 mg/dL; no other cause of cirrhosis found, but published before availability of tests for hepatitis C).

Szanto E, Sandstedt B, Kollberg B. Hepatotoxicity associated with low-dose, long-term methotrexate treatment of rheumatoid arthritis. Scand J Rheumatol. 1987;16:229–34. PubMed PMID: 3629206.

(Among 17 patients with rheumatoid arthritis treated with methotrexate for 1-5 years, liver biopsies were normal in 16 with only mild fatty change and nuclear variability; 1 patient had mild fibrosis [0.6 g total dose and normal ALT levels]).

Weber BL, Tanyer G, Poplack DG, Reaman GH, Feusner JH, Miser JS, Bleyer WA. Transient acute hepatotoxicity of high-dose methotrexate therapy during childhood. NCI Monogr. 1987;5:207–12. PubMed PMID: 3481038.

(Among 24 children with acute leukemia treated with 75 cycles of very high dose methotrexate [33.6 g/24 hr] and leucovorin rescue, ALT elevations occurred in 30% after first course but in >92% after 3 courses, values reaching 1500 U/L, Alk P and bilirubin elevations peaking later, sometimes with symptoms, but without any long term clinically apparent consequences).

Zachariae H, Schrøder H, Foged E, Søgaard H. Methotrexate hepatotoxicity and concentrations of methotrexate and folate in erythrocytes - relation to liver fibrosis and cirrhosis. Acta Derm Venereol. 1987;67:336–40. PubMed PMID: 2445154.

(Assessment of red cell folate levels and liver histology in 30 patients with psoriasis receiving long term methotrexate therapy found no correlation of folate levels with severity of liver injury, duration of therapy or dose).

Zachariae H, Søgaard H. Methotrexate-induced liver cirrhosis. A follow-up. Dermatologica. 1987;175:178–82. PubMed PMID: 3653467.

(Analysis of 113 liver biopsies from 25 patients with psoriasis who developed cirrhosis on methotrexate therapy; cirrhosis found after 0.6-10 g [mean=3.1 g] of methotrexate; 21 patients were continued on therapy [at lowest possible dose and with prohibition against alcohol] for up to 9 years without evidence of worsening liver disease or clinical decompensation).

Hendel J, Poulsen H, Nyfors B, Nyfors A. Changes in liver histology during methotrexate therapy of psoriasis correlated to the concentration of methotrexate and folate in erythrocytes. Acta Pharmacol Toxicol (Copenh). 1985;56:321–6. PubMed PMID: 4024960.

(Letter in response to Zachariae et al. [1987] stressing the need to monitor serial red blood cell folate levels in assessing methotrexate hepatotoxicity).

Aponte J, Petrelli M. Histopathologic findings in the liver of rheumatoid arthritis patients treated with long-term bolus methotrexate. Arthritis Rheum. 1988;31:1457–64. PubMed PMID: 3196364.

(Among 23 patients with rheumatoid arthritis treated with methotrexate for more than 1 years [total dose 4.7-10.2 g] using weekly regimens, 52% had serum enzyme elevations and 21 underwent liver biopsy which was normal in 68% and showed mild fibrosis in 24%; none had severe fibrosis or cirrhosis).

Paramsothy J, Strange R, Shariff H, Collins M, Shaw P, Lawrence CM. The use of antipyrine clearance to measure liver damage in patients receiving methotrexate. Br J Dermatol. 1988;119:761–5. PubMed PMID: 3203069.

(Among 15 patients with psoriasis on methotrexate, antipyrine saliva clearance tests correlated with degree of liver abnormality, but without clear demarcation of abnormal result).

Banerjee AK, Lakhani S, Vincent M, Selby P. Dose-dependent acute hepatitis associated with administration of high dose methotrexate. Hum Toxicol. 1988;7:561–2. PubMed PMID: 3229766.

(18 year old girl with osteosarcoma given high dose methotrexate [20 g] and leucovorin rescue had rise of ALT to 908 U/L at day 10, rapidly falling to normal with minimal rise with subsequent dose of 0.8 g intravenously).

Bjorkman DJ, Hammond EH, Lee RG, Clegg DO, Tolman KG. Hepatic ultrastructure after methotrexate therapy for rheumatoid arthritis. Arthritis Rheum. 1988;31:1465–72. PubMed PMID: 3196365.

(Liver biopsy analyses in 26 patients treated with methotrexate for 1 to 10 years, most had some abnormality and all had increased collagen in space of Disse by electron microscopy; by light microscopy, 62% had steatosis, 12% inflammation and 15% mild pericentral fibrosis not seen in control biopsy material).

Kevat S, Ahern M, Hall P. Hepatotoxicity of methotrexate in rheumatic diseases. Med Toxicol Adverse Drug Exp. 1988;3:197–208. PubMed PMID: 3041245.

(Detailed review of liver histology changes associated with methotrexate use and authors' recommendations for liver biopsy before and during therapy [after 1.5 g and every 2 years thereafter]).

Lewis JH, Schiff E. Methotrexate-induced chronic liver injury: guidelines for detection and prevention. The ACG Committee on FDA-related matters. American College of Gastroenterology. Am J Gastroenterol. 1988;83:1337–45. PubMed PMID: 3057873.

(Review of methotrexate induced liver disease and recommendations for monitoring).

Kremer JM, Lee JK. A long-term prospective study of the use of methotrexate in rheumatoid arthritis. Update after a mean of fifty-three months. Arthritis Rheum. 1988;31:577–84. PubMed PMID: 3288222.

(Further follow up on cohort of 29 patients with rheumatoid arthritis treated with methotrexate for average of 4 years [2.5-6 years] found sustained improvements in 25 patients, 22 had at least one elevation in AST levels).

Risteli J, Sød H, Oikarinen A, Risteli L, Karvonen J, Zachariae H. Aminoterminal propeptide of type III procollagen in methotrexate-induced liver fibrosis and cirrhosis. Br J Dermatol. 1988;119:321–5. PubMed PMID: 3179204.

(Among 24 patients with psoriasis on methotrexate therapy, PIIIP elevations found in none of 9 with normal liver biopsy, 5 of 9 with fibrosis and 2 of 5 with cirrhosis).

Shergy WJ, Polisson RP, Caldwell DS, Rice JR, Pisetsky DS, Allen NB. Methotrexate-associated hepatotoxicity: retrospective analysis of 210 patients with rheumatoid arthritis. Am J Med. 1988;85:771–4. PubMed PMID: 3195601.

(Analysis of 538 liver biopsies done on 399 patients with various diagnoses being monitored during methotrexate therapy, found 2 with cirrhosis and 12 with fibrosis; but only 6 of 210 patients with rheumatoid arthritis had fibrosis and none had cirrhosis; the 6 with fibrosis included 5 with obesity, 3 with diabetes, but only one with liver test abnormalities [all <2 times ULN]).

Weinblatt ME, Trentham DE, Fraser PA, Holdsworth DE, Falchuk KR, Weissman BN, Coblyn JS. Long-term prospective trial of low-dose methotrexate in rheumatoid arthritis. Arthritis Rheum. 1988;31:167–75. PubMed PMID: 3279962.

(Among 26 patients with rheumatoid arthritis treated long term, 8 [31%] had ALT or AST elevations >2 times ULN, but all resolved and none required permanent discontinuation; liver biopsies done in 17 showed no fibrosis, but minor degrees of fat and inflammation [15 grade I, 2 grade II Roenigk changes]).

Roenigk HH Jr, Auerbach R, Maibach HI, Weinstein GD. Methotrexate in psoriasis: revised guidelines. J Am Acad Dermatol. 1988;19:145–56. PubMed PMID: 3042816.

(Expert advice and guidelines for use of methotrexate in psoriasis; recommends pretreatment liver biopsy, serum enzymes every 3-4 months, biopsy after 1.5 g total dose and repeat biopsies based upon liver test abnormalities and second biopsy results; discusses Roenigk grading system of I-IV and recommends stopping methotrexate if grades IIIB or IV are found).

Alarcón GS, Tracy IC, Blackburn WD Jr. Methotrexate in rheumatoid arthritis. Toxic effects as the major factor in limiting long-term treatment. Arthritis Rheum. 1989;32:671–6. PubMed PMID: 2735960.

(Among 152 patients with rheumatoid arthritis started on methotrexate, only 50% remained on long-term [>5 year] therapy; toxicity accounted for 60% of discontinuations; none were hepatic and liver biopsies in 9 showed no fibrosis).

McKendry RJ, Cyr M. Toxicity of methotrexate compared with azathioprine in the treatment of rheumatoid arthritis. A case-control study of 131 patients. Arch Intern Med. 1989;149:685–9. PubMed PMID: 2919941.

(Among 131 patients with rheumatoid arthritis treated for up to 5 years, elevated liver tests > twice the ULN occurred in 14% of 94 patients on methotrexate vs none of 37 on azathioprine).

Bridges SL Jr, Alarcón GS, Koopman WJ. Methotrexate-induced liver abnormalities in rheumatoid arthritis. J Rheumatol. 1989;16:1180–3. PubMed PMID: 2681761.

(Editorial on hepatotoxicity of methotrexate in rheumatoid arthritis comments on the infrequency of significant fibrosis in cohorts studied from the United States and recommends that routine pretreatment and during-treatment liver biopsies are not needed in patients with normal liver tests and no risk factors for liver disease).

Clegg DO, Furst DE, Tolman KG, Pogue R. Acute, reversible hepatic failure associated with methotrexate treatment of rheumatoid arthritis. J Rheumatol. 1989;16:1123–6. PubMed PMID: 2585411.

(Two women with rheumatoid arthritis developed liver disease on methotrexate; 38 year old developed steatosis and fibrosis after 4 years and cirrhosis with ascites after 5 years, improving on stopping therapy: Case 1; 54 year old with mild fibrosis on liver biopsy before therapy developed ascites and jaundice after two years, improving on stopping methotrexate).

O'Connor GT, Olmstead EM, Zug K, Baughman RD, Beck JR, Dunn JL, Seal P, et al. Detection of hepatotoxicity associated with methotrexate therapy for psoriasis. Arch Dermatol. 1989;125:1209–17. PubMed PMID: 2774596.

(Retrospective analysis of 147 liver biopsies done in 78 patients with psoriasis treated with methotrexate found fibrosis or cirrhosis in 5 [10%] before and 23 [24%] on therapy; individual liver tests had poor sensitivity and

specificity for detecting fibrosis, but authors developed an algorithm with reasonable accuracy; final model included age, sex, AST, Alk P, cholecystitis history and cumulative dose).

Kremer JM, Lee RG, Tolman KG. Liver histology in rheumatoid arthritis patients receiving long-term methotrexate therapy: a prospective study with baseline and sequential biopsy samples. Arthritis Rheum. 1989;32:121–7. PubMed PMID: 2920047.

(27 patients with rheumatoid arthritis treated with methotrexate for 1-6 years underwent 101 liver biopsies; no patient had fibrosis on pretreatment biopsy, but rates increased to 8% at 2, 16% at 3, and 40% at 4 years; correlated with duration of therapy, patient age and history of alcohol use, but not AST or ALT elevations which were often raised; no cirrhosis).

Kremer JM, Kaye GI. Electron microscopic analysis of sequential liver biopsy samples from patients with rheumatoid arthritis: correlation with light microscopic findings. Arthritis Rheum. 1989;32:1202–13. PubMed PMID: 2803323.

(Analysis of 52 liver biopsies from 22 patients with rheumatoid arthritis treated with methotrexate for 2-6 years found only minor, nonspecific changes by electron microscopy).

Rau R, Karger T, Herbern G, Fernzel H. Liver biopsy findings in patients with rheumatoid arthritis undergoing long-term treatment with methotrexate. J Rheumatol. 1989;16:489–93. PubMed PMID: 2473207.

(Analysis of liver biopsies from 60 patients with rheumatoid arthritis, comparing 60 from before therapy to 40 taken during therapy [mean total dose 1.3 g] found no significant difference using a semiquantitative analysis of 10 features including fibrosis, fat, ballooning, necrosis and inflammation; normal findings in 68% before vs 58% on therapy, fibrosis in 15% vs 25%; ALT elevations in 15% vs 50%).

Newman M, Auerbach R, Feiner H, Holzman RS, Shupack J, Migdal P, Culubret M, et al. The role of liver biopsies in psoriatic patients receiving long-term methotrexate treatment improvement in the abnormalities after cessation of treatment. Arch Dermatol. 1989;125:1218–24. PubMed PMID: 2774597.

(Retrospective analysis of 364 liver biopsies from 168 patients with psoriasis treated with methotrexate for 0 to 19 years [mean=4 years]; among 83 biopsies before therapy, 80% were normal, 20% had fibrosis, none cirrhosis [those with cirrhosis were not treated]; during treatment, fibrosis scores increased but rarely by much and most improved with subsequent withdrawal of therapy).

Brick JE, Moreland LW, Al-Kawas F, Chang WWL, Layne RD, DiBartolomeo AG. Prospective analysis of liver biopsies before and after methotrexate therapy in rheumatoid arthritis patients. Semin Arthritis Rheum. 1989;19:31–44. PubMed PMID: 2772658.

(Among liver biopsies done in 96 patients with rheumatoid arthritis before or after methotrexate therapy, fibrosis was found in 3% of 62 pretreatment and 10-12% of 88 posttreatment biopsies, cirrhosis was found in 2 patients, but alcohol was blamed in one instance).

Zachariae H, Søgaard H, Heickendorff L. Serum aminoterminal propeptide of type III procollagen. A non-invasive test for liver fibrogenesis in methotrexate-treated psoriatics. Acta Derm Venereol. 1989;69:241–4. PubMed PMID: 2566230.

(Serum PIIIP levels were assessed in 72 patients with psoriasis before or during methotrexate therapy; mean levels were higher in patients with fibrosis [5.2 vs 3.3 μg/L] but considerable overlap in values; serial results in 11 patients were normal in most).

Drosos AA, Psychos D, Andonopoulos AP, Stefanaki-Nikou S, Tsianos EB, Moutsopoulos HM. Methotrexate therapy in rheumatoid arthritis. A two year prospective follow-up. Clin Rheumatol. 1990;9:333–41. PubMed PMID: 2261732.

(Among 130 Greek patients with rheumatoid arthritis treated with methotrexate [7.5-15 mg/week] for up to 2 years, 25% developed raised serum enzymes, requiring discontinuation in 4%; liver biopsies in 41 patients [mean total dose 1550 mg] showed mild fibrosis in 15%, no cirrhosis and no correlation with ALT elevations).

Fries JF, Singh G, Lenert L, Furst DE. Aspirin, hydroxychloroquine, and hepatic enzyme abnormalities with methotrexate in rheumatoid arthritis. Arthritis Rheum. 1990;33:1611–9. PubMed PMID: 2242059.

(Among "nearly" 2,600 patients with rheumatoid arthritis in the ARAMIS database, abnormal ALT values were present in <5%, highest rates in those on salicylates [7.6%], sulindac [8.3%], methotrexate [9.5%] and lowest in those on hydroxychloroquine even in combination with methotrexate and salicylates).

Flowers MA, Heathcote J, Wanless IR, Sherman M, Reynolds WJ, Cameron RG, Levy GA, et al. Fulminant hepatitis as a consequence of reactivation of hepatitis B virus infection after discontinuation of low-dose methotrexate therapy. Ann Intern Med. 1990;112:381–2. PubMed PMID: 2306066.

(57 year old woman with rheumatoid arthritis and inactive HBsAg carrier state, developed severe hepatitis 22 days after stopping methotrexate [given for 7 years] for pulmonary toxicity with appearance of HBV DNA and IgM anti-HBc, progression to hepatic failure and successful liver transplantation after which she remained HBsAg positive; use of corticosteroids not mentioned).

Gilbert SC, Klintmalm G, Menter A, Silverman A. Methotrexate-induced cirrhosis requiring liver transplantation in three patients with psoriasis. A word of caution in light of the expanding use of this 'steroid-sparing' agent. Arch Intern Med. 1990;150:889–91. PubMed PMID: 2327848.

(Three patients with psoriasis underwent liver transplantation for methotrexate induced cirrhosis; ages 39, 46 and 59 years, treated for 5, 10 and 12 years, total doses of 9.5-26 g, presenting with anasarca, liver failure and variceal hemorrhage, two survived and had excellent remission in psoriasis; none had undergone surveillance liver biopsies; no mention of hepatitis C testing or alcohol history).

Kaito K, Katayama T, Yoshida M, Saito A, Kobayashi M, Ochiai S, Masuoka S, et al. Rinsho Ketsueki. 1990;31:1862–7. [Fulminant hepatic failure induced by intermediate dose methotrexate in a case of non-Hodgkin's lymphoma]. Japanese. PubMed PMID: 2287073.

Keim D, Ragsdale C, Heidelberger K, Sullivan D. Hepatic fibrosis with the use of methotrexate for juvenile rheumatoid arthritis. J Rheumatol. 1990;17:846–8. PubMed PMID: 2388211.

(17 year old girl with juvenile rheumatoid arthritis had a normal liver biopsy after 1.5 years of methotrexate therapy, but had mild fibrosis (Roenigk IIIA) on biopsy after 3.5 years and methotrexate was stopped; AST levels were minimally and transiently elevated during the first 2 years of therapy and repeatedly normal thereafter).

Gabriel S, Cregsen E, O'Fallen WM, Jaquith J, Bunch T. Treatment of rheumatoid arthritis with higher dose intravenous methotrexate. J Rheumatol. 1990;17:460–5. PubMed PMID: 2348423.

(Pilot study of intravenous, higher dose methotrexate for resistant rheumatoid arthritis; AST values increased by an average of 13 U/L; maximum level was 50 U/L).

Furst DE, Erickson N, Clute L, Koehnke R, Burmeister L, Kohler J. Adverse experience with methotrexate during 176 weeks of a long-term prospective trial in rheumatoid arthritis patients. J Rheumatol. 1990;17:1628–35. PubMed PMID: 2084236.

(Among 45 patients with rheumatoid arthritis treated with methotrexate for up to 3 years, 97% had side effects leading to dose modifications in 71%; ALT elevations above 3 times ULN occurred in 33% of patients, but were usually not a reason for changing the dose on their own).

Mitchell D, Smith A, Rowan B, Warnes TW, Haboubi NY, Lucas SB, Chalmers RJ. Serum type III procollagen peptide, dynamic liver function tests and hepatic fibrosis in psoriatic patients receiving methotrexate. Br J Dermatol. 1990;122:1–7. PubMed PMID: 2297495.

(PIIIP levels were measured in 51 patients with psoriasis on methotrexate for 1-13 years [10 with fibrosis, 3 cirrhosis] and controls; levels were often raised in treated patients [69%], but with somewhat poor correlation to hepatic histology and serum enzyme elevations; BSP and galactose clearance tests were similarly poorly predictive and of limited practicality).

