

Liver fibrosis in patients with psoriasis and psoriatic arthritis on long-term, high cumulative dose methotrexate therapy

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Objectives. Dermatologists and rheumatologists have differed in their use of serial liver biopsy and liver function tests (LFT) to monitor the risk of hepatic fibrosis in long-term MTX therapy. It is judged safe to monitor LFT only in RA. Whilst there are few studies in PsA to justify this approach, it is widely used in rheumatology practice. The study aimed to assess prevalence of hepatic fibrosis in both psoriasis and PsA patients on long-term MTX therapy.

Methods. A prospective study of 54 patients with psoriatic disease had a liver biopsy according to dermatology guidelines on long-term MTX treatment with full assessment of risk factors. Previously, monitoring these patients was in accordance with ACR guidelines with 3-monthly LFT.

Results. MTX treatment duration was a mean of 6.9 years, with a mean cumulative dose of 4396 mg. There were no cases of advanced fibrosis or of cirrhosis and mild early fibrosis in 11 (22%) patients. The presence of early mild changes was related to the number of risk factors that the patient had for hepatic fibrosis [also the risk factors for non-alcoholic steatohepatitis (NASH)]. Pro-collagen 3N-terminal peptide (PIIINP) was unhelpful in PsA and frequently elevated despite normal liver biopsy.

Conclusions. Despite other risk factors for NASH, monitoring for hepatic fibrosis using serial liver function and ACR guidelines tests alone as in RA appears safe in psoriasis and PsA. Liver biopsy ought to be considered to assess the liver if LFT are persistently elevated. PIIINP is misleading in active PsA.

KEY WORDS: Liver fibrosis, Psoriasis, Psoriatic arthritis, Methotrexate therapy, Safety incidence, Liver biopsy.

Introduction

Long-term low-dose MTX given orally or injected once weekly is the most effective of the traditional DMARD agents for RA and PsA and is also used widely for skin psoriasis. The risk of cirrhosis from long-term treatment with MTX has resulted in successive monitoring guidelines being proposed [1, 2]. Dermatologists originally began using MTX for psoriasis in the 1950s when reports of cirrhosis and death attributed to its use were published [3]. Drug-induced hepatic fibrosis and cirrhosis in RA and psoriasis are said to be dose dependent; late complications of MTX therapy are more common when associated with certain risk factors. Diabetes, obesity, impaired renal function, alcohol consumption or significant pre-MTX changes on liver biopsy have been implicated as risk factors in psoriasis [4]. MTX hepatotoxicity has similar risk factors in rheumatoid disease, namely pre-treatment hepatic abnormalities, diabetes, obesity, current and previous heavy alcohol use [2]. Non-alcoholic steatohepatitis (NASH) or non-alcoholic fatty liver disease (NAFLD) is increasingly common given the rise in obesity and can lead to cirrhosis particularly when present with another hepatic insult such as alcohol or MTX. It causes abnormal liver function tests (LFT) and is associated with the same risk factors as MTX hepatotoxicity, namely diabetes, age and obesity. Undoubtedly, NASH has been responsible for an overestimate of the incidence and severity of MTX hepatotoxicity from previous studies and will continue to confound future studies [5].

Guidelines for MTX monitoring in cutaneous psoriasis suggest that a baseline liver biopsy should be performed at 2–4 months if

there are recognized risk factors for hepatic fibrosis and thereafter, at a cumulative dose of 1–1.5 g of MTX [6]. Rheumatologists have developed guidelines separately by monitoring the LFT only in RA based on long-term safety data [2]. There is a paucity of data on this topic in PsA; however, a meta-analysis of studies of long-term MTX treatment in RA, psoriasis and PsA suggests that there may be three times greater risk of hepatic fibrosis in psoriatic disease [7]. A small retrospective study of 17 patients with PsA on MTX showed no advanced liver fibrosis; however, there was again poor correlation with LFT and the cumulative dose was low [8]. Some of the potential causes for the apparent difference between liver fibrosis in psoriasis and rheumatoid disease have been discussed previously; namely increased alcohol consumption in psoriasis, anti-inflammatory medications suppressing hepatic inflammation in RA and better availability of long-term safety data in RA [9]. It remains a concern that patients with PsA monitored by LFT alone could be at risk of undetected advanced liver fibrosis [9, 10] as it is in NAFLD [11].