Willkens RF, Leonard PA, Clegg DO, Tolman KG, Ward JR, Marks CR, Greene ML, et al. Liver histology in patients receiving low dose pulse methotrexate for the treatment of rheumatoid arthritis. Ann Rheum Dis. 1990;49:591–3. PubMed PMID: 2396863.

(Liver biopsies were done on 52 patients with rheumatoid arthritis treated with methotrexate [7.5-15 mg/week] for 2-8 years [773-3913 mg]; fibrosis found in 29%, cirrhosis in none, and only 2 were normal; grade of abnormality did not correlate with age, duration of treatment, total dose or serum enzyme elevations [elevated at least once in 90%]).

Odeh M. Methotrexate, liver abnormalities and RA. J Rheumatol. 1990;17:853–4. PubMed PMID: 2257004.

(Letter in response to Rau et al. [1989] arguing against the conclusion that methotrexate does not induce liver injury; reply by the authors).

Kujala GA, Shamma'a JM, Chang WL, Brick JE. Hepatitis with bridging fibrosis and reversible hepatic insufficiency in a woman with rheumatoid arthritis taking methotrexate. Arthritis Rheum. 1990;33:1037–41. PubMed PMID: 2369419.

(58 year old woman with rheumatoid arthritis on oral methotrexate 10 mg weekly for 6 years [2.7 g total dose] developed ascites with bilirubin 1.6 mg/dL, Alk P 100 U/L, ALT 12 U/L, albumin 3 g/dL, platelets 133,000 μ/L, liver biopsy showing bridging fibrosis, responding to diuretics).

Zachariae H. Methotrexate side-effects. Br J Dermatol. 1990;122 Suppl 36:127–33. PubMed PMID: 2196079.

(Review of side effects of methotrexate; table showing results of 25 patients with psoriasis who developed cirrhosis after 1-10 years of therapy [total dose 0.5-6.5 g], many of whom were able to continue methotrexate for another 1-8 years).

Weinblatt ME, Kaplan H, Germain BF, Merriman RC, Solomon SD, Wall B, Anderson L, et al. Low-dose methotrexate compared with auranofin in adult rheumatoid arthritis. A thirty-six-week, double-blind trial. Arthritis Rheum. 1990;33:330–8. PubMed PMID: 2180405.

(Among 281 patients with rheumatoid arthritis treated for 36 weeks, those treated with methotrexate had higher, earlier and better clinical responses; ALT elevations >2 times ULN occurred in 24% of methotrexate- vs 7% of gold-treated patients, requiring discontinuation in 6% vs 1.4%).

Schmiegelow K, Pulczynska M. Prognostic significance of hepatotoxicity during maintenance chemotherapy of childhood acute leukemia. Br J Cancer. 1990;61:767–72. PubMed PMID: 2337515.

(Among 115 children on maintenance chemotherapy for leukemia with methotrexate and mercaptopurine, ALT levels were on average elevated [>40 U/L] in 60% and this group had a lower rate of relapse; elevations tended to decrease over time during long-term therapy).

Rose CD, Singsen B, Eichenfield AH, Goldsmith DP, Athreya BH. Safety and efficacy of methotrexate therapy for juvenile rheumatoid arthritis. J Pediatr. 1990;117:653–9. PubMed PMID: 2213397.

(29 children with juvenile rheumatoid arthritis were treated with methotrexate [~7 mg/m^2/week] for 8 to 39 months; >80% response rate and only 1 child had ALT elevations, which were transient, resolving with dose reduction).

Martini A, Ravelli A, Viola S, Burgio RG. Methotrexate hepatotoxic effects in children with juvenile rheumatoid arthritis. J Pediatr. 1991;119:333–4. PubMed PMID: 1861227.

(Letter in response to Rose et al. [1990]; authors treated 27 children with methotrexate for 6 to 30 months [~9 mg/m^2] with 74% response rate; 56% had ALT elevations, all self-limiting or resolving with stopping).

Zachariae H, Aslam HM, Bjerring P, Sogaard H, Zachariae E, Heickendorff L. Serum aminoterminal propeptide of type III precollagen in psoriasis and psoriatic arthritis: relation to liver fibrosis and arthritis. J Am Acad Dermatol. 1991;25:50–3. PubMed PMID: 1880254.

(PIIIP levels were assessed in 170 patients with psoriasis being treated with methotrexate; levels were usually elevated in those with psoriatic arthritis [38% without fibrosis], but elevations in those with psoriasis alone were reliable markers for fibrosis or cirrhosis on liver biopsy [67% of 24] vs nonspecific or normal findings [4% of 52]; no correlation between ALT and PIIIP levels).

Mehdi A, Marteau P, Lavergne A, Molho-Sabatier P, Cochand-Priollet B, Caen J, Rambaud JC. Gastroenterol Clin Biol. 1991;15:464–5. [Hepatocellular carcinoma in a patient with psoriasis and methotrexate-induced cirrhosis]. French. PubMed PMID: 1649062.

(64 year old man with psoriasis presented with 16 cm hepatocellular carcinoma having a history of 2 years of therapy with methotrexate [total dose 3 g] and arsenic [1.5 g] 20 years earlier; negative for HCV, HBV and iron markers).

Scully CJ, Anderson CJ, Cannon GW. Long-term methotrexate therapy for rheumatoid arthritis. Semin Arthritis Rheum. 1991;20:317–31. PubMed PMID: 2068577.

(Analysis of 124 patients with rheumatoid arthritis treated with methotrexate, 39 for more than 5 years; elevated serum enzymes in 70% which resulted in stopping in 7%; 57 liver biopsies done in 40 patients after mean of 2.7 years [1.3 g] of which 17 [30%] showed fibrosis but none cirrhosis, but only 2 of these stopped therapy).

Hall PD, Ahern MJ, Jarvis LR, Stoll P, Jenner MA, Harley H. Two methods of assessment of methotrexate hepatotoxicity in patients with rheumatoid arthritis. Ann Rheum Dis. 1991;50:471–6. PubMed PMID: 1877853.

(Comparison of two methods of assessing collagen in serial liver biopsies from 18 patients with rheumatoid arthritis on methotrexate for 1-12 years; mild increases in pericellular collagen were best shown by computerized morphometry, but presence of collagen did not correlate with total methotrexate dose).

Ahern MJ, Kevat S, Hill W, Hayball PJ, Harley H, Hall PD. Hepatic methotrexate content and progression of hepatic fibrosis: preliminary findings. Ann Rheum Dis. 1991;50:477–80. PubMed PMID: 1715157.

(Among 16 patients with rheumatoid arthritis treated with methotrexate for 1-6 years undergoing paired liver biopsies and quantitative assessment of fibrosis [image analysis], the 3 patients with the most progression [>3.5%] had high levels of methotrexate and its glutamates in liver).

Wolfe F, Cathey MA. The effect of age on methotrexate efficacy and toxicity. J Rheumatol. 1991;18:973–7. PubMed PMID: 1920331.

(Among 235 patients with rheumatoid arthritis treated with methotrexate, at least one AST elevation occurred in 26% of 51 elderly [>65 years] compared to 31% of 184 younger patients).

Whiting-O'Keefe QE, Fye KH, Sack KD. Methotrexate and histologic hepatic abnormalities: a meta-analysis. Am J Med. 1991;90:711–6. PubMed PMID: 1828327.

(Metaanalysis of 15 studies of liver histology during long term, low dose methotrexate therapy in psoriasis [n=299] and rheumatoid arthritis [n=334]; progression in one Roenigk score after each gram of methotrexate in 6.9% of patients, correlating with cumulative dose and alcohol use; advanced fibrosis [Roenigk IIIB and IV] in 5%, higher in alcoholics and in psoriasis).

Singh G, Fries JF, Williams CA, Zatarain E, Spitz P, Bloch DA. Toxicity profiles of disease modifying antirheumatic drugs in rheumatoid arthritis. J Rheumatol. 1991;18:188–94. PubMed PMID: 1673721.

(Analysis of side effects of 7 agents from the ARAMIS database including 2,479 patients with rheumatoid arthritis [497 on methotrexate for 735 person-years] reported 41 instances of liver abnormalities and 2 of jaundice in patients on methotrexate, rates higher than gold, hydroxychloroquine, penicillamine, azathioprine and cyclophosphamide).

Watson RG, Smallwood RA. Low-dose methotrexate therapy and hepatotoxicity. The view of the hepatologist. Med J Aust. 1991;155:428–30. PubMed PMID: 1921807.

(Editorial on hepatotoxicity of long term, low dose methotrexate therapy stressed the lack of progression of fibrosis found in many publications and that 0-22% of patients had fibrosis and 0-1.5% had cirrhosis even before therapy; "the balance of evidence indicates that the risk of liver damage is small").

Grosflam J, Weinblatt ME. Methotrexate: mechanism of action, pharmacokinetics, clinical indications, and toxicity. Curr Opin Rheumatol. 1991;3:363–8. PubMed PMID: 1883690.

(Review of recent literature on mechanism of action, pharmacokinetics, clinical indications and toxicity; summary of 7 papers on hepatotoxicity).

Korman MG. Low-dose methotrexate therapy and hepatotoxicity. Med J Aust. 1992;156:221. PubMed PMID: 1545730.

(Letter in response to Watson and Smallwood [1991] questioning wisdom of using routine liver tests to monitor for methotrexate liver injury).

Aponte J, Petrelli M, von Dawson N. Liver enzyme levels in arthritis patients treated with long-term bolus methotrexate. Arthritis Rheum. 1992;35:126–8. PubMed PMID: 1346249.

(Analysis of ALT, AST and GGT levels in 40 patients treated with methotrexate for more than 10 years found no difference in serum enzymes or liver histology in patients with or without concurrent hydroxychloroquine treatment).

Kremer JM, Phelps CT. Long term prospective study of the use of methotrexate in the treatment of rheumatoid arthritis: update after mean of 90 months. Arthritis Rheum. 1992;35:138–45. PubMed PMID: 1734902.

(Update on clinical trial of long term methotrexate in 29 patients with rheumatoid arthritis, including 18 patients still on therapy [for 6-9 years; total dose ~6 g]; no discussion of hepatotoxicity).

Kremer JM. Liver biopsies in patients with rheumatoid arthritis receiving methotrexate. Where are we going? J Rheumatol. 1992;19:189–91. PubMed PMID: 1629814.

(Editorial on liver biopsy recommendations for patients with rheumatoid arthritis receiving methotrexate; recommended baseline biopsy only for patients with abnormal liver tests or at high risk for having liver disease and repeat biopsy on therapy for repeated AST elevations or decrease in serum albumin, stopping therapy if significant fibrosis is found [Roenigk grade IIIB or IV]).

Tishler M, Caspi D, Halperin Z, Baratz M, Moshkowitz M, Yaron M. A prospective analysis of liver biopsies in rheumatoid arthritis patients receiving long term methotrexate therapy. Rheumatol Int. 1992;12:39–41. PubMed PMID: 1598500.

(Analysis of paired liver biopsies from 10 patients with rheumatoid arthritis before and after methotrexate therapy for 4-7.5 years [total dose 1.4 to 7.5 g], showed no progression in fibrosis, despite AST elevations in 30%; 1 patient had mild fibrosis before therapy and amount did not change).

Graham LD, Myones BL, Rivas-Chacon RF, Pachman LM. Morbidity associated with long-term methotrexate therapy in juvenile rheumatoid arthritis. J Pediatr. 1992;120:468–73. PubMed PMID: 1538301.

(Among 62 children with juvenile rheumatoid arthritis treated with methotrexate for 1-6 years, 9 had ALT elevations [119-1500 U/L], resolving with stopping but no recurrence on restarting; liver biopsy in 12 [after 0.8 to 1.4 g] found none with fibrosis).

Locasciulli A, Mura R, Fraschini D, Gornati GL, Scoven E, Gervasoni A, Uderzo C, et al. High-dose methotrexate administration and acute liver damage in children treated for acute lymphoblastic leukemia. A prospective study. Haematologica. 1992;77:49–53. PubMed PMID: 1398282.

(Among 68 children with acute leukemia treated with high dose methotrexate monitored with liver tests before and 1 and 2 weeks after each of 272 courses, 88% had ALT elevations during induction courses and 38% during consolidation; 85% had mild indirect hyperbilirubinemia, but only 1 patient had hepatotoxicity [peak ALT 700 U/L and jaundice], which resolved rapidly).

Phillips CA, Cera PJ, Mangan TF, Newman ED. Clinical liver disease in patients with rheumatoid arthritis taking methotrexate. J Rheumatol. 1992;19:229–33. PubMed PMID: 1629819.

(Among 134 patients with rheumatoid arthritis treated with methotrexate, 3 [2%] developed histologic signs of severe liver disease; ages 58-68 years, treated for 2-4 years [total dose 1.3-1.6 g] with biopsy showing advanced fibrosis [n=2] or cirrhosis [n=1], 2 with ascites, 1 died; none were alcoholic, 2 had normal pretreatment biopsy; AST levels elevated on therapy in 2, GGT in the third).

Themido R, Loureiro M, Pecegueiro M, Brandão M, Campos MC. Methotrexate hepatotoxicity in psoriatic patients submitted to long-term therapy. Acta Derm Venereol. 1992;72:361–4. PubMed PMID: 1361285.

(Analysis of paired liver biopsies done in 30 Portuguese patients with psoriasis before and on methotrexate [0.2-7 g], 8 had fibrosis before therapy; 7 [23%] developed fibrosis and 3 [10%] cirrhosis on treatment).

McHenry PM, Bingham EA, Callender ME, Delvin PB, O'Hara MD, Ferguson WR, Laird JD, et al. Dynamic hepatic scintigraphy in the screening of patients for methotrexate-induced hepatotoxicity. Br J Dermatol. 1992;127:122–5. PubMed PMID: 1390139.

(Among 63 patients with psoriasis having 87 dynamic scintigraphy scans during methotrexate therapy, 20 scans were abnormal, including 83% of 6 with moderate-severe fibrosis and 22% of 81 without fibrosis).

Weinblatt ME, Weissman BN, Holdsworth DE, Fraser PA, Maier AL, Falchuk KR, Coblyn JS. Long-term prospective study of methotrexate in the treatment of rheumatoid arthritis: 84-month update. Arthritis Rheum. 1992;35:129–37. PubMed PMID: 1734901.

(26 patients with rheumatoid arthritis enrolled in study of methotrexate [7.5-15 mg weekly], liver biopsies showed no fibrosis at 2 years [n=17; mean dose 1.1 g], one at 4 years [n=15; 2.0 g], and another at 6 years [n=10, 3.1 g]; both cases were Roenigk IIIA only, but both had normal biopsy previously).

Arias JM, Morton KA, Albro TE, Patch GG, Valdivia S, Greenberg HE, Christian PE, et al. Comparison of methods for identifying early methotrexate-induced hepatotoxicity in patients with rheumatoid arthritis. J Nucl Med. 1993;34:1905–9. PubMed PMID: 8229232.

(Analysis of 16 patients undergoing 22 sets of noninvasive tests of liver disease while on methotrexate for 0.5 to 8 years; comparing 13 patients with minimal or no histologic changes to 9 patients with Roenigk II and III changes, liver enzymes were elevated in 0% vs 22%, aminopyrine breath tests 54% vs 55%, hepatic technetium scans 0% vs 11%; none being adequately sensitive and specific compared to liver biopsy).

Walker AM, Funch D, Dreyer NA, Tolman KG, Kremer JM, Alarcón GS, Lee RG, et al. Determinants of serious liver disease among patients receiving low-dose methotrexate for rheumatoid arthritis. Arthritis Rheum. 1993;36:329–35. PubMed PMID: 8452577.

(In a survey of 107 US rheumatologists, they identified 24 verifiable cases of cirrhosis attributable to methotrexate and compared them to 39 matched controls; patients with cirrhosis were older [54 vs 42 years],

received a higher cumulative dose [1.9 vs 0.7 g], but did not differ by body weight, diabetes, sex, other medication use or recorded alcohol use; estimated rate of serious liver disease as 0.1% after 5 years of methotrexate use).

Minocha A, Dean HA, Pittsley RA. Liver cirrhosis in rheumatoid arthritis patients with long-term methotrexate. Vet Hum Toxicol. 1993;35:45–8. PubMed PMID: 8434456.

(Among 25 patients with rheumatoid arthritis undergoing 29 surveillance liver biopsies during methotrexate therapy [1-5 years], 1 had fibrosis and 2 cirrhosis [both had elevations in serum enzymes and were obese and diabetic]).

Brass EP. Hepatic toxicity of antirheumatic drugs. Cleve Clin J Med. 1993;60:466–72. PubMed PMID: 8287508.

(Short review of hepatotoxicity of nonsteroidals, salicylates, methotrexate, penicillamine and gold).

Nohlgård C, Rubio CA, Kock Y, Hammar H. Liver fibrosis quantified by image analysis in methotrexate-treated patients with psoriasis. J Am Acad Dermatol. 1993;28:40–5. PubMed PMID: 7678843.

(Sirius red staining on 46 liver biopsies from 26 patients with psoriasis analyzed by image analysis found higher percent of fibrosis in patients with psoriasis than controls [0.9%], but no correlation with methotrexate therapy, total dose, nor with Roenigk classification [Grade I with 11.4%, IIIA with 9.3%, IIIB 24% and IV 11.8%]).

Carvallo A, Wolff C, Armas R, Villanueva P, Donoso G, Náira N, Lobo G, et al. Rev Med Chil. 1993;121:777–84. [Rheumatoid arthritis. Therapeutic efficacy of methotrexate and its hepatotoxic effects]. Spanish. PubMed PMID: 8296082.

Lacki JK, Samborski W, Machiewicz SH. Transient increase of aminotransferases in RA patients treated with methotrexate. Z Rheumatol. 1993;52:232–5. PubMed PMID: 8212923.

Shiroky JB, Neville C, Esdaile JM, Choquette D, Summer M, Hazeltine M, Bykerk V, et al. Low-dose methotrexate with leucovorin(folinic acid) in the management of rheumatoid arthritis. Results of a multicenter randomized, double-blind, placebo-controlled trial. Arthritis Rheum. 1993;36:795–803. PubMed PMID: 8507221.

(Among 92 patients with rheumatoid arthritis treated with methotrexate and either placebo or folinic acid, there were fewer side effects in those on folate [60% reduction in enzyme elevations] with no difference in efficacy).

McKendry RJ, Dale P. Adverse effects of low dose methotrexate therapy in rheumatoid arthritis. J Rheumatol. 1993;20:1850–6. PubMed PMID: 8308769.

(Among 144 patients with rheumatoid arthritis starting methotrexate therapy, 75% stopped therapy before 5 years; 53% for adverse events, 14% for elevated liver tests, usually in first 2 years).

Morgan SL, Baggott JE, Vaughn WH, Austin JS, Veitch TA, Lee JY, Koopman WJ, et al. Supplementation with folic acid during methotrexate therapy for rheumatoid arthritis. A double-blind placebo-controlled trial. Ann Intern Med. 1994;121:833–41. PubMed PMID: 7978695.

(79 patients with rheumatoid arthritis treated with methotrexate were given placebo or 5 or 27.5 mg of folate weekly; efficacy was similar, but side effects were less with folate treatment, particularly at higher dose; also prevented folate deficiency which occurred by one year in placebo recipients).

Kremer JMAlarcon GSLightfoot RWWilkens RFFurst DEWillliams HJDent PB,

Kremer JM, Alarcón GS, Lightfoot RW Jr, Willkens RF, Furst DE, Williams HJ, Dent PB, et al. Methotrexate for rheumatoid arthritis. Suggested guidelines for monitoring liver toxicity. Arthritis Rheum. 1994;37:316–28. PubMed PMID: 8129787.

(Review of hepatotoxicity of methotrexate in rheumatoid arthritis and delineation of guidelines; among 295 biopsies taken before therapy, only 3.7% had fibrosis and none cirrhosis, compared to fibrosis rates of 15% and cirrhosis of 0.3% on treatment; ALT elevations >2 times ULN occurred in 3.4% on methotrexate vs 0.4% on placebo or gold usually during first 2-3 years; recommend pretreatment biopsy only in patients with raised enzymes or risk factors for liver disease, regular liver test monitoring at 4-8 week intervals and repeat liver biopsy if AST elevations occur [at least 5] or albumin levels fall; discontinue if Roenigk grade IIIB or IV or if AST elevations present and unable to do liver biopsy).

Petrazzuoli M, Rothe MJ, Grin-Jorgensen C, Ramsey WH, Grant-Kels JM. Monitoring patients taking methotrexate for hepatotoxicity. J Am Acad Dermatol. 1994;31:969–77. PubMed PMID: 7962779.

(Survey of 70 gastroenterologists in practice; only 33% were monitoring patients with psoriasis or rheumatoid arthritis on methotrexate therapy).

Breithaupt H. Z Rheumatol. 1994;53:250–4. [Drug-induced liver damage caused by antirheumatic drugs - antirheumatic therapy in pre-existing liver damage]. German. PubMed PMID: 7975937.

Exadaktylos P, Reiss T, Schobess R, Hommann M, Höhne S, Beck A. Klin Padiatr. 1994;206:315–8. [Acute hepatotoxicity with intermediate-dose methotrexate in children with leukemia and non-Hodgkin's lymphoma]. German. PubMed PMID: 7967431.

Fabbri A, Motta E, Ferrari S, Longhi C, Marchi E, Bacci G, Figus E, et al. High-dose methotrexate treatment and liver function in patients with osteosarcoma. J Intern Med. 1994;236:209–14. PubMed PMID: 8046321.

(Among 14 patients with osteosarcoma who had received high dose methotrexate therapy [30-57 g/m^2], galactose elimination decreased minimally while aminopyrine clearance and routine liver tests did not change between baseline and end of therapy).

Goodman TA, Polisson RP. Methotrexate: adverse reactions and major toxicities. Rheum Dis Clin North Am. 1994;20:513–28. PubMed PMID: 8016424.

(Review of side effects of methotrexate therapy in rheumatoid arthritis).

Schnabel A, Reinhold-Keller E, Willmann V, Gross WL. Tolerability of methotrexate starting with 15 or 25 mg/week for rheumatoid arthritis. Rheumatol Int. 1994;14:33–8. PubMed PMID: 7939138.

(Controlled trial of methotrexate starting at either 15 or 25 mg/week in 168 patients with rheumatoid arthritis found slightly higher side effects with higher initial dose, but similar withdrawal rates [~23%] at 12 months; ALT or AST elevations occurred in 38% starting with 15 mg/week and 44% with 25 mg/week).

Van Dooren-Greebe RJ, Kuijpers AL, Mulder J, De Boo T, Van de Kerkhof PC. Methotrexate revisited: effects of long-term treatment in psoriasis. Br J Dermatol. 1994;130:204–10. PubMed PMID: 8123573.

(Retrospective analysis of 113 patients with psoriasis treated with methotrexate [7.5-15 mg/week] for an average of 9 years [mean total dose 4.8 g]; methotrexate was discontinued in 71 patients, 12 [17%] for liver test abnormalities; 105 liver biopsies done in 55 patients, 7 [13%] had fibrosis and 2 [4%] cirrhosis with poor correlation with total dose, duration of therapy or abnormal liver tests).

Chandran G, Ahern MJ, Hall PD, Geddes R, Smith MD, Hill W, Harley JH. Cirrhosis in patients with rheumatoid arthritis receiving low dose methotrexate. Br J Rheumatol. 1994;33:981–4. PubMed PMID: 7921763.

(Three cases; 68-70 year old men with long standing rheumatoid arthritis treated with methotrexate for 5, 7 and 11 years [3.9, 7.2 and 10 g total dose] presented with varices or ascites; 2 had no alcohol use and all had minimally and only intermittently abnormal AST values during long term monitoring).

Bergquist SR, Felson DT, Prashker MJ, Freedberg KA. The cost-effectiveness of liver biopsy in rheumatoid arthritis patients treated with methotrexate. Arthritis Rheum. 1995;38:326–33. PubMed PMID: 7880186.

(Cost effectiveness of liver biopsy during methotrexate therapy was dependent on the likelihood of cirrhosis and was $52,000 per year of life saved at 10 years, but $1.9 million per year of life saved at 5 years).

Kremer JM, Kaye GI, Kaye NW, Ishak KG, Axiotis CA. Light and electron microscopic analysis of sequential liver biopsy samples from rheumatoid arthritis patients receiving long-term methotrexate therapy: follow up over long treatment intervals and correlation with clinical and laboratory variables. Arthritis Rheum. 1995;38:1194–203. PubMed PMID: 7575712.

(Analysis of 170 liver biopsies from 27 patients with rheumatoid arthritis treated with methotrexate for 2 to 11 years [0.8-10.4 g]; there were minimal increases in average Roenigk score [1.8 at baseline to 2.3 at year 3 and 2.4 at year 6] and no significant change in semiquantitative estimates of electron microscopic features of fat, bile, collagen or smooth endoplasmic reticulum).

Oogarah PK, Rowland PL, Mitchell DM, Smith A, Chalmers RG, Rowan B, Haboubi NY. Abnormalities of serum type III procollagen aminoterminal peptide in methotrexate-treated psoriatic patients with normal liver histology do not correlate with hepatic ultrastructural changes. Br J Dermatol. 1995;133:512–8. PubMed PMID: 7577576.

(Electron microscopic analysis of liver biopsies described by Mitchell et al. [1990] showed no correlation of changes with PIIIP levels; collagen in space of Disse present in 82% of biopsies and amount did not correlate with light microscopic or PIIIP elevations).

al-Lamki Z, Thomas E, el-Banna N, Jaffe N. Acute urticaria and hepatitis complicating high-dose methotrexate therapy. Med Pediatr Oncol. 1995;24:137–40. PubMed PMID: 7990763.

(3.5 year old girl with osteosarcoma given 22 courses of methotrexate with leucovorin rescue with excellent response, but then had anaphylactic reaction with 23rd course with urticaria, facial edema, and jaundice [bilirubin 19.7 mg/dL, ALT 4278 U/L, LDH 10,968 U/L, protime 15.3 sec], resolving in 4 weeks with immediate erythema and nausea on brief methotrexate rechallenge).

Boffa MJ, Chalmer RJ, Haboubi NY, Shomaf M, Mitchell DM. Sequential liver biopsies during long-term methotrexate treatment for psoriasis: a reappraisal. Br J Dermatol. 1995;133:774–8. PubMed PMID: 8555032.

(Analysis of 124 liver biopsies taken from 49 patients with psoriasis treated with methotrexate; between the initial and last biopsy, 24% improved, 57% did not change and 18% worsened, but none developed cirrhosis and rates of fibrosis fell from 22% to 20% despite another average 2.4 g of methotrexate).

Erickson AR, Reddy V, Vogelgesang SA, West SG. Usefulness of the American College of Rheumatology recommendations for liver biopsy in methotrexate-treated rheumatoid arthritis. Arthritis Rheum. 1995;38:1115–9. PubMed PMID: 7639808.

(Using the initial Psoriatic Task Force recommendations, 66 of 112 patients with rheumatoid arthritis treated with methotrexate underwent 110 liver biopsies and 5 were found to have advanced fibrosis or cirrhosis [Roenigk IIIB or IV], whereas applying the new American College of Rheumatology guidelines only 15 would have undergone 18 biopsies and 4 of the 5 with advanced fibrosis would have been identified, the case of cirrhosis missed being a patient with diabetes and perhaps deserving histological monitoring).

Lower EE, Baughman RP. Prolonged use of methotrexate for sarcoidosis. Arch Intern Med. 1995;155:846–51. PubMed PMID: 7717793.

(Among 50 patients with sarcoidosis treated with methotrexate for 2-6 years, liver biopsy histology became abnormal in 6 [15%], but findings were not reflected in serum enzyme elevations).

Reiff A, Shaham B, Wood BP, Bernstein BH, Stanley P, Szer IS. High dose methotrexate in the treatment of refractory juvenile rheumatoid arthritis. Clin Exp Rheumatol. 1995;13:113–8. PubMed PMID: 7774090.

(Use of higher doses of methotrexate in 21 children with severe juvenile rheumatoid arthritis was beneficial in only 33% of patients; transient ALT or AST elevations occurred in 38% and all resolved with holding dose, not requiring permanent discontinuation).

Tamaro G, Danek GM, Mangiarotti MA, Tamaro P, Zanazzo GA. Methotrexate therapy and liver fibrosis: are human prolyl hydroxylase and type IV collagen reliable and sensitive markers? Int J Clin Lab Res. 1995;25:55. PubMed PMID: 7787212.

(Among 13 children with leukemia treated with high dose methotrexate, 62% had elevations in serum prolyl hydroxylase and type IV collagen, suggesting that these tests may identify patients with significant liver injury; but histological verification was not done).

Salaffi F, Carotti M, Sartini A, Cervini C. A prospective study of the long-term efficacy and toxicity of low-dose methotrexate in rheumatoid arthritis. Clin Exp Rheumatol. 1995;13:23–8. PubMed PMID: 7774099.

(Among 51 Italian patients with rheumatoid arthritis treated with methotrexate weekly for up to 3 years, 14% had transient ALT or AST elevations, all resolving spontaneously or with dose modification).

Franck H, Rau R, Herborn G. Thrombocytopenia in patients with rheumatoid arthritis on long-term treatment with low dose methotrexate. Clin Rheumatol. 1996;15:163–7. PubMed PMID: 8777850.

(Among 315 patients with rheumatoid arthritis treated with methotrexate, 13 developed thrombocytopenia [<100,000/μL], after 1-100 [mean=41] months of therapy [mean total dose 1.9 g], most instances improved when methotrexate or other medications were withdrawn).

ter Borg EJ, Seldenrijk CA, Timmer R. Liver cirrhosis due to methotrexate in a patient with rheumatoid arthritis. Neth J Med. 1996;49:244–6. PubMed PMID: 8990864.

(49 year old woman with rheumatoid arthritis underwent liver biopsy after ~8 years of methotrexate therapy [total dose 6 g] with ALT 52 U/L, Alk P 180 U/L, albumin 3.5 g/dL, and platelet count 76,000/μL; ultrasound showed splenomegaly; biopsy [previously normal] showing early cirrhosis; liver tests fell to normal on stopping methotrexate but platelets remained low [124,000/μL]).

Dufour JF, Kaplan MM. Methotrexate therapy and liver disease. N Engl J Med. 1996;335:898–9. PubMed PMID: 8778622.

(Patient with sclerosing cholangitis started on methotrexate had an increase in ALT [rising from 51 to 467 U/L] for two months, but a liver biopsy showed no change from earlier specimen and ALT levels subsequently fell to normal).

Furuya T, Totokawa S, Nakajima A, Suzuki T, Kashiwazaki S. Ryumachi. 1996;36:746–52. [Adverse effects of low-dose methotrexate therapy in rheumatoid arthritis]. Japanese. PubMed PMID: 8969553.

Kawabe Y, Eguchi K, Tsuboi M, Kita M, Tsukada T, Takashima H, Mizokami A, et al. Ryumachi. 1996;36:514–21. [Untoward effects of low dose methotrexate therapy in rheumatoid arthritis]. Japanese. PubMed PMID: 8779788.

Malatjalian 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;10:369–75. PubMed PMID: 9193771.

(Among 104 patients with psoriasis treated with methotrexate for 1-11 years undergoing 477 liver biopsies, 7% had mild fibrosis before treatment; 46% developed fibrosis [26% mild, 20% moderate] and 3% cirrhosis; progression to fibrosis correlating with diabetes, but not social alcohol intake).

Kugathasan S, Newman AJ, Dahms BB, Boyle JT. Liver biopsy findings in patients with juvenile rheumatoid arthritis receiving long-term, weekly methotrexate therapy. J Pediatr. 1996;128:149–51. PubMed PMID: 8551408.

(Nine children with juvenile rheumatoid arthritis treated for at least 3 years with weekly methotrexate [total dose 0.8-2.3 g] underwent liver biopsy and all were normal [Roenigk I], and only one had mild steatosis).

vanDooren-Greebe RJ, Kuijpers AL, Buijs WC, Kniest PH, Corstens FH, Nagengast FM, de Boo T, et al. The value of dynamic hepatic scintigraphy and serum aminoterminal propeptide of type III procollagen for early detection of methotrexate-induced hepatic damage in psoriasis patients. Br J Dermatol. 1996;134:481–7. PubMed PMID: 8731673.

(25 patients with psoriasis treated with methotrexate [total dose 0.2-11 g; mean 3.9 g] underwent liver biopsy, PIIIP testing and dynamic scintigraphy; only 1 patient had fibrosis [Roenigk IIIA] who had both an elevated PIIIP and abnormal scan).

Biasi D, Bambara LM, Carletto A, Casaril M, Capra F, Caramaschi P, Corrocher R. Effects on fibrogenesis markers of rheumatoid arthritis therapy with methotrexate. J Rheumatol. 1996;23:453–4. PubMed PMID: 8832981.

(Among 20 patients with rheumatoid arthritis treated with methotrexate for 1 year, PIIIP levels were slightly higher than controls before therapy but actually decreased on average during therapy, while laminin levels did not change).

Jaskiewicz K, Voigt H, Blakolmer K. Increased matrix proteins, collagen and transforming growth factor are early markers of hepatotoxicity in patients on long-term methotrexate therapy. J Toxicol Clin Toxicol. 1996;34:301–5. PubMed PMID: 8667468.

(76 liver biopsies from 36 patients with psoriasis treated with methotrexate for 1-5 years were studied by immunohistochemistry showing slight and progressive increases in laminin, fibronectin and collagen in biopsies, with minimal or no changes by light microscopy).

Rebora A. Is methotrexate liver toxicity modest worldwide? Br J Dermatol. 1996;135:1003–4. PubMed PMID: 8977730.

(Letter in response to Boffa et al. [1995] raising issue of hepatitis C contributing to apparent hepatotoxicity of methotrexate; reply by authors that HCV testing was not done but is rare in Manchester UK).

Weinblatt ME. Methotrexate in rheumatoid arthritis: toxicity issues. Br J Rheumatol. 1996;35:403–5. PubMed PMID: 8646427.

(Editorial on methotrexate hepatotoxicity and guidelines for monitoring).

Zachariae H, Sød H, Heickendorff L. Methotrexate-induced liver cirrhosis. Clinical, histological and serological studies - a further 10-year follow-up. Dermatology. 1996;192:343–6. PubMed PMID: 8864370.

(Long term follow up on 25 patients with psoriasis who developed cirrhosis on methotrexate therapy [reported in 1987]; the majority continued on lower doses of methotrexate and tolerated therapy well; 13 died, but only one of liver failure [all with autopsies had cirrhosis]; 13 appeared not to have cirrhosis on follow up liver biopsy and PIIIP levels were largely normal, suggesting that methotrexate induced cirrhosis is rarely progressive even with continuing therapy, at least at low doses).

Boffa MJ, Smith A, Chalmer RJG, Mitchell DM, Rowan B, Warnes TW, Shomaf M, et al. Serum type III procollagen aminopeptide for assessing liver damage in methotrexate-treated psoriasis patients. Br J Dermatol. 1996;135:538–44. PubMed PMID: 8915142.

(Serum PIIIP levels were measured at time of 147 liver biopsies in 87 patients with psoriasis on methotrexate; raised PIIIP levels found in 18% of 28 patients with a normal biopsy, 42% of 12 with steatosis, 54% of 26 with inflammation, 78% of 18 with fibrosis and 100% of 3 with cirrhosis; among 17 patients followed serially, elevations in PIIIP occurred in all 6 with progression vs only 3 of 11 without).

Kremer JM, Furst DE, Weinblatt ME, Blotner SD. Significant changes in serum AST across hepatic histological biopsy grades: prospective analysis of 3 cohorts receiving methotrexate therapy for rheumatoid arthritis. J Rheumatol. 1996;23:459–61. PubMed PMID: 8832983.

(Among 94 patients with rheumatoid arthritis treated with methotrexate who underwent 354 liver biopsies, AST levels were higher in those with higher Roenigk scores and elevations were associated with abnormal liver biopsy grade).

Bologna C, Viu P, Picot MC, Jorgensen C, Sany J. Long-term follow-up of 453 rheumatoid arthritis patients treated with methotrexate: an open retrospective, observational study. Br J Rheumatol. 1997;36:535–40. PubMed PMID: 9189054.

(Among 453 French patients with rheumatoid arthritis treated with methotrexate given weekly for an average of 3 years [0.3 to 9 years], 13% had elevated liver tests leading to withdrawal in 2.3%; no deaths from liver disease and no mention of cirrhosis or liver biopsies).

Beyeler C, Reichen J, Thomann SR, Lauterburg BH, Gerber NJ. Quantitative liver function in patients with rheumatoid arthritis treated with low-dose methotrexate: a longitudinal study. Br J Rheumatol. 1997;36:338–44. PubMed PMID: 9133966.

(Among 117 patients with rheumatoid arthritis treated with methotrexate and monitored yearly with galactose elimination, aminopyrine breath tests and bile acids, there was a decline in liver function tests with little correlation with routine test abnormalities; elevations in ALT occurred in 8%, GGT in 23%, bile acid levels in 2.4%; no correlation found between Roenigk score and decline in liver function tests in 16 patients with liver biopsy).

Hashkes PJ, Balistreri WF, Bove KE, Ballard ET, Passo MH. The long-term effect of methotrexate therapy on the liver in patients with juvenile rheumatoid arthritis. Arthritis Rheum. 1997;40:2226–34. PubMed PMID: 9416861.

(Liver biopsies done on 14 children with juvenile rheumatoid arthritis treated with long term methotrexate found no fibrosis but minor changes found in 13, anisonucleosis, mild portal or lobular inflammation, and 3 with mild steatosis).

Kremer JM. Safety, efficacy, and mortality in a long-term cohort of patients with rheumatoid arthritis taking methotrexate: followup after a mean of 13.3 years. Arthritis Rheum. 1997;40:984–5. PubMed PMID: 9153566.

(Further follow up on initial cohort of 29 patients with rheumatoid arthritis [Kremer 1986] treated with long term methotrexate; 52% of patients remained on therapy for >10 years; 9 of the cohort had died, none of liver disease; among 10 still actively followed [mean total dose 9.7 g], none had clinically apparent liver disease).

Lewis JH. Monitoring for methotrexate hepatotoxicity in patients with rheumatoid arthritis: another hepatologist's perspective. J Rheumatol. 1997;24:1459–60. PubMed PMID: 9263133.

(Editorial on methotrexate hepatotoxicity in rheumatoid arthritis endorsing the use of serial ALT and AST determinations to identify patients at risk of developing significant fibrosis during therapy and thus avoiding liver biopsy in most patients).

Stein CM, Brooks RH, Pincus T. Effect of combination therapy with cyclosporine and methotrexate on liver function test results in rheumatoid arthritis. Arthritis Rheum. 1997;40:1721–3. PubMed PMID: 9324030.

(No differences in ALT elevations between patients on methotrexate alone [3%] vs its combination with cyclosporine [2%] for 24 weeks).

Kremer JM. Liver toxicity does not have to follow methotrexate therapy of patients with rheumatoid arthritis. Am J Gastroenterol. 1997;92:194–6. PubMed PMID: 9040190.

(Editorial on issue of monitoring patients with rheumatoid arthritis on methotrexate therapy suggested that frequent determinations of ALT and AST [at least 9 per year] allows for identification of patients at risk for developing progressive fibrosis; those with >50% of values elevated based upon results from Kremer et al. 1996).

West SG. Methotrexate hepatotoxicity. Rheum Dis Clin North Am. 1997;23:883–915. PubMed PMID: 9361160.

(Extensive review of methotrexate hepatotoxicity with discussion of both Psoriasis Task Force and American College of Rheumatology recommendations).

Ahern MJ, Smith MD, Roberts-Thomson PJ. Methotrexate hepatotoxicity: what is the evidence? Inflamm Res. 1998;47:148–51. PubMed PMID: 9628257.

(Editorial on American College of Rheumatology recommendations for monitoring for liver injury during methotrexate therapy of rheumatoid arthritis, guidelines prudent but of unproven benefit).

Hakim NS, Kobienia B, Benedetti E, Bloomer J, Payne WD. Methotrexate-induced hepatic necrosis requiring liver transplantation in a patient with rheumatoid arthritis. Int Surg. 1998;83:224–5. PubMed PMID: 9870779.

(40 year old man with rheumatoid arthritis developed acute liver failure after 6 months of methotrexate therapy when he presented with rapid rise in ALT ["levels of several thousands"] and presence of HBsAg without anti-HBc in serum requiring liver transplantation, but no information on HBsAg status in follow up).

Narváez J, Rodriguez-Moreno J, Martinez-Aguilá MD, Clavaguera MT. Severe hepatitis linked to B virus infection after withdrawal of low dose methotrexate therapy. J Rheumatol. 1998;25:2037–8. PubMed PMID: 9779869.

(67 year old man with rheumatoid arthritis treated with methotrexate [7.5 mg/week] and prednisone [5 mg/day] for 2 years [previous HBsAg status not known] developed acute hepatitis 3 weeks after stopping methotrexate because of pulmonary toxicity [bilirubin 1.8 mg/dL, ALT 252 U/L, Alk P 135 U/L, presence of HBsAg, IgM anti-HBc, anti-HBe, and HBV DNA], progressing to hepatic failure and death 6 months later).

Roenigk HH Jr, Auerbach R, Maibach H, Weinstein G, Lebwohl M. Methotrexate in psoriasis: consensus conference. J Am Acad Dermatol. 1998;38:478–85. PubMed PMID: 9520032.

(Update of recommendations for use of methotrexate and monitoring for side effects; pretreatment liver biopsy recommended for patients with evidence of liver disease or significant risk factors; monitoring of liver chemistries every 4-8 weeks; liver biopsy on treatment after each 1.5 g of therapy and more frequent if liver tests are abnormal).

Burak KW, Urbanski SJ, Swain MG. Successful treatment of refractory type 1 autoimmune hepatitis with methotrexate. J Hepatol. 1998;29:990–3. PubMed PMID: 9875647.

(52 year old woman with refractory autoimmune hepatitis that worsened on azathioprine had a remission on methotrexate [7.5 mg/wk orally]).

Hashkes PJ, Balistreri WF, Bove KE, Ballard ET, Passo MH. The relationship of hepatotoxic risk factors and liver histology in methotrexate therapy for juvenile rheumatoid arthritis. J Pediatr. 1999;134:47–52. PubMed PMID: 9880448.

(Among 33 liver biopsies from 25 patients with juvenile rheumatoid arthritis treated with methotrexate for 1.5-12 years [total dose 0.5-8.4 g], 82% were normal and 6% had fibrosis [Roenigk IIIA only]; obesity and ALT or AST elevations were found to be risk factors for abnormal histology).

Locatelli M, Colleoni M, Noberasco C, Nolé F, Orlando L, Munzone E, Peruzzotti G, et al. Hepatic toxicity from cyclophosphamide, methotrexate, fluorouracil (CMF regimen). Ann Oncol. 1999;10:1394–5. PubMed PMID: 10631475.

(Among 264 patients given methotrexate and fluorouracil intravenously twice monthly and oral cyclophosphamide for breast cancer, 40% had ALT elevations, 19% above 5 times ULN, but all resolved within 30 days).

Suzuki Y, Uehara R, Tajima C, Noguchi A, Ide M, Ichikawa Y, Mizushima Y, et al. Elevation of serum hepatic aminotransferases during treatment of rheumatoid arthritis with low-dose methotrexate. Risk factors and response to folic acid. Scand J Rheumatol. 1999;28:273–81. PubMed PMID: 10568423.

(Among 14 patients with rheumatoid arthritis treated with methotrexate who were started on folate [5 mg weekly, 36 hours after dosing], serum ALT levels fell in all within 3 months; two had exacerbations of arthritis and stopped folate).

Haustein UF, Rytter M. Methotrexate in psoriasis: 26 years' experience with low-dose long-term treatment. J Eur Acad Dermatol Venereol. 2000;14:382–8. PubMed PMID: 11305380.

(Retrospective analysis of clinical experience using methotrexate in 157 patients treated for up to 15 years [mean=5 years]; abnormal liver tests arose in 40 [25%] leading to stopping in 22 [14%], but no clinically apparent liver disease or cirrhosis).

Mok MY, Ng WL, Yuen MF, Wong RW, Lau CS. Safety of disease modifying anti-rheumatic agents in rheumatoid arthritis patients with chronic viral hepatitis. Clin Exp Rheumatol. 2000;18:363–8. PubMed PMID: 10895374.

(Among 29 Chinese patients with rheumatoid arthritis and chronic hepatitis [23 HBV; 6 HCV], ALT elevations occurred in 41% on hydroxychloroquine, 30% on methotrexate and 14% on gold vs 14% of 94 control patients without viral hepatitis).

Hirshberg B, Muszkat M, Schlesinger O, Rubinow A. Safety of low dose methotrexate in elderly patients with rheumatoid arthritis. Postgrad Med J. 2000;76:787–9. PubMed PMID: 11085770.

(Retrospective analysis of 33 patients with rheumatoid arthritis above age of 65 treated with methotrexate for at least 2 years; two patients stopped because of raised serum enzymes, but none developed clinically apparent liver injury).

Richard S, Guerret S, Gerard F, Tebib JG, Vignon E. Hepatic fibrosis in rheumatoid arthritis patients treated with methotrexate: application of a new semi-quantitative scoring system. Rheumatology. 2000;39:50–4. PubMed PMID: 10662873.

(Analysis of 74 liver biopsies from 57 patients with rheumatoid arthritis before or during methotrexate therapy using a new scoring system for fibrosis [graded at 4 sites giving scores of 0 to 35] found good correlation with Roenigk score, but no change in scores with methotrexate therapy).

Kuijpers AL, van de Kerkhof PC. Risk-benefit assessment of methotrexate in the treatment of severe psoriasis. Am J Clin Dermatol. 2000;1:27–39. PubMed PMID: 11702302.

(Review article on mechanism of action, pharmacology, efficacy and safety of methotrexate in psoriasis; in a study of 55 patients who underwent liver biopsy on therapy, 4% had cirrhosis and 13% fibrosis).

Lémann M, Zenjari T, Bouhnik Y, Cosnes J, Mesnard B, Rambaud J-C, Modigliani R, et al. Methotrexate in Crohn's disease: long-term efficacy and toxicity. Am J Gastroenterol. 2000;95:1730–4. PubMed PMID: 10925976.

(Among 49 patients with Crohn disease treated with methotrexate for more than 6 months, serum enzyme elevations occurred in 10 leading to withdrawal in 2 patients; liver biopsies showed mild steatosis in 1 and mild fibrosis in two others).

Zachariae H. Liver biopsies and methotrexate: a time for reconsideration? J Am Acad Dermatol. 2000;42:531–4. PubMed PMID: 10688735.

(Review of role of liver biopsy in monitoring methotrexate hepatotoxicity in patients with psoriasis and rheumatoid arthritis; PIIIP levels may provide a means of reducing number of biopsies, restricting surveillance biopsies to patients with high risk of having fibrosis).

Te HS, Schiano TD, Kuan SF, Hanauer SB, Conjeevaram HS, Baker AL. Hepatic effects of long-term methotrexate use in the treatment of inflammatory bowel disease. Am J Gastroenterol. 2000;95:3150–6. PubMed PMID: 11095334.

(Among 32 patients with Crohn disease treated with methotrexate for 1-4 years, 20 underwent liver biopsy after 1.5-5.4 g of therapy given for 1-5 years; only 1 had fibrosis which was mild, and ALT and AST elevations were rare).

Weinblatt ME, Dixon JA, Falchuk KR. Serious liver disease in a patient receiving methotrexate and leflunomide. Arthritis Rheum. 2000;43:2609–11. PubMed PMID: 11083289.

(51 year old man with rheumatoid arthritis was treated with leflunomide and methotrexate and had several ALT elevations and decline in platelet count during first 1-2 years of therapy and, after 3.5 years [total dose 4.5 g], a liver biopsy showed cirrhosis and mild steatosis without inflammation: Case 2).

Langman G, Hall PM, Todd G. Role of non-alcoholic steatohepatitis in methotrexate-induced liver injury. J Gastroenterol Hepatol. 2001;16:1395–401. PubMed PMID: 11851839.

(Retrospective review of paired liver biopsies from 24 patients with methotrexate associated liver injury; 17 had features suggestive of nonalcoholic steatohepatitis [NASH] of whom 13 had risk factors such as obesity and diabetes).

Wollina U, Ständer K, Barta U. Toxicity of methotrexate treatment in psoriasis and psoriatic arthritis - short- and long-term toxicity in 104 patients. Clin Rheumatol. 2001;20:406–10. PubMed PMID: 11771523.

(Analysis of adverse events occurring in 104 patients with psoriasis treated with methotrexate for undefined period, ALT and AST elevations were the most frequent adverse event both during early and long term therapy).

van Ede AE, Laan RF, Rood MJ, Huizinga TW, van de Laar MA, van Denderene CJ, Westgeest TAA, et al. Effect of folic or folinic acid supplementation on the toxicity and efficacy of methotrexate in rheumatoid arthritis: a forty-eight week, multicenter, randomized, double-blind, placebo-controlled study. Arthritis Rheum. 2001;44:1515–24. PubMed PMID: 11465701.

(Randomized controlled trial of folic acid [1 mg/day] vs folinic acid [7.5 mg/week] vs placebo in 434 patients with rheumatoid arthritis treated with methotrexate [7.5-25 mg/week] for 48 weeks, found higher toxicity related withdrawals with placebo [38%] compared to folate [17%] or folinic acid [12%]; elevated ALT levels occurred in 26% on placebo, 4% on folic acid and 4% on folinic acid; no differences in efficacy).

Venkataramani A, Jones MB, Sorrell MF. Methotrexate therapy for refractory chronic active autoimmune hepatitis. Am J Gastroenterol. 2001;96:3432–4. PubMed PMID: 11774963.

(59 year old man with refractory autoimmune hepatitis and allergy to azathioprine had a biochemical remission on methotrexate [15 mg/wk]).

Zachariae H, Heickendorff L, Sogaard H. The value of amino-terminal propeptide of type III collagen in routine screening for methotrexate-induced liver fibrosis: a 10-year follow-up. Br J Dermatol. 2001;144:100–3. PubMed PMID: 11167689.

(Retrospective analysis of 70 patients with psoriasis on methotrexate therapy who were monitored with PIIIP levels after an initial liver biopsy; only 4 [6%] developed fibrosis, all of whom had elevations in PIIIP levels compared to only 2 of 66 who did not develop fibrosis).

Ito S, Nakazono K, Murasawa A, Mita Y, Hata K, Saito N, Kikuchi M, et al. Development of fulminant hepatitis B (precore variant mutant type) after the discontinuation of low-dose methotrexate therapy in a rheumatoid arthritis patient. Arthritis Rheum. 2001;44:339–42. PubMed PMID: 11229464.

(75 year old with rheumatoid arthritis and HBsAg carrier state [normal ALT and no HBeAg] was treated with methotrexate and prednisone for 3 years, but discontinued when ALT began to rise [112 U/L], and within a few weeks she presented with acute hepatitis [bilirubin 9.7 mg/dL, ALT 1016 U/L, prothrombin index 32%, presence of HBeAg and HBV DNA polymerase], dying of hepatic failure a few weeks later).

Cutolo M, Seriolo B, Pizzorni C, Craviotto C, Sulli A. Methotrexate in psoriatic arthritis. Clin Exp Rheumatol. 2002;20(6 Suppl 28):S76–80. PubMed PMID: 12463453.

(Review of status of methotrexate therapy in psoriatic arthritis, makes claim that folate therapy reduces efficacy of methotrexate).

Kumar B, Saraswat A, Kaur I. Short-term methotrexate therapy in psoriasis: a study of 197 patients. Int J Dermatol. 2002;41:444–8. PubMed PMID: 12121564.

(Retrospective review of 243 short term cycles of methotrexate therapy in 197 patients with psoriasis in India, with low rate of serum enzyme elevations [1.2%], and no evidence of progressive liver injury in 8 patients who underwent paired liver biopsy).

Lahdenne P, Rapola J, Ylijoki H, Haapasaari J. Hepatotoxicity in patients with juvenile idiopathic arthritis receiving longterm methotrexate therapy. J Rheumatol. 2002;29:2442–5. PubMed PMID: 12415606.

(Among 10 patients with juvenile rheumatoid arthritis undergoing liver biopsy during methotrexate therapy, all had fat, 5 had inflammation but none had fibrosis; Roenigk scores were 1-2 only).

van Outryve S, Schrijvers D, van den Brande J, Wilmes P, Bogers J, van Marck E, Vermorken JH. Methotrexate-associated liver toxicity in a patient with breast cancer: case report and literature review. Neth J Med. 2002;60:216–22. PubMed PMID: 12365478.

(60 year old woman with breast cancer developed fatigue and mild ALT elevations [64 to 98 U/L] during cycles 2 to 4 of methotrexate-fluorouracil-cyclophosphamide, resolving when methotrexate was replaced by mitoxantrone; biopsy showed centrolobular fat and ballooning).

Choi HK, Hernan MA, Seeger JD, Robins JM, Wolfe F. Methotrexate and mortality in patients with rheumatoid arthritis: a prospective study. Lancet. 2002;359:1173–7. PubMed PMID: 11955534.

(In a retrospective analysis of a large cohort of patients with rheumatoid arthritis, methotrexate use was associated with decrease in all-cause mortality and particularly cardiovascular).

Kwoh CK, Anderson LG, Greene JM, Johnson DA, O'Dell JR, Robbins ML, Roberts WN Jr, et al; American College of Rheumatology Subcommittee on Rheumatoid Arthritis Guidelines. Guidelines for the management of rheumatoid arthritis: 2002 update. Arthritis Rheum. 2002;46:328–46. PubMed PMID: 11840435.

(Guidelines for management of rheumatoid arthritis; recommended serial monitoring during methotrexate therapy with routine liver tests and liver biopsy in those with risk factors of liver disease or persistent liver test abnormalities).

Ros S, Juanola X, Condom E, Cañas C, Riera J, Guardiola J, Del Blanco J, et al. Light and electron microscopic analysis of liver biopsy samples from rheumatoid arthritis patients receiving long-term methotrexate therapy. Scand J Rheumatol. 2002;31:330–6. PubMed PMID: 12492247.

(Analysis of liver biopsies by light and electron microscopy taken from 42 Spanish patients with rheumatoid arthritis before and after 4 years of methotrexate found mild fibrosis in 14% at baseline vs 12% at year 4; mild increase in steatosis, smooth endoplasmic reticulum, and number of lysosomes after therapy, but no change in amount of collagen in the space of Disse).

Penalva Polo JC, Gómez Andrés A, Vela P, Niveiro M. Rev Esp Enferm Dig. 2002;94:440–1. [Acute liver failure in a patient with methotrexate therapy]. Spanish. PubMed PMID: 12432845.

Fathi NH, Mitros F, Hoffman J, Straniero N, Labreque D, Koehnke R, Furst DE. Longitudinal measurement of methotrexate liver concentrations does not correlate with liver damage, clinical efficacy, or toxicity during a 3.5 year double blind study in rheumatoid arthritis. J Rheumatol. 2002;29:2092–8. PubMed PMID: 12375317.

(40 patients enrolled in a controlled trial of methotrexate in varying weekly oral doses underwent liver biopsy before and after 1, 2 and 3.5 years; at least one ALT abnormality occurred in ~50%, and AST ~25% of patients; the average Roenigk and "Iowa" histological scores did not change, but 13% developed some degree of fibrosis [none cirrhosis], abnormalities did not correlate with methotrexate concentrations in liver, use of folic acid, but some correlation was found between AST values and worsening of Iowa score).

Yazici Y, Erkan D, Paget SA. Monitoring methotrexate hepatic toxicity in rheumatoid arthritis: is it time to update the guidelines? J Rheumatol. 2002;29:1586–9. PubMed PMID: 12180713.

(Among 182 patients with rheumatoid arthritis treated with methotrexate, 17% had at least one abnormal liver test, but no instances of cirrhosis or clinically apparent liver disease arose; authors questioned the need of extensive monitoring).

Kremer JM. Not yet time to change the guidelines for monitoring methotrexate liver toxicity: they have served us well. J Rheumatol. 2002;29:1590–2. PubMed PMID: 12180714.

(Review of the data that supported initial guidelines for monitoring serum enzymes during methotrexate therapy of rheumatoid arthritis suggesting that any elevation may be indicative of hepatic injury and that monitoring reduces occurrence of severe fibrosis).

Farrell GC. Drugs and steatohepatitis. Semin Liver Dis. 2002;22:185–94. PubMed PMID: 12016549.

(Hepatic changes similar to nonalcoholic steatohepatitis [NASH] occur with long term use of amiodarone, methotrexate and some nucleoside analogues; in contrast, corticosteroids, estrogens and tamoxifen appear to cause fatty liver by exacerbating pre-existing NASH).

Hoekstra M, van Ede AE, Haagsma CJ, van de Laar MAFJ, Huizinga TWJ, Kruijsen MWM, Laan RFJM. Factors associated with toxicity, final dose, and efficacy of methotrexate in patients with rheumatoid arthritis. Ann Rheum Dis. 2003;62:423–6. PubMed PMID: 12695153.

(Randomized trial of 48 weeks of methotrexate with or without folate supplementation in 411 patients with rheumatoid arthritis; ALT elevations >3 times ULN occurred in 26% of placebo vs 4% of folate supplemented groups; hepatotoxicity also more common with higher body weight index; folate did not affect efficacy but decreased withdrawals because of toxicity).

Hoekstra M, van de Laar MA, Bernelot Moens HJ, Kruijsen MW, Haagsma CJ. Longterm observational study of methotrexate use in a Dutch cohort of 1022 patients with rheumatoid arthritis. J Rheumatol. 2003;30:2325–9. PubMed PMID: 14677172.

(Retrospective analysis of database on 1022 Dutch patients with rheumatoid arthritis treated with methotrexate, 64% remained on therapy for 5 and 50% after 9 years; factors favoring continuing therapy included folic acid supplementation; reason for stopping was liver test abnormalities in 14%).

Heydendael VMR, Spuls PhI, Opmeer BC, de Borgie CA, Saccozzi R, Luini A, Agullar M, et al. Methotrexate versus cyclosporine in moderate-to-severe chronic plaque psoriasis. N Engl J Med. 2003;349:658–65. PubMed PMID: 12917302.

(Controlled trial of 16 weeks of cyclosporine vs methotrexate in 88 patients with psoriasis found similar efficacy, but high dropout rate because of raised ALT levels in methotrexate group [27%]).

Vanhoof J, Landewe S, Van Wijngaerden E, Geusens P. High incidence of hepatotoxicity of isoniazid treatment for tuberculosis chemoprophylaxis in patients with rheumatoid arthritis treated with methotrexate or sulfasalazine and anti-tumour necrosis factor inhibitors. Ann Rheum Dis. 2003;62:1241–2. PubMed PMID: 14644871.

(Among 88 patients with rheumatoid arthritis receiving disease modifying therapies, 8 were given isoniazid for latent tuberculosis half of whom developed hepatotoxicity, ALT levels rising to 82-330 U/L after 7-16 weeks and resolving 4-11 weeks after stopping; none were clinically apparent).

Baughman RP, Koehler A, Bejarano PA, Lower EE, Weber FL Jr. Role of liver function tests in detecting methotrexate-induced liver damage in sarcoidosis. Arch Intern Med. 2003;163:615–20. PubMed PMID: 12622609.

(Among 68 patients with sarcoidosis undergoing 100 liver biopsies during 2-8 years of methotrexate therapy, 14% showed evidence of mild methotrexate toxicity, but no association found with ALT, AST or Alk P elevations or total dose).

Hytiroglou P, Tobias H, Saxena R, Abramidou M, Papadimitrian CS, Theise ND. The canals of Hering might represent a target of methotrexate hepatic toxicity. Am J Clin Pathol. 2004;121:324–9. PubMed PMID: 15023035.

(Analysis of 16 liver biopsies from 7 patients receiving methotrexate for psoriasis using special stains [cytokeratin 7] to identify the canals of Hering found a reduction of these structures in 13 patients with fibrosis due to methotrexate, the fibrosis following the distribution of the canals).

Boffa MJ. Methotrexate for psoriasis: current European practice. A postal survey. J Eur Acad Dermatol Venereol. 2005;19:196–202. PubMed PMID: 15752290.

(Survey of 69 European dermatologists on use of methotrexate in psoriasis; 59 [85%] used methotrexate but none requested baseline liver biopsies and <20% monitored patients with biopsies during therapy; among 10 fatalities attributed to methotrexate, 8 were caused by myelosuppression and two from liver failure).

Kent PD, Luthra HS, Michet C Jr. Risk factors for methotrexate-induced abnormal laboratory monitoring results in patients with rheumatoid arthritis. J Rheumatol. 2004;31:1727–31. PubMed PMID: 15338491.

(Retrospective chart review of 483 patients with rheumatoid arthritis treated with methotrexate [average 5 years], 4.6% of patients discontinued therapy because of liver test abnormalities, correlated with lack of folate supplementation, high BMI and untreated hyperlipidemia).

Whittle SL, Hughes RA. Folate supplementation and methotrexate treatment in rheumatoid arthritis: a review. Rheumatology. 2004;43:267–71. PubMed PMID: 14963199.

(Review of publications on folate supplementation during weekly methotrexate therapy of rheumatoid arthritis found no evidence that folate decreased efficacy, but clear evidence of fewer side effects including lower rates of ALT elevations; authors recommend 5 mg of folic acid weekly on the day after methotrexate is taken).

Kremer JM. Toward a better understanding of methotrexate. Arthritis Rheum. 2004;50:1370–2. PubMed PMID: 15146406.

(Review of proposed mechanism of action and toxicity of methotrexate in autoimmune diseases; may cause increase in intracellular and extracellular adenosine levels which bind to its cellular membrane receptors and increase intracellular cyclic AMP which has immunosuppressive consequences).

Hagiyama H, Kubota T, Komano Y, Kurosaki M, Watanabe M, Miyasaka N. Fulminant hepatitis in an asymptomatic chronic carrier of hepatitis B virus mutant after withdrawal of low-dose methotrexate therapy for rheumatoid arthritis. Clin Exp Rheumatol. 2004;22:375–6. PubMed PMID: 15144137.

(72 year old with rheumatoid arthritis and HBsAg carrier state [normal ALT and no HBeAg] developed elevations in serum ALT [246 U/L] 2 years after starting methotrexate [4 mg/week] and prednisone [5 mg daily]; 2 months after stopping, she presented with acute liver failure [ALT 569 U/L, prothrombin index 65%, presence of HBeAg and HBV DNA] and died).

Ortiz-Alvarez O, Morishita K, Avery G, Green J, Petty RE, Tucker LB, Malleson PN, et al. Guidelines for blood test monitoring of methotrexate toxicity in juvenile idiopathic arthritis. J Rheumatol. 2004;31:2501–6. PubMed PMID: 15570658.

(Monitoring liver enzymes in 89 children with juvenile rheumatoid arthritis at monthly intervals for an average of 3 years, identified 13 instances [15%] of ALT or AST elevations >2 times ULN, all resolved rapidly and methotrexate was either continued or restarted without recurrence).

Heydendael VM, Spuls PI, Bossuyt PM, Bos JD, de Rie MA. Analysis of risk factors in psoriatic patients with methotrexate-induced increases in transaminase levels. Arch Dermatol. 2004;140:1289–90. PubMed PMID: 15492205.

(Reanalysis of high rate [28%] of ALT elevations in controlled trial of methotrexate vs cyclosporine A, inconclusive results).

Aithal GP, Haugk B, Das S, Card T, Burt AD, Record CO. Monitoring methotrexate-induced hepatic fibrosis in patients with psoriasis: are serial liver biopsies justified? Aliment Pharmacol Ther. 2004;19:391–9. PubMed PMID: 14871278.

(Analysis of 121 biopsies from 66 patients with psoriasis treated with methotrexate for average of 5.4 years found advanced fibrosis arose in 2.6% of biopsies after 1.4-3 g, 8.2% after 4.5-6 g, and 32% after 10 g total dose; total number of cases uncertain; Roenigk score has less helpful than Ishak or Scheuer fibrosis scales).

Suissa S, Ernst P, Hudson M, Bitton A, Kezouh A. Newer disease-modifying antirheumatic drugs and the risk of serious hepatic adverse events in patients with rheumatoid arthritis. Am J Med. 2004;117:87–92. PubMed PMID: 15234643.

(Case control analysis of hepatic events in two US cohorts of 41,885 patients with rheumatoid arthritis treated with disease modifying agents, found no increase in cases of serious or non-serious events with leflunomide [rate ratio 0.9] compared to methotrexate, but higher rates with etanercept and infliximab [rate ratio 5.3]).

Gupta R, Gupta SK. Severe hepatotoxicity in a rheumatoid arthritis patient switched from leflunomide to methotrexate. MedGenMed. 2005;7:9. PubMed PMID: 16369235.

(44 year old woman with rheumatoid arthritis found to have elevated ALT [341 U/L] 9 months after starting leflunomide, resolving within 2 months of stopping, but recurring after 3 months of oral methotrexate which was tolerated for many years in the past [bilirubin 3.5 mg/dL, ALT 1297 U/L], resolving within 4 weeks of stopping).

Kinder AJ, Hassell AB, Brand J, Brownfield A, Grove M, Shadforth MF. The treatment of inflammatory arthritis with methotrexate in clinical practice: treatment duration and incidence of adverse drug reactions. Rheumatology (Oxford). 2005;44:61–6. PubMed PMID: 15611303.

(Among 673 patients with rheumatic diseases treated with methotrexate between 1986 and 1999, 74% continued on therapy for 5 years or more; 37 patients stopped because of abnormal liver tests; 25 patients died, but none from liver disease).

Mathew J, Leong MY, Morley N, Burt AD. A liver fibrosis cocktail? Psoriasis, methotrexate and genetic hemochromatosis. BMC Dermatol. 2005;5:12. PubMed PMID: 16316460.

(Two patients with hemochromatosis and psoriasis on long term methotrexate had minor abnormalities on liver biopsy without fibrosis).

Nieminen U, Höök-Nikanne J, Kärkäinen P, Niemelä S. Duodecim. 2005;121:2680–8. [Liver damage in methotrexate-treated patients. When liver biopsy is necessary in the follow-up?]. Finnish. PubMed PMID: 16454249.

Yazici Y, Erkan D, Harrison MJ, Nikolov NP, Paget SA. Methotrexate use in rheumatoid arthritis is associated with few clinically significant liver function test abnormalities. Clin Exp Rheumatol. 2005;23:517–20. PubMed PMID: 16095122.

(Retrospective analysis of 182 patients with rheumatoid arthritis treated with methotrexate between 1985-1999; 16.5% had at least 1 abnormal ALT or AST, but only 2 discontinued drug for these findings and no patient developed clinically apparent liver injury; routine liver biopsies were not done).

Yazici Y, Sokka T, Kautiainen H, Swearingen C, Kulman I, Pincus T. Long term safety of methotrexate in routine clinical care: discontinuation is unusual and rarely the result of laboratory abnormalities. Ann Rheum Dis. 2005;64:207–11. PubMed PMID: 15208176.

(Among 248 patients with rheumatoid arthritis treated with methotrexate, 79% continued for at least 5 years; AST elevations occurred in 7% per year, but usually transient and <2 times ULN, none requiring permanent discontinuation).

Zachariae H. Have methotrexate-induced liver fibrosis and cirrhosis become rare? A matter for reappraisal of routine liver biopsies. Dermatology. 2005;211:307–8. PubMed PMID: 16286736.

(Editorial on issue of monitoring for liver fibrosis in patients with psoriasis on methotrexate; rates of cirrhosis in treated patients have decreased but major rates of cirrhosis were in those treated for >10 years, often with other hepatotoxic exposures).

Thomas JA, Aithal GP. Monitoring liver function during methotrexate therapy for psoriasis. Are routine biopsies really necessary? Am J Clin Dermatol. 2005;6:357–63. PubMed PMID: 16343024.

(Review of role liver biopsy in monitoring patients with psoriasis on low dose methotrexate therapy; authors recommend pretreatment liver biopsy only in patients with evidence for liver disease or risk factors and routine surveillance biopsy only after total dose of 4 g, and use of Ishak or Scheuer fibrosis staging systems rather than Roenigk scale).

Maurice PD, Maddox AJ, Green CA, Tatnall F, Schofield JK, Stott DJ. Monitoring patients on methotrexate : hepatic fibrosis not seen in patients with normal serum assays of aminoterminal peptide of type III procollagen. Br J Dermatol. 2005;152:451–8. PubMed PMID: 15787813.

(Among 38 patients with psoriasis on methotrexate undergoing 70 liver biopsies and routine PIIIP testing, 4 patients had fibrosis and all 4 had at least one abnormal PIIIP level as did half of patients with normal liver biopsies; in 23 patients undergoing 2 biopsies, 4 worsened and all 4 had at least one abnormal PIIIP as did

63% of patients with no change; 46% of patients had persistently normal PIIIP values and none had fibrosis or worsening histology and might have avoided need for liver biopsy).

Chalmers RJG, Kirby B, Smith A, Burrows P, Little R, Horan M, Hextall JM, et al. Replacement of routine liver biopsy by procollagen III aminopeptide for monitoring patients with psoriasis receiving long-term methotrexate: a multicentre audit and health economic analysis. Br J Dermatol. 2005;152:444–50. PubMed PMID: 15787812.

(Comparison of costs between UK centers using PIIIP monitoring versus routine liver biopsy at different total methotrexate doses suggested seven-fold decrease in need for liver biopsy with serum fibrosis marker).

Berends MA, Snoek J, de Jong EM, van de Kerkhof PC, van Oijen MG, van Krieken JH, Drenth JP. Liver injury in long-term methotrexate treatment in psoriasis is relatively infrequent. Aliment Pharmacol Ther. 2006;24:805–11. PubMed PMID: 16918884.

(125 patients with psoriasis treated with methotrexate for average of 4.4 years underwent 278 liver biopsies; 71% did not change from baseline; 15% developed fibrosis including 2% with cirrhosis; poor correlation of fibrosis with ALT and AST elevations; over half had risk factors such as obesity, diabetes or alcohol use).

Khan S, Subedi D, Chowdhury MMU. Use of amino terminal type III procollagen peptide(P3MP) assay in methotrexate therapy for psoriasis. Postgrad Med J. 2006;82:353–4. PubMed PMID: 16679477.

(Retrospective analysis on 15 patients with psoriasis on long-term methotrexate who had abnormal PIIIP levels and underwent liver biopsy; one showing cirrhosis and two fibrosis).

Goujon C, Bérd F, Dahel K, Guillot I, Hennino A, Nosbaum A, Saad N, et al. Methotrexate for the treatment of adult atopic dermatitis. Eur J Dermatol. 2006;16:155–8. PubMed PMID: 16581567.

(20 patients with atopic dermatitis were treated with methotrexate, 15 having a response at 3 months and continuing therapy [7.5-25 mg/week], 10% had serum enzyme elevations, but none required stopping).

La Montagna G, Tirri R, Vitello R, Malesci D, Buono R, Mennillo G, Valentini G. Reumatismo. 2006;58:261–7. [Safety of methotrexate in rheumatoid arthritis: a retrospective cohort study in clinical practice]. Italian. PubMed PMID: 17216014.

(Among 224 patients with rheumatoid arthritis treated with methotrexate for an average of 4 years, 9 [4%] had ALT or AST elevations requiring discontinuation).

Tilling L, Townsend S, David J. Methotrexate and hepatic toxicity in rheumatoid arthritis and psoriatic arthritis. Clin Drug Investig. 2006;26:55–62. PubMed PMID: 17163236.

(Prospective study of 550 patients with rheumatoid arthritis and 69 with psoriasis treated with methotrexate [1-30 mg/week] for up to 13 years [mean=3 years], rise in ALT or AST to >3 times ULN occurred in 14.5% of psoriasis vs 7.5% of rheumatoid arthritis patients; differences and most abnormalities were not explained by differences in alcohol use).

Berends MA, van Oijen MG, Snoek J, van de Kerkhof PC, Drenth JP, Han van Krieken J, de Jong EM. Reliability of the Roenigk classification of liver damage after methotrexate treatment for psoriasis: a clinicopathologic study of 160 liver biopsy specimens. Arch Dermatol. 2007;143:1515–9. PubMed PMID: 18087000.

(Among 160 liver biopsies from 95 patients with psoriasis treated with oral methotrexate, reading for Roenigk score gave highly concordant results with initial local readings).

Correa G H, Paredes S N. Rev Med Chil. 2007;135:1002–8. [Serum liver tests in patients treated with methotrexate. A retrospective analysis]. Spanish. PubMed PMID: 17989857.

(Among 63 patients with psoriasis treated with methotrexate in Chile, 32% had elevation in liver tests; 10% had ALT values above 2 times ULN [97-321 U/L], most were transient, one resolved rapidly with stopping).

Gwak GY, Koh KC, Kim HY. Fatal hepatic failure associated with hepatitis B virus reactivation in a hepatitis B surface antigen-negative patient with rheumatoid arthritis receiving low dose methotrexate. Clin Exp Rheumatol. 2007;25:888–9. PubMed PMID: 18173926.

(59 year old woman with rheumatoid arthritis [with anti-HBs without HBsAg] who was treated with methotrexate [10 mg/week] and prednisone [5 mg/day] for 7 years developed acute hepatitis B reactivation [bilirubin 5.7 rising to 29.5 mg/dL, ALT 378 U/L, INR 3.4, presence of HBsAg, HBeAg and HBV DNA ~15 million copies/mL], progressing to hepatic failure and death within 8 weeks of onset).

Shimada K, Matsui T, Kawakami M, Nakayama H, Ozawa Y, Mitomi H, Tohma S. Methotrexate-related lymphomatoid granulomatosis: a case report of spontaneous regression of large tumours in multiple organs after cessation of methotrexate therapy in rheumatoid arthritis. Scand J Rheumatol. 2007;36:64–7. PubMed PMID: 17454938.

(54 year old woman with rheumatoid arthritis on methotrexate for 10 years presented with widespread lymphomatoid granulomatosis which spontaneously disappeared 3 months after stopping methotrexate).

Ting TV, Hashkes PJ. Methotrexate/naproxen-associated severe hepatitis in a child with juvenile idiopathic arthritis. Clin Exp Rheumatol. 2007;25:928–9. PubMed PMID: 18173932.

(2 year old girl with idiopathic arthritis treated with methotrexate and naproxen for 8 months had elevated AST [88 rising to 2372 U/L] with lethargy, hypoglycemia and high ammonia but normal bilirubin and INR and rapid recovery upon stopping methotrexate).

Saag KG, Teng GG, Patkar NM, Anuntiyo J, Finney C, Curtis JR, Paulus HE, et al; American College of Rheumatology. American College of Rheumatology 2008 recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis. Arthritis Rheum. 2008;59:762–84. PubMed PMID: 18512708.

(Recommendations on use of disease modifying agents in rheumatoid arthritis including monitoring for liver disease).

Chalasani N, Fontana RJ, Bonkovsky HL, Watkins PB, Davern T, Serrano J, Yang H, Rochon J; Drug Induced Liver Injury Network (DILIN). Causes, clinical features, and outcomes from a prospective study of drug-induced liver injury in the United States. Gastroenterology. 2008;135:1924–34. PubMed PMID: 18955056.

(Among 300 cases of drug induced liver disease in the US collected between 2004 and 2008, no case was attributed to methotrexate).

Carneiro SC, Cássia FF, Lamy F, Chagas VL, Ramos-e-Silva M. Methotrexate and liver function: a study of 13 psoriasis cases treated with different cumulative dosages. J Eur Acad Dermatol Venereol. 2008;22:25–9. PubMed PMID: 18181969.

(13 Brazilian patients with psoriasis underwent liver biopsy before and after 1-4 g of oral methotrexate therapy; fibrosis found in none of 18 who received <2 g, in 1 of 7 after 3 g, and 2 of 4 after 4 g including 2 with cirrhosis; no mention of folate supplementation).

Cheng KK. Association of plasma methotrexate, neutropenia, hepatic dysfunction, nausea/vomiting and oral mucositis in children with cancer. Eur J Cancer Care(Engl). 2008;17:306–11. PubMed PMID: 18419635.

(Case control study in 28 children with leukemia given high dose iv methotrexate [5-12 g/m^2]; found those with mucositis had higher serum methotrexate levels, but similar rates of ALT or AST elevations as those without mucositis).

Domènech E, Mañosa M, Navarro M, Masnou H, Garcia-Planella E, Zabana Y, Cabré E, et al. Long-term methotrexate for Crohn's disease: safety and efficacy in clinical practice. J Clin Gastroenterol. 2008;42:395–9. PubMed PMID: 18277899.

(Retrospective analysis of 44 patients with Crohn disease treated with methotrexate for average of 2 years [total dose 1.2 g]; ALT or AST elevations developed in 30% of patients requiring stopping therapy in 7%, but none developed cirrhosis or clinically apparent liver injury).

Hartmann U, Schmitt S, Reuss-Borst M. Z Rheumatol. 2008;67:440–4. [Elevated liver enzymes in rheumatoid arthritis: differential diagnostic considerations based on a case report]. German. PubMed PMID: 18418614.

(Case report of apparent autoimmune hepatitis arising in 17 year old woman with rheumatoid arthritis after 18 months of leflunomide therapy, controlled with prednisone and azathioprine).

Laharie D, Terrebonne E, Vergniol J, Chanteloup E, Chabrun E, Couzigou P, de Ledinghen V. Gastroenterol Clin Biol. 2008;32:134–42. [The liver and methotrexate]. French. PubMed PMID: 18494155.

(Review of hepatotoxicity of methotrexate).

Lapalus MG, Hot A, Fontana A, Guillaud O, Miossec P, Xcozaec J-Y, Dumorteir J. Epstein Barr virus-induced hepatitis associated with methotrexate treatment. J Clin Gastroenterol. 2008;42:217–9. PubMed PMID: 18209599.

(62 year old woman with systemic lupus on methotrexate and prednisone developed ascites [bilirubin 0.5 mg/dL, ALT 42 U/L, Alk P 85 U/L, albumin 3.1 and IgM anti-EBV], biopsy showing cirrhosis and "superimposed acute hepatitis", ultimately resolving).

Prey S, Paul C. Effect of folic or folinic acid supplementation on methotrexate-associated safety and efficacy in inflammatory disease: a systematic review. Br J Dermatol. 2009;160:622–8. PubMed PMID: 18945303.

(Systematic review of 6 studies of folic or folinic acid supplementation [648 patients] during methotrexate therapy of rheumatoid arthritis [n=5] or psoriasis [n=1]; significant reduction in liver adverse events by 36%, but not on other side effects and no difference between folinic or folic acid; whether folate supplemental affects effectiveness of methotrexate could not be assessed adequately).

Taylor WJ, Korendowych E, Nash P, Helliwell PS, Choy E, Krueger GG, Soriano ER, et al. Drug use and toxicity in psoriatic disease: focus on methotrexate. J Rheumatol. 2008;35:1454–7. PubMed PMID: 18609744.

(Survey of rheumatologists regarding use of methotrexate in psoriasis and rheumatoid arthritis found a wide variability in practice of monitoring; use of folate was not assessed; 40 respondents had observed a case of cirrhosis due to methotrexate).

Dwyer N, Jones G, Kilpatrick D. Severe hepatotoxicity in a patient on bosentan upon addition of methotrexate: reversible with resumption of methotrexate without bosentan. J Clin Rheumatol. 2009;15:88–9. PubMed PMID: 19265355.

(45 year old with scleroderma on bosentan therapy developed liver test abnormalities 4 months after starting escalating doses of methotrexate [bilirubin 9.5 mg/dL, ALT 1189 U/L, Alk P 550 U/L, INR 1.3], resolving in 1 month of stopping both drugs; later tolerated methotrexate alone).

Katchamart W, Trudeau J, Phumethum V, Bombardier C. Efficacy and toxicity of methotrexate (MTX) monotherapy versus MTX combination therapy with non-biological disease-modifying antirheumatic drugs in rheumatoid arthritis: a systematic review and meta-analysis. Ann Rheum Dis. 2009;68:1105–12. PubMed PMID: 19054823.

(Systematic review of 19 trials comparing methotrexate alone to its combination with other disease modifying agents in 2025 patients showed no improvement in efficacy by addition of other agents to methotrexate, but an increase in toxicity with combination therapy, including increased frequency of ALT elevations).

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 (Oxford). 2009;48:569–72. PubMed PMID: 19273538.

(Retrospective analysis of liver biopsies in 54 patients with psoriasis treated with methotrexate for an average of 7 years; mild fibrosis [IIIA] was found in 22% of patients, but none had cirrhosis; history of alcohol use and PIIIP levels did not predict presence of fibrosis).

Boffa MJ, Smith A, Chalmers RJ. Comment on: Liver fibrosis in patients with psoriasis and psoriatic arthritis on long-term, high cumulative dose methotrexate therapy. Rheumatology (Oxford). 2009;48:1464–Author reply 1465. PubMed PMID: 19671697.

(Letter in response to Lindsay et al. [2009] suggesting that serial normal PIIIP values in patients with psoriasis on methotrexate are helpful in providing reassurance that ongoing liver fibrosis will not be missed; response by authors suggests that more studies are needed).

Lu LJ, Bao CD, Dai M, Teng JL, Fan W, Du F, Yang NP, et al. Multicenter, randomized, double-blind, controlled trial of treatment of active rheumatoid arthritis with T-614 compared with methotrexate. Arthritis Rheum. 2009;61:979–87. PubMed PMID: 19565542.

(T-614, a novel immunomodulatory agent, was compared to methotrexate in a randomized controlled trial of 24 weeks in 489 patients with rheumatoid arthritis; similar efficacy; ALT elevations occurred in 24% on methotrexate vs 6% to 13.5% on T-614).

Neves C, Jorge R, Barcelos A. Acta Rheumatol Port. 2009;34:11–34. [The network of methotrexate toxicity]. Portuguese.

(Systematic review of methotrexate toxicities).

Periáñez-Párraga L, Pérez-Rodríguez O, do Pazo-Oubiña F, Crespí-Monjo M. Farm Hosp. 2009;33:172–3. [Acute toxicity of high doses of methotrexate in treatment of ALL in children: a case study]. Spanish. PubMed PMID: 19712601.

(12 year old boy with acute leukemia developed raised ALT and bilirubin during high dose methotrexate therapy attributed to concurrent renal toxicity, resolving rapidly).

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;68:1100–4. PubMed PMID: 19060002.

(Systematic review of 21 prospective studies [3463 patients] on the safety of methotrexate in rheumatoid arthritis; using average dose of 9 mg/week for 3 years, 73% had at least one adverse event and 18.5% had a liver related event; overall in 769 patients followed prospectively, 20% had at least one elevation in liver enzymes, 13% above 2 times ULN, and 3.7% discontinued therapy for this reason).

Varatharajan N, Lim IG, Anandacoomarasamy A, Russo R, Byth K, Spencer DG, Manolios N, et al. Methotrexate: long-term safety and efficacy in an Australian consultant rheumatology practice. Intern Med J. 2009;39:228–36. PubMed PMID: 19402861.

(Retrospective analysis of outcomes of methotrexate therapy in 790 patients with chronic arthritis; therapy stopped in 18 patients [2%] because of liver test abnormalities, but no one developed cirrhosis or died of liver disease).

Ongaro A, De Mattei M, Della Porta MG, Rigolin G, Ambrosio C, Di Raimondo F, Pellati A, et al. Gene polymorphisms in folate metabolizing enzymes in adult acute lymphoblastic leukemia: effects on methotrexate-related toxicity and survival. Haematologica. 2009;94:1391–8. PubMed PMID: 19648163.

(Polymorphisms of the two genes involved in folate metabolism correlated with an increased rate of hepatotoxicity [odds ratio 4.6 and 5.2] which was 29% overall; no correction was made for the multiple comparisons).

Amital H, Arnson Y, Chodick G, Shalev V. Hepatotoxicity rates do not differ in patients with rheumatoid arthritis and psoriasis treated with methotrexate. Rheumatology (Oxford). 2009;48:1107–10. PubMed PMID: 19578136.

(Retrospective analysis of a health management organization records on 119 patients with rheumatoid arthritis and 690 with psoriasis treated with methotrexate showing that 45% of patients had at least one abnormal liver test, with no difference in rates of AST elevation between the two diagnostic groups).

Collin B, Vani A, Ogboli M, Moss C. Methotrexate treatment in 13 children with severe plaque psoriasis. Clin Exp Dermatol. 2009;34:295–8. PubMed PMID: 19175782.

(Retrospective analysis of 13 children with severe psoriasis treated with methotrexate for 6 weeks to 5 years [total dose 0.04-3.6 g]; 9 had transient and mild ALT elevations and 1 discontinued therapy after 6 weeks when ALT rose to 516 U/L).

Lynch M, Kirby B. Comment on: Hepatotoxicity rates do not differ in patients with rheumatoid arthritis and psoriasis treated with methotrexate. Rheumatology(Oxford). 2010;49:196–7author reply 197-8. PubMed PMID: 19858119.

(Another letter in response to Amital [2009] arguing that standard liver tests alone are insufficient in monitoring for potential hepatotoxicity).

Ferrajolo C, Capuano A, Verhamme KM, Schuemie M, Rossi F, Stricker BH, Sturkenboom MC. Drug-induced hepatic injury in children: a case/non-case study of suspected adverse drug reactions in VigiBase. Br J Clin Pharmacol. 2010;70:721–8. PubMed PMID: 21039766.

(Worldwide pharmacovigilance database contained 9036 hepatic adverse drug reactions in children, methotrexate accounted for 134 cases [ranking 5th] with an adjusted risk odds ratio of 4.2).

Reuben A, Koch DG, Lee WM; Acute Liver Failure Study Group. Drug-induced acute liver failure: results of a U.S. multicenter, prospective study. Hepatology. 2010;52:2065–76. PubMed PMID: 20949552.

(Among 1198 patients with acute liver failure enrolled in a US prospective study between 1998 and 2007, 133 [11%] were attributed to drug induced liver injury, none of which were thought to be due to methotrexate).

Curtis JR, Beukelman T, Onofrei A, Cassell S, Greenberg JD, Kavanaugh A, Reed G, et al. Elevated liver enzyme tests among patients with rheumatoid arthritis or psoriatic arthritis treated with methotrexate and/or leflunomide. Ann Rheum Dis. 2010;69:43–7. PubMed PMID: 19147616.

(In a large, observational US database, ALT or AST elevations found in 17% of patients on leflunomide alone, 22% on methotrexate alone, and 31% on both; levels >2 times ULN in only 2% vs 1% vs 5% [on both]; risk factors for elevations were methotrexate dose, history of liver disease and alcohol use [1-2 drinks/day]).

Toscano E, Cotta J, Robles M, Lucena MA, Andrade RJ. Gastroenterol Hepatol. 2010;33:54–65. [Hepatotoxicity induced by new immunosuppressants]. Spanish. PubMed PMID: 19889479.

(Review of hepatotoxicity of different immunosuppressive agents including methotrexate).

Fournier MR, Klein J, Minuk GY, Bernstein CN. Changes in liver biochemistry during methotrexate use for inflammatory bowel disease. Am J Gastroenterol. 2010;105:1620–6. PubMed PMID: 20160715.

(Among 87 patients with inflammatory bowel disease treated with methotrexate for an average of 2 years, 24% had liver test abnormalities, but most resolved without dose modification and no fibrosis or cirrhosis were found in liver biopsies from 20 patients).

Rogler G. Gastrointestinal and liver adverse effects of drugs used for treating IBD. Best Pract Res Clin Gastroenterol. 2010;24:157–65. PubMed PMID: 20227029.

(Review of recent literature on adverse effects of drugs used to treat inflammatory bowel disease including sulfasalazine, thiopurines, methotrexate, cyclosporine and tacrolimus).

Triantafyllou K, Vlachogiannakos J, Ladas SD. Gastrointestinal and liver side effects of drugs in elderly patients. Best Pract Res Clin Gastroenterol. 2010;24:203–15. PubMed PMID: 20227033.

(Review of drug adverse events in the elderly; injury seems to be more severe in older subjects, but frequency has not been proven to be increased and elderly may be at increased risk of hepatic fibrosis caused by methotrexate perhaps due to impaired renal function and frequent use of other medications).

Attar SM. Adverse effects of low dose methotrexate in rheumatoid arthritis patients. A hospital-based study. Saudi Med J. 2010;31:909–15. PubMed PMID: 20714691.

(Abstract: Among 71 patients with rheumatoid arthritis treated with methotrexate, 14% developed liver tests elevations).

Khokhar OS, Lewis JH. Hepatotoxicity of agents used in the management of inflammatory bowel disease. Dig Dis. 2010;28:508–18. PubMed PMID: 20926880.

(Review of hepatotoxicity of drugs used to treat inflammatory bowel disease including sulfasalazine, thiopurines, methotrexate and anti-TNF agents).

Ferrajolo C, Capuano A, Verhamme KM, Schuemie M, Rossi F, Stricker BH, Sturkenboom MC. Drug-induced hepatic injury in children: a case/non-case study of suspected adverse drug reactions in VigiBase. Br J Clin Pharmacol. 2010;70:721–8. PubMed PMID: 21039766.

(Among 624,673 adverse event reports in children between 2000 and 2006 in the WHO VigiBase, 1% were hepatic and most common agents were isotretinoin, acetaminophen, valproic acid, carbamazepine, methotrexate, minocycline, lamotrigine, zidovudine, pemoline and ceftriaxone).

Barker J, Horn E, Lebwohl M, Warren R, Nast A, Rosenberg W, Smith C; International Psoriasis Council. Assessment and management of methotrexate hepatotoxicity in psoriasis patients: report from a consensus conference to evaluate current practice and identify key questions toward optimizing methotrexate use in the clinic. J Eur Acad Dermatol Venereol. 2011;25:758–64. PubMed PMID: 21198946.

(Review of the issue of hepatotoxicity of methotrexate and the reliability of monitoring with comparison of US, UK, European Union, German and Dutch guidelines; folate supplementation is recommended by most; pattern of details of monitoring and use of liver biopsy is variable and there is clearly a need for more accurate and less invasive means of assessing liver injury during methotrexate therapy).

Scientific Registry of Transplant Recipients. January 31, 2010.

(Among 46,633 liver transplants done in the US between 2000 and 2009 in the SRTR registry, 31 [<0.1%] had the primary diagnosis of methotrexate induced cirrhosis).

Aithal GP. Medscape. Hepatotoxicity related to antirheumatic drugs. Nat Rev Rheumatol. 2011;7:139–50. PubMed PMID: 21263458.

(Review of hepatotoxicity of drugs used in rheumatic diseases; methotrexate causes ALT elevations and fibrosis in variable proportions of patients, more common in those with alcohol use, obesity, hyperlipidemia, metabolic syndrome and NASH).

Sultan MI, Biank VF, Telega GW. Successful treatment of autoimmune hepatitis with methotrexate. J Pediatr Gastroenterol Nutr. 2011;52:492–4. PubMed PMID: 21240019.

(Two girls, ages 7 and 11 years with autoimmune hepatitis refractory to therapy were switched from azathioprine to methotrexate [10 mg/wk subcutaneously] and had a complete biochemical response allowing eventual discontinuation of prednisone and maintained remission for more than 5 years on methotrexate alone).

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;137:637–9. PubMed PMID: 21719043.

(Among 53 patients with autoimmune diseases being treated with methotrexate [for 2 weeks to 10 years], transient elastography was abnormal in 4 [8%], but did not correlate with duration of therapy or total dose; liver histology was not studied).

Montaudié H, Sbidian E, Paul C, Maza A, Gallini A, Aractingi S, Aubin F, et al. Methotrexate in psoriasis: a systematic review of treatment modalities, incidence, risk factors and monitoring of liver toxicity. J Eur Acad Dermatol Venereol. 2011;25 Suppl 2:12–8. PubMed PMID: 21388454.

(Systematic review of literature on hepatotoxicity of methotrexate in psoriasis identified 23 studies; "published studies do not confirm the incidence of hepatic fibrosis", the rate varying from 6-71% in 5 studies of 22-96 patients each followed for 1-11 years).

Moreno-Otero R, García-Buey L, García-Sanchez A, Trapero-Marugán M. Autoimmune hepatitis after long-term methotrexate therapy for rheumatoid arthritis. Curr Drug Saf. 2011;6:197–200. PubMed PMID: 22122395.

(57 year old man with rheumatoid arthritis developed jaundice 3 years after starting long term methotrexate [bilirubin 3.3 mg/dL, ALT 1715 U/L, Alk P 167 U/L, ANA 1:160 and previously negative], responding to corticosteroid therapy which was later stopped without relapse; unclear whether methotrexate was stopped).

Bishnoi P, Kumari R, Thappa DM. Monitoring methotrexate hepatotoxicity in psoriasis. Indian J Dermatol Venereol Leprol. 2011;77:545–8. PubMed PMID: 21860151.

(Review of safety and efficacy of methotrexate in psoriasis).

Gupta R, Bhatia J, Gupta SK. Risk of hepatotoxicity with add-on leflunomide in rheumatoid arthritis patients. Arzneimittelforschung. 2011;61:312–6. PubMed PMID: 21755815.

(Among 46 patients with rheumatoid arthritis who had leflunomide added to conventional disease modifying therapies, 22% had ALT or AST elevations, but none developed clinically apparent liver injury).

Anelli MG, Scioscia C, Grattagliano I, Lapadula G. Old and new antirheumatic drugs and the risk of hepatotoxicity. Ther Drug Monit. 2012;34:622–8. PubMed PMID: 23128910.

(Review of currently used antirheumatic drugs and their potential for hepatotoxicity).

Santiago García D, Saturansky E, Poncino D, Ortiz V, Martínez Artola Y, Rosenberg S, Abritta G, Palermo C, Enriquez N, Cravero A. Acta Gastroenterol Latinoam. 2012;42:112–9. [Liver diseases in rheumatoid and psoriatic arthritis]. Spanish. PubMed PMID: 22876713.

(Among 118 patients with inflammatory arthritis, 47 [40%] had evidence of liver disease, including 35 [30%] with nonalcoholic fatty liver and 15 [13%] drug induced liver injury).

Tugnet N, Cooper SC, Douglas KM. Methotrexate therapy, rheumatoid arthritis, and life-threatening liver complications: should we be monitoring more closely? Scand J Rheumatol. 2012;41:163–4. PubMed PMID: 22420415.

(26 year old woman with rheumatoid arthritis developed variceal hemorrhage after 4 years of methotrexate therapy [bilirubin 4.1 mg/dL, ALT 377 U/L, Alk P 166 U/L, platelets 80,000/μL, INR 2.4], improving after stopping and switching to etanercept).

Gilani ST, Khan DA, Khan FA, Ahmed M. Adverse effects of low dose methotrexate in rheumatoid arthritis patients. J Coll Physicians Surg Pak. 2012;22:101–4. PubMed PMID: 22313647.

(Methotrexate levels and clinical toxicity in 140 patients with rheumatoid arthritis on 10 mg/week found ALT or AST elevations in 2.1% and higher toxicity in those with higher levels in plasma).

Khan N, Abbas AM, Whang N, Balart LA, Bazzano LA, Kelly TN. Incidence of liver toxicity in inflammatory bowel disease patients treated with methotrexate: a meta-analysis of clinical trials. Inflamm Bowel Dis. 2012;18:359–67. PubMed PMID: 21751301.

(Metaanalysis of trials of methotrexate for inflammatory bowel disease identified 13 trials with 632 participants treated for 2.7-18 months; risk of ALT elevations [>2 times ULN] was 0.9 per 100 person-months).

Dávila-Fajardo CL, Swen JJ, Cabeza Barrera J, Guchelaar HJ. Genetic risk factors for drug-induced liver injury in rheumatoid arthritis patients using low-dose methotrexate. Pharmacogenomics. 2013;14:63–73. PubMed PMID: 23252949.

(Review of pharmacogenomics of methotrexate toxicity focusing upon MTHFR).

Björnsson ES, Bergmann OM, Björnsson HK, Kvaran RB, Olafsson S. Incidence, presentation and outcomes in patients with drug-induced liver injury in the general population of Iceland. Gastroenterology. 2013;144:1419–25. PubMed PMID: 23419359.

(In a population based study of drug induced liver injury from Iceland, 96 cases were identified over a 2 year period, one of which was attributed to methotrexate).

van Swelm RP, Laarakkers CM, Kooijmans-Otero M, de Jong EM, Masereeuw R, Russel FG. Biomarkers for methotrexate-induced liver injury: urinary protein profiling of psoriasis patients. Toxicol Lett. 2013;221:219–24. PubMed PMID: 23830989.

(Analysis of urinary protein profiles of patients on long term methotrexate therapy for psoriasis identified several urinary proteins that might serve as noninvasive markers of fibrosis progression including N-cadherin, ITIH4, haptoglobin and serotransferrin).

Ng LC, Lee YY, Lee CK, Wong SM. A retrospective review of methotrexate-induced hepatotoxicity among patients with psoriasis in a tertiary dermatology center in Malaysia. Int J Dermatol. 2013;52:102–5. PubMed PMID: 23278617.

(Among 66 patients with psoriasis treated with methotrexate between 2000 and 2009 at a Malaysian medical center, 58% had ALT or AST elevations during treatment, but therapy was stopped for enzyme elevations in only 6 patients and no patient developed cirrhosis).

Dávila-Fajardo CL, Swen JJ, Cabeza Barrera J, Guchelaar HJ. Genetic risk factors for drug-induced liver injury in rheumatoid arthritis patients using low-dose methotrexate. Pharmacogenomics. 2013;14:63–73. PubMed PMID: 23252949.

(Review of literature on clinical and genetic risk factors for methotrexate hepatotoxicity, mentions routine factors of obesity, alcohol use, diabetes, lack of folate supplementation, concurrent hepatotoxic medications, duration of therapy and total dose, and polymorphisms of the MTHFR gene, the role of which is not well supported by the literature).

Ksouda K, Affes H, Atheymen R, Ezzeddine M, Zeghal K, Hammami S. Autoimmune hepatitis as an adverse effect of long-term methotrexate therapy. Indian J Pharmacol. 2014;46:649–50. PubMed PMID: 25538339.

(53 year old woman with psoriatic arthritis on long term methotrexate therapy [15 mg weekly] with a clinical response and minimal ALT and AST elevations developed fatigue, weight loss and jaundice [bilirubin 12 mg/dL, ALT 620 U/L Alk P 170 U/L, GGT 146 U/L and both ANA and AMA positivity], with resolution of stopping methotrexate and high dose corticosteroid therapy which could eventually be withdrawn).

Hardwick RN, Clarke JD, Lake AD, Canet MJ, Anumol T, Street SM, Merrell MD, et al. Increased susceptibility to methotrexate-induced toxicity in nonalcoholic steatohepatitis. Toxicol Sci. 2014;142:45–55. PubMed PMID: 25080921.

(Rats given a methionine-choline deficient diet developed steatohepatitis and were more susceptible to hepatic and renal toxicity from high dose methotrexate).

Bath RK, Brar NK, Forouhar FA, Wu GY. A review of methotrexate-associated hepatotoxicity. J Dig Dis. 2014;15:517–24. PubMed PMID: 25139707.

(Review of the mechanism of action of methotrexate and its hepatotoxicity including clinical features, risk factors, guidelines for monitoring, liver biopsy findings and recommendations for minimizing risk).

Schmajuk G, Miao Y, Yazdany J, Boscardin WJ, Daikh DI, Steinman MA. Identification of risk factors for elevated transaminases in methotrexate users through an electronic health record. Arthritis Care Res (Hoboken). 2014;66:1159–66. PubMed PMID: 24470205.

(Among 659 "users" of methotrexate identified in the electronic health records from the National Veterans Administration Hospital database who were followed for at least 180 days, 126 [19%] had ALT or AST elevations; in multivariate analysis, risk factors for developing abnormalities were obesity, elevated cholesterol levels, baseline liver test abnormalities, use of biologics and no folic acid use).

Strober BE. Practice gaps. Methotrexate-induced liver toxicity: replacing the liver biopsy. JAMA Dermatol. 2014;150:862–3. PubMed PMID: 24965863.

(Commentary on Lynch et al [2014] mentions that most noninvasive tests such as "Fibrosure", procollagen III peptide and elastography have unsatisfactory rates of sensitivity and specificity in cross sectional studies; they may perform better when applied prospectively and recommends that "dermatology should abandon the liver biopsy").

Lynch M, Higgins E, McCormick PA, Kirby B, Nolan N, Rogers S, Lally A, et al. The use of transient elastography and FibroTest for monitoring hepatotoxicity in patients receiving methotrexate for psoriasis. JAMA Dermatol. 2014;150:856–62. PubMed PMID: 24964792.

(Among 77 adults with psoriasis treated with methotrexate, ultrasound elastography was successful in only 50 [65%] and were abnormally high in 9 [18%], but only one had an elevated ALT level and abnormalities did not correlate with duration of treatment or total dose).

te Loo DM, Hagleitner MM, Coenen MJ. Is there a role for the MTHFR 677C>T and 1298A>C polymorphisms in methotrexate-induced liver toxicity? Pharmacogenomics. 2014;15:1401–3. PubMed PMID: 25303291.

(Commentary on the possible role of testing for polymorphisms of folate pathway enzymes [MTHFR and DHFR] for their effects on folate metabolism and risk of methotrexate hepatotoxicity, concludes that "it is still unclear").

Khabbazi A, Kolahi S, Dastgiri S, Hajialiloo M, Nazeri M, Nazeri L, Sheikholeslami Salmasi A, et al. Safety of less frequent monitoring of liver transaminases levels in rheumatic patients treated with low-dose methotrexate. Int J Rheum Dis. 2014;17:646–52. PubMed PMID: 24965662.

(Among 809 Iranian patients with connective tissue diseases treated with methotrexate for a mean of 32 months who were monitored every 3 months, ALT or AST elevations arose in 108 [13%], leading to dose reduction in 26 [3.2%] and discontinuation in only 4 [0.5%]; no patient developed cirrhosis or end-stage liver disease).

Kubota M, Nakata R, Adachi S, Watanabe K, Heike T, Takeshita Y, Shima M. Plasma homocysteine, methionine and S-adenosylhomocysteine levels following high-dose methotrexate treatment in pediatric patients with acute lymphoblastic leukemia or Burkitt lymphoma: association with hepatotoxicity. Leuk Lymphoma. 2014;55:1591–5. PubMed PMID: 24090503.

(Among 16 children with cancer receiving 26 courses of high dose methotrexate, sequential changes in plasma homocysteine, methionine and S-adenosylhomocysteine levels correlated with concurrent peak elevations in serum ALT [median 28 to 86 U/L] during the 3 days after the infusions).

Park HJ, Park MC, Park YB, Lee SK, Lee SW. The concomitant use of meloxicam and methotrexate does not clearly increase the risk of silent kidney and liver damages in patients with rheumatoid arthritis. Rheumatol Int. 2014;34:833–40. PubMed PMID: 24362788.

(Among 101 Korean patients with rheumatoid arthritis treated with methotrexate and meloxicam for six months, changes in estimated glomerular filtrate rate and liver stiffness measurements by elastography did not correlate with either the weekly and total doses of either drug).

Hagleitner MM, Coenen MJ, Aplenc R, Patiño-Garcia A, Chiusolo P, Gemmati D, De Mattei M, et al. The role of the MTHFR 677C>T polymorphism in methotrexate-induced liver toxicity: a meta-analysis in patients with cancer. Pharmacogenomics J. 2014;14:115–9. PubMed PMID: 23648444.

(Among 98 Dutch children receiving high dose methotrexate for acute lymphoblastic leukemia or osteosarcoma, the distribution of 677C >T polymorphisms of the methylene-tetra-hydro-folate reductase gene [MTHFR] showed a trend for a higher rate of hepatotoxicity with TT compared to CC [specific proportions not provided], but the results were considered "indecisive").

Willner N, Storch S, Tadmor T, Schiff E. Almost a tragedy: severe methotrexate toxicity in a hemodialysis patient treated for ectopic pregnancy. Eur J Clin Pharmacol. 2014;70:261–3. PubMed PMID: 24276413.

(21 year old woman on long term hemodialysis developed fever, rash and desquamation within 24 hours of receiving intravenous methotrexate [100 mg] for an ectopic pregnancy along with tramadol and dipyrone as analgesics, followed by transient but severe myelosuppression treated with leucovorin rescue; no mention of hepatotoxicity).

Topaloğlu S, Çalık A, Kalaycı O, Çeşmecioğlu E, Çobanoğlu Ü, Uzun Y. Fibrosing cholestatic hepatitis after methotrexate and prednisone therapy for rheumatoid arthritis. Exp Clin Transplant. 2014;12 Suppl 1:95–7. PubMed PMID: 24635802.

(55 year old woman with chronic hepatitis B and rheumatoid arthritis developed worsening liver tests 5 months after starting methotrexate [15 mg/week] and prednisone [10 mg/day] with evidence of HBV reactivation [bilirubin 20 mg/dL, ALT 2272 U/L, HBV DNA > 20 million IU/mL], progressing to hepatic failure despite stopping methotrexate and therapy with lamivudine, and undergoing liver transplantation, the explant demonstrating fibrosing cholestatic hepatitis).

Valentino PL, Church PC, Shah PS, Beyene J, Griffiths AM, Feldman BM, Kamath BM. Hepatotoxicity caused by methotrexate therapy in children with inflammatory bowel disease: a systematic review and meta-analysis. Inflamm Bowel Dis. 2014;20:47–59. PubMed PMID: 24280876.

(Review of 12 published studies of methotrexate safety, reported 57 of 457 [10.2%] children with inflammatory bowel disease developed varying degrees of biochemical abnormalities which led to discontinuation in approximately half).

Hernández N, Bessone F, Sánchez A, di Pace M, Brahm J, Zapata R, A, Chirino R, et al. Profile of idiosyncratic drug induced liver injury in Latin America: an analysis of published reports. Ann Hepatol. 2014;13:231–9. PubMed PMID: 24552865.

(Among 176 reports of drug induced liver injury from Latin America published between 1996 and 2012, ten were attributed to antineoplastic agents, 6 were due to methotrexate).

Chalasani N, Bonkovsky HL, Fontana R, Lee W, Stolz A, Talwalkar J, Reddy KR, et al.; United States Drug Induced Liver Injury Network. Features and outcomes of 899 patients with drug-induced liver injury: The DILIN Prospective Study. Gastroenterology 2015; 148: 1340-52. e7.

(Among 899 cases of drug induced liver injury enrolled in a US prospective study between 2004 and 2013, 49 cases were attributed to antineoplastic agents, 3 of which were due to methotrexate).

Conway R, Low C, Coughlan RJ, O'Donnell MJ, Carey JJ. Risk of liver injury among methotrexate users: A meta-analysis of randomised controlled trials. Semin Arthritis Rheum. 2015;45:156–62. PubMed PMID: 26088004.

(Metaanalysis of 32 published controlled trials of methotrexate in inflammatory arthridities and inflammatory bowel disease in 13,177 participants found increased rates of minor and major liver enzyme abnormalities with methotrexate compared to comparator arms, but no increased risk of death, cirrhosis or liver failure).

Kim TY, Kim JY, Sohn JH, Lee HS, Bang SY, Kim Y, Kim MY, et al. Assessment of substantial liver fibrosis by real-time shear wave elastography in methotrexate-treated patients with rheumatoid arthritis. J Ultrasound Med. 2015;34:1621–30. PubMed PMID: 26269292.

(Among 185 adults with rheumatoid arthritis being treated with methotrexate, liver stiffness as measured by real-time shear wave elastography was greater than in 81 healthy controls [5.9 vs 5.4 kPa] and was above 8.6 kPa in 9 patients [5%]; liver stiffness did not correlate with total methotrexate dose but did with body mass index).

Schröder T, Schmidt KJ, Olsen V, Möller S, Mackenroth T, Sina C, Lehnert H, et al. Liver steatosis is a risk factor for hepatotoxicity in patients with inflammatory bowel disease under immunosuppressive treatment. Eur J Gastroenterol Hepatol. 2015;27:698–704. PubMed PMID: 25923946.

(Among 259 patients with inflammatory bowel disease, 73 [28%] had evidence of hepatic steatosis on ultrasound; those with steatosis were older, had higher BMIs and were more likely to have elevated liver tests [29% vs 15%] than those without steatosis but were similar in regards to sex, disease, and immunosuppressive regimen).

Mengual-Moreno E, Lizarzábal-García M, Ruiz-Soler M, Silva-Suarez N, Andrade-Bellido R, Lucena-González M, Bessone F, et al. Invest Clin. 2015;56:3–12. [Case reports of drug-induced liver injury in a reference hospital of Zulia state, Venezuela]. Spanish. PubMed PMID: 25920181.

(Among 14 patients with drug induced liver injury seen at a single hospital in Venezuela in 2012-2013, the most common implicated drugs were ibuprofen [n=3], acetaminophen [3], isoniazid [2], and Herbalife products [2]; 1 case was attributed to methotrexate, a 51 year old woman with sarcoidosis treated for 12 months [ALT 214 U/L, Alk P [68 U/L], bilirubin 1.0 mg/dL], resolving with discontinuation).

Osuga T, Ikura Y, Kadota C, Hirano S, Iwai Y, Hayakumo T. Significance of liver biopsy for the evaluation of methotrexate-induced liver damage in patients with rheumatoid arthritis. Int J Clin Exp Pathol. 2015;8:1961–6. PubMed PMID: 25973089.

(Four patients with methotrexate hepatotoxicity who underwent liver biopsy, ages 67 to 80 years on therapy for 3-20 years [ALT 13, 29, 119 and 136 U/L, GGT 16, 14, 32 and 129 U/L, albumin 2.9, 3.0, 4.1 and 4.0 g/dL], liver biopsies not showing cirrhosis in cases 1 and 2 both of whom had ascites, splenomegaly and atrophic liver by CT scan, leading the authors to conclude that "liver biopsy is an unavoidable examination").

Tsurusawa M, Gosho M, Mori T, Mitsui T, Sunami S, Kobayashi R, Fukano R, et al. lymphoma committee of the Japanese Pediatric Leukemia/lymphoma Study Group. Statistical analysis of relation between plasma methotrexate concentration and toxicity in high-dose methotrexate therapy of childhood non-Hodgkin lymphoma. Pediatr Blood Cancer. 2015;62:279–84. PubMed PMID: 25359701.

(Among 304 children with non-Hodgkin Lymphoma treated with high doses of methotrexate who had drug levels measured at 24, 48 and 72 hours, rates and severity of renal but not liver and gastrointestinal [GI] toxicities correlated with higher methotrexate levels and rates of liver and GI toxicities were highest with the first and decreased with subsequent courses).

Rabinowich L, Shibolet O. Drug induced steatohepatitis: An uncommon culprit of a common disease. Biomed Res Int. 2015;2015:168905. PubMed PMID: 26273591.

(Review of the clinical and histologic features of drug induced fatty liver including that caused by aspirin [Reyes], glucocorticoids, iv tetracycline, valproate, alcohol, amiodarone, irinotecan, tamoxifen and methotrexate; mentions that liver enzyme abnormalities develop in 6-24% of patients receiving long term methotrexate but that significant fibrosis or cirrhosis is uncommon [~5%], and end-stage liver disease requiring transplantation is rare [representing 0.07% of liver transplants done in the U.S.]).

Miyagawa K, Shibata M, Noguchi H, Hayashi T, Oe S, Hiura M, Abe S, et al. Methotrexate-related primary hepatic lymphoma in a patient with rheumatoid arthritis. Intern Med. 2015;54:401–5. PubMed PMID: 25748956.

(56 year old woman with rheumatoid arthritis on methotrexate for six years developed primary large B-cell lymphoma primarily involving the liver [bilirubin 0.7 mg/dL, ALT 23 U/L, Alk P 490 U/L], the tumors responding to stopping methotrexate and six courses of R-CHOP).

Howard SC, McCormick J, Pui CH, Buddington RK, Harvey RD. Preventing and Managing Toxicities of High-Dose Methotrexate. Oncologist. 2016;21:1471–82. PubMed PMID: 27496039.

(Review of toxicities of high doses of methotrexate and their management focusing upon rehydration, urine alkalinization and use of leucovorin doses that reverse the inhibition of intracellular dihydrofolate reductase).

Warren RB, Weatherhead SC, Smith CH, Exton LS, Mohd Mustapa MF, Kirby B, Yesudian PD. British Association of Dermatologists' guidelines for the safe and effective prescribing of methotrexate for skin disease 2016. Br J Dermatol. 2016;175:23–44. PubMed PMID: 27484275.

(Guidelines for the use of methotrexate in inflammatory skin diseases as well as monitoring for liver injury during therapy recommends routine liver tests and procollagen III peptide levels before and every 3 months during methotrexate therapy, with referral to specialist if levels remain elevated; routine liver biopsy not recommended).

Tang KT, Hung WT, Chen YH, Lin CH, Chen DY. Methotrexate is not associated with increased liver cirrhosis in a population-based cohort of rheumatoid arthritis patients with chronic hepatitis B. Sci Rep. 2016;6:22387. PubMed PMID: 26928373.

(Analysis of the Taiwan National Health Insurance Research Database identified 631 incidence cases of rheumatoid arthritis among patients with concurrent chronic hepatitis B, and over an average of 6 years of follow up, the rate of subsequent diagnosis of cirrhosis was the same in those on methotrexate [22 of 358: 6%] as in those who were not [17 of 273: 7%], similarly decompensated cirrhosis arose in 1% of both groups; factors associated with a higher rate of developing cirrhosis were age, male sex and concurrent nonalcoholic fatty liver disease).

Villegas Rubio JA, Cacciavillano W, Rose A, Zubizarreta P, Scopinaro M. Ambulatory high-dose methotrexate administration in pediatric osteosarcoma patients at a single institution in Argentina. J Pediatr Hematol Oncol. 2017;39:e349–e352. PubMed PMID: 28937522.

(Over a 4 year period, 150 of 447 courses of high dose methotrexate were given to 24 Argentinian children with osteosarcoma as outpatients, 39% of which were associated with ALT or AST elevations above 5 times ULN, but there were no life threatening events or toxicity related deaths and a total of 324 hospital days were saved).

Humphreys JH, Warner A, Costello R, Lunt M, Verstappen SMM, Dixon WG. Quantifying the hepatotoxic risk of alcohol consumption in patients with rheumatoid arthritis taking methotrexate. Ann Rheum Dis. 2017;76:1509–14. PubMed PMID: 28341765.

(Among 11,839 patients with rheumatoid arthritis receiving methotrexate who were followed in the Clinical Practice Research Datalink, there were 530 episodes of aminotransferase elevations in whom there was a borderline association with 15-21 units of alcohol consumption per week and statistically significant at above 21, suggesting that weekly alcohol intake should be less than 14 per week in persons receiving methotrexate).

Talme T, Nikamo P, Rosenberg P, Ståhle M. Transient elastography may improve detection of liver fibrosis in psoriasis patients treated with methotrexate. Acta Derm Venereol. 2017;97:952–4. PubMed PMID: 28422266.

(Among 201 patients with psoriasis undergoing transient elastography, mild and severe increase in hepatic stiffness was identified in 38% and 3% on biologics and methotrexate <6 months, 32% and 6% on methotrexate for <24 months and 38% and 9% for >24 months, the major associations with increased stiffness being age, body mass index and diabetes).

Shetty A, Cho W, Alazawi W, Syn WK. Methotrexate hepatotoxicity and the impact of nonalcoholic fatty liver disease. Am J Med Sci. 2017;354:172–81. PubMed PMID: 28864376.

(Review of the epidemiology, clinical features, histology and natural history of nonalcoholic fatty liver and possible interaction of it with methotrexate hepatotoxicity).

Cabello Zurita C, Grau Pérez M, Hernández Fernández CP, González Quesada A, Valerón Almazán P, Vilar Alejo J, Carretero Hernández G. Effectiveness and safety of methotrexate in psoriasis: an eight-year experience with 218 patients. J Dermatolog Treat. 2017;28:401–5. PubMed PMID: 28001499.

(Among 218 Spanish patients with psoriasis followed for up to 8 years, 67% received methotrexate as the first systemic treatment, for an average of 17 months, half achieving a clinical response and only 3% stopping therapy because of liver abnormalities, none requiring liver biopsy or developing cirrhosis or end-stage liver disease).

Rongngern P, Chularojanamontri L, Wongpraparut C, Silpa-Archa N, Chotiyaputta W, Pongpaibul A, Charatcharoenwitthaya P. Diagnostic performance of transient elastography for detection of methotrexate-induced liver injury using Roenigk classification in Asian patients with psoriasis: a retrospective study. Arch Dermatol Res. 2017;309:403–8. PubMed PMID: 28303329.

(Among 41 patients with psoriasis on long term methotrexate [mean 6.4 years] who underwent both liver biopsy and transient elastography [TE] over a 11 year period, 8 had mild [F1, Roenigk stage 3b: TE 4.4-10.0], 2 had moderate fibrosis [F3, Roenigk stage 3a: TE 6.6 and 10], 31 had no fibrosis [Roenigk stage 1: TE 3.4-11.8]; the TE cutoff value for possible fibrosis of 7.1 having a sensitivity of only 50% and specificity of 77%).

Tran-Minh ML, Sousa P, Maillet M, Allez M, Gornet JM. Hepatic complications induced by immunosuppressants and biologics in inflammatory bowel disease. World J Hepatol. 2017;9:613–26. PubMed PMID: 28539989.

(Review of the liver adverse effects of drugs used to treat inflammatory bowel disease [IBD] mentions that the rate of liver abnormalities in IBD patients receiving methotrexate appears to be low in the range of 5-10% depending upon risk factors such as alcohol intake, obesity, diabetes and concurrent medications as well as use of folic acid; recommends regular monitoring of liver tests and possibly prospective use of transient elastography and other noninvasive means for assessing fibrosis).

Raaby L, Zachariae C, Østensen M, Heickendorff L, Thielsen P, Grønbæk H, Skov L, et al. Methotrexate use and monitoring in patients with psoriasis: a consensus report based on a Danish expert meeting. Acta Derm Venereol. 2017;97:426–32. PubMed PMID: 27958611.

(A Danish expert meeting on methotrexate monitoring in patients with psoriasis concludes that hepatotoxicity remains a clinical challenge and recommends monitoring with liver enzymes [every 2 weeks for 2 months

followed by every 3 months stopping therapy if they are more than 3 fold elevated] and with procollagen III peptide every 6 months [with transient elastography if levels are elevated]).

Ebbesen MS, Nygaard U, Rosthøj S, Sørensen D, Nersting J, Vettenranta K, Wesenberg F, et al. Hepatotoxicity during maintenance therapy and prognosis in children with acute lymphoblastic leukemia. J Pediatr Hematol Oncol. 2017;39:161–6. PubMed PMID: 28060115.

(Among 385 children with acute lymphoblastic leukemia enrolled in a prospective study of methotrexate and mercaptopurine maintenance therapy, the median ALT values during treatment were 100 U/L, elevations occurring in 91% of children and correlating with mercaptopurine dose and TPMT activity but not with subsequent relapse).

Miele L, Liguori A, Marrone G, Biolato M, Araneo C, Vaccaro FG, Gasbarrini A, et al. Fatty liver and drugs: the two sides of the same coin. Eur Rev Med Pharmacol Sci. 2017;21(1 Suppl):86–94. PubMed PMID: 28379591.

(Review of drugs that can cause fatty liver including methotrexate).

Massart J, Begriche K, Moreau C, Fromenty B. Role of nonalcoholic fatty liver disease as risk factor for drug-induced hepatotoxicity. J Clin Transl Res. 2017;3 Suppl 1:212–32. PubMed PMID: 28691103.

(Extensive review of drug induced liver injury and the role of preexisting obesity and nonalcoholic fatty liver disease [NAFLD] as risk factors and evidence that drugs that cause fatty liver can exacerbate NAFLD).

Tang KT, Chen YM, Chang SN, Lin CH, Chen DY. Psoriatic patients with chronic viral hepatitis do not have an increased risk of liver cirrhosis despite long-term methotrexate use: Real-world data from a nationwide cohort study in Taiwan. J Am Acad Dermatol. 2018;79:652–8. PubMed PMID: 29753054.

(Analysis of the Taiwan National health Insurance Research Database identified 2417 psoriasis patients with chronic hepatitis B [370 on methotrexate] and 1127 with chronic hepatitis C [174 on methotrexate] who were followed for more than 9 years since the diagnosis and found that the rate of cirrhosis development was the same in those of methotrexate and those who were not: 5% vs 4-5% with hepatitis B and 11% vs 11% with hepatitis C).

Bielen L, Kralj I, Ćurčić E, Vodanović M, Boban A, Božina N. Acute kidney injury, agranulocytosis, drug-induced liver injury, and posterior reversible encephalopathy syndrome caused by high-dose methotrexate-possible role of low activity ABC and SLC drug transporters. Eur J Clin Pharmacol. 2018;74:1191–2. PubMed PMID: 29789870.

(26 year old man with acute lymphoblastic leukemia developed combined bone marrow, renal, hepatic, central nervous system toxicities perhaps due to a heterozygous variant for MTHFR C677T and A1298C as well as coadministration of pantoprazole, ciprofloxacin, piperacillin and ketoprofen).

Shamberg L, Vaziri H. Hepatotoxicity of inflammatory bowel disease medications. J Clin Gastroenterol. 2018;52:674–84. PubMed PMID: 30036242.

(Review of drugs for inflammatory bowel disease and their potential for hepatotoxicity mentions that rates of serum enzyme elevations with methotrexate therapy is lower in IBD than in rheumatic diseases).

Ortega-Alonso A, Andrade RJ. Chronic liver injury induced by drugs and toxins. J Dig Dis. 2018;19:514–21. PubMed PMID: 29808546.

(Review of the frequency, course and causes of chronic liver injury from medications, rates of which have varied from 6-39% depending upon definition, clinical patterns being steatohepatitis [as with methotrexate], nodular regenerative hyperplasia and cirrhosis [possibly with methotrexate], autoimmune hepatitis [reported with methotrexate] and vanishing bile duct syndrome [usually due to severe acute cholestatic hepatitis]).

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. PubMed PMID: 30142184.

(Among 846 Japanese patients with rheumatoid arthritis on methotrexate therapy monitored for 1 year, 51 had persistent ALT or AST elevations and were on average older, more like to be obese, to have diabetes, and elevated cholesterol and uric acid levels, but had similar total methotrexate dose and duration of treatment to those without elevations; ultrasonography showing increased hepatic fat in 42 while liver biopsy in 32 showed steatosis, 22 with NASH- like changes, 15 with advanced fibrosis but none with cirrhosis).

Svanström H, Lund M, Melbye M, Pasternak B. Concomitant use of low-dose methotrexate and NSAIDs and the risk of serious adverse events among patients with rheumatoid arthritis. Pharmacoepidemiol Drug Saf. 2018;27:885–93. PubMed PMID: 29797447.

(Analysis of 17,200 new users of low dose methotrexate from the Danish National Patient Register found an increased risk of serious adverse events among those taking an NSAID concurrently compared to those on methotrexate alone; rates per 1000 person-years being 12.1 vs 11.0, rates of renal and hematologic adverse events being higher but hepatotoxicity rates being lower [0.3 vs 0.6 per 1000 person-years]).

Hakamata J, Hashiguchi M, Kaneko Y, Yamaoka K, Shimizu M, Maruyama J, Takeuchi T, et al. Risk factors for abnormal hepatic enzyme elevation by methotrexate treatment in patients with rheumatoid arthritis: A hospital based-cohort study. Mod Rheumatol. 2018;28:611–20. PubMed PMID: 29252093.

(Among 114 Japanese patients with rheumatoid arthritis starting treatment with methotrexate and monitored for one year, 32 developed liver enzyme elevations [28%], rates being higher in those with in those with genetic polymorphisms of ABCB1 3435C>T [34% vs 16%] but not for rates of elevations >2 times ULN [14% vs 14%]).

Cheng HS, Rademaker M. Monitoring methotrexate-induced liver fibrosis in patients with psoriasis: utility of transient elastography. Psoriasis (Auckl). 2018;8:21–9. PubMed PMID: 29785393.

(Review of issues of monitoring patients with psoriasis on methotrexate therapy, recommending use of transient elastography at baseline and every three years if stiffness measurements are <7.5, yearly if 7.5-9.5, stopping therapy or further investigations and possibly liver biopsy if >9.5).

Fiore M, Leone S, Maraolo AE, Berti E, Damiani G. Liver Illness and Psoriatic Patients. Biomed Res Int. 2018;2018:3140983. PubMed PMID: 29546055.

(Review of liver complications of psoriasis and its therapy discusses methotrexate hepatotoxicity which may be more frequent in patients with psoriasis than in those with rheumatoid arthritis or inflammatory bowel disease).

Wood PR, Caplan L. Drug-induced gastrointestinal and hepatic disease associated with biologics and nonbiologic disease-modifying antirheumatic drugs. Rheum Dis Clin North Am. 2018;44:29–43. PubMed PMID: 29149926.

(Review of drug induced gastrointestinal and liver injury due to disease modifying antirheumatic drugs including methotrexate, azathioprine, tofacitinib, sulfasalazine, hydroxychloroquine and leflunomide as well as biologics such as tocilizumab, ustekinumab and infliximab).

Drugs for inflammatory bowel disease. Med Lett Drugs Ther. 2018;60(1550):107–14. PubMed PMID: 30036352.

(Concise review of the management of inflammatory bowel disease and safety and efficacy of drugs used, includes mention of methotrexate as an alternative to azathioprine and mercaptopurine, its adverse events including hepatotoxicity).

Efe C, Ozaslan E, Purnak T. Methotrexate in the treatment of autoimmune hepatitis. Clin Gastroenterol Hepatol. 2018;16:149. PubMed PMID: 28844782.

(37 year old woman developed autoimmune hepatitis that was satisfactorily controlled with prednisolone and azathioprine, later developing rheumatoid arthritis and switched to methotrexate which controlled both the arthritis and the hepatitis, serum aminotransferase levels remaining normal).

Haridy J, Nicoll A, Sood S. Methotrexate therapy for autoimmune hepatitis. Clin Gastroenterol Hepatol. 2018;16:288–9. PubMed PMID: 28711687.

(Among 11 Australian patients with refractory autoimmune hepatitis and lack of response or intolerance to azathioprine, switching to methotrexate [7.5-20 mg/wk] lead to a complete biochemical remission in 6 who had a long term response, but was associated with worsening of the hepatitis in the remaining 5 which led to discontinuation of methotrexate).

Alfaro-Lara R, Espinosa-Ortega HF, Arce-Salinas CA; PRECIS study group. all physicians belong to Division of Internal Medicine. Hospital Central Sur de Pemex. Systematic review and meta-analysis of the efficacy and safety of leflunomide and methotrexate in the treatment of rheumatoid arthritis. Reumatol Clin. 2019;15:133–9. PubMed PMID: 28867467.

(Systematic review of 6 publications on efficacy and safety of leflunomide vs methotrexate indicated that leflunomide was probably as effective as methotrexate, and was less likely to cause serum aminotransferase elevations [6.3% vs 15%]).

Miyata M, Kuroda M, Unakami M, Tasaki K, Migita K, Ohira H. Validation of the fibrosis-4 (FIB-4) index in the diagnosis of liver disease of rheumatoid arthritis patients treated with methotrexate. Mod Rheumatol. 2019;29:936–42. PubMed PMID: 30379089.

(Fib-4 scores were calculated on 395 patients with rheumatoid arthritis on long term methotrexate therapy focusing on 14 who underwent liver biopsy for suspect hepatotoxicity among whom Fib-4 scores improved after stopping therapy).

Karlsson Sundbaum J, Eriksson N, Hallberg P, Lehto N, Wadelius M, Baecklund E. Methotrexate treatment in rheumatoid arthritis and elevated liver enzymes: A long-term follow-up of predictors, surveillance, and outcome in clinical practice. Int J Rheum Dis. 2019;22:1226–32. PubMed PMID: 31012257.

(Among 213 patients with rheumatoid arthritis started on methotrexate and followed for an average of 4.3 years with regular monitoring, 44 [21%] developed ALT elevations and 7 [3%] stopped therapy because of persistent elevations, most of whom had elevations during follow up off of methotrexate, but no patients develop cirrhosis or signs hepatic failure).

Pivovarov K, Zipursky JS. Low-dose methotrexate toxicity. CMAJ. 2019;191:E423. PubMed PMID: 30988043.

(Recommendations on use of low dose methotrexate in rheumatoid arthritis, inflammatory arthritidies and Crohn disease advises measuring routine liver tests liver tests before starting, followed by monitoring every 2-4 weeks for the first 3 months, every 8-12 weeks for the second 3 months and every 12 weeks thereafter, and taking folic acid [1 mg] on days that methotrexate is not taken).

Labadie JG, Jain M. Noninvasive tests to monitor methotrexate-induced liver injury. Clin Liver Dis (Hoboken). 2019;13:67–71. PubMed PMID: 30988939.

(Brief review of noninvasive tests of fibrosis that can be used to monitor for methotrexate hepatotoxicity including transient elastography, procollagen III peptide and Fibrosure).

Lertnawapan R, Chonprasertsuk S, Siramolpiwat S. Association between cumulative methotrexate dose, non-invasive scoring system and hepatic fibrosis detected by Fibroscan in rheumatoid arthritis patients receiving methotrexate. Int J Rheum Dis. 2019;22:214–21. PubMed PMID: 30565876.

(Among 108 patients with rheumatoid arthritis treated with low dose methotrexate who underwent transient elastography, 29 had elevations in liver stiffness measurements [kPa >7] and had significantly higher average BMI, longer duration of therapy and total methotrexate dose, and higher ALT, GGT and INR levels than those with normal liver stiffness; but were similar in age, gender, alcohol and concurrent medication use, levels of HbA1c, creatinine and cholesterol, and scores for APRI and Fib-4).

Allard J, Le Guillou D, Begriche K, Fromenty B. Drug-induced liver injury in obesity and nonalcoholic fatty liver disease. Adv Pharmacol. 2019;85:75–107. PubMed PMID: 31307592.

(Summary of clinical and histologic features of drug induced liver injury in patients with obesity and nonalcoholic fatty liver disease (NAFLD), methotrexate having similar clinical and histologic features with NAFLD and hepatotoxicity seemingly more common in obese patients and those with underlying NAFLD).

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;18:765–9. PubMed PMID: 31105018.

(Application of the Roussel Uclaf Causality Assessment Method to 5 patients with psoriatic arthritis who developed ALT elevations during therapy suggested that all 5 were "improbable", 3 being more likely due to concurrent use of NSAIDs and 2 being more likely due to nonalcoholic fatty liver).

Kelgeri C, Ramakrishna SH, Brown RM, Al-Abadi E, Gupte GL. Liver injury in children with long-term low-dose methotrexate. Acta Paediatr. 2019 Dec 4. [Epub ahead of print]. PubMed PMID: 31799754.

(Among 742 children on long term methotrexate for nonmalignant disease, 14 underwent liver biopsy to guide therapy, 12 of whom were advised to continue or restart methotrexate and the two who stopped therapy had moderate-to-severe fibrosis and both had subsequent normalization of serum enzyme elevations).