Developments in non-invasive monitoring of hepatic fibrosis and composites of several available serological markers of collagen turnover, imaging techniques and tests of liver stiffness are reducing the requirement for serial liver biopsies in hepatitis C and NAFLD [12]. Given that our hepatology colleagues' increasing familiarity of using long-term MTX, they may lead on the use of alternatives to liver biopsy in monitoring long-term MTX use, but they are not currently available to rheumatologists [13].

Pro-collagen 3N-terminal peptide (PIIINP), a serum marker of hepatic fibrosis, has been developed and is a readily available clinical test currently used routinely in dermatology practice to reduce the frequency of liver biopsy in psoriasis, although it has not been validated in psoriatic or RA and there is evidence that it may be artificially elevated in patients with active arthritis [14, 15]. Other markers of liver fibrosis are not validated in PsA at the time of our study. The liver biopsy therefore remains the gold standard for investigating suspected hepatic fibrosis [10]. The aims of this study were to investigate the prevalence of liver fibrosis in a group of patients with predominantly psoriatic arthritis on long-term MTX therapy and to pursue the clinical usefulness of PIIINP in the context of PsA treated with long-term MTX.

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Patients and methods

All patients with PsA and psoriasis alone on long-term MTX therapy were recruited to this prospective study from dermatology and rheumatology outpatient clinics in Leeds General Infirmary and Harrogate District hospital between October 2002 and May 2004. All patients gave their informed consent and the study was reviewed and approved by the local ethics committees.

ACR guidelines for long-term MTX monitoring in RA had previously been followed for those patients with PsA alone if seen predominantly in rheumatology clinic; but LFT were just as frequent as in the dermatology clinic [2]. Folic acid is given at 5 mg once daily except on the day of MTX. All had been on MTX and had been advised against alcohol consumption at the time of starting MTX. Liver biopsy was performed if >1 g of MTX had been taken cumulatively in keeping with dermatology guidelines [6]. Two days prior to liver biopsy, patients were assessed clinically for signs of cutaneous and joint psoriasis, liver disease, obesity (with height, weight, hip and waist measurements, and with obesity defined as BMI > 30), the presence of type I or II diabetes or chronic renal impairment. All current medications were documented and a quantitative history of alcohol consumption was obtained in units per week. The patients were also asked if they had ever consumed alcohol excessively in the past and the number of the above risk factors was counted for each patient, with either current or previous excess alcohol consumption counting as one of the risk factors. This was arbitrarily defined as greater than the recommended weekly amounts in the UK (14 U of alcohol for women and 21 U for men). Safety blood tests including full blood count, electrolytes, LFT, clotting studies and PIIINP was obtained. On the same day, joint disease activity was assessed using tender joint count, swollen joint count and enthesial tender point count.

Liver biopsy

A liver biopsy was performed by a consultant radiologist under ultrasound guidance. It was assessed by NHS consultant histopathologist and also reviewed by a special hepatic histopathologist for validation.

Statistics

Mann-Whitney U-tests for non-parametric data were used to determine the impact of risk factors on hepatic fibrosis.

Results

Demographic data

Fifty-four patients were recruited with both psoriatic skin and joint disease on long-term MTX and had liver biopsy between October 2002 and March 2004. The demographics data of patients are provided in Table 1. Fourteen patients were on subcutaneous MTX.

Psoriatic disease

Table 2 highlights the numbers of patients with PsA and psoriasis (PsA and Ps, respectively).

Risk factors

Four patients had insulin-dependent diabetes. Fifteen had a BMI >30 and were therefore obese. Of those who consumed alcohol, the mean number of self-reported alcoholic units consumed by our cohort was 10.9 per week. However, 16 consumed no alcohol at all. One had no alcohol history available. Nine patients had admitted to excessive alcohol consumption in the past and six of those were currently drinking greater than recommended amounts (males 22, 24, 34 and 42 U; females: 15, 18, 31 and 40 U).

TABLE 1. Demographic data and methotrexate cumulative dose for patients having liver biopsy

	Mean \pm s.d.	Range
Age, years	54.4 \pm 11	30–78
Disease duration, years	27.3 \pm 15	3–68
Skin disease duration, years	25.8 \pm 16	0–68
Arthritis duration, years	18.6 \pm 13	0–38
MTX duration, years	6.59 \pm 4.22	1.33–30
Weekly dose, mg	15.5 \pm 6.17	0–25
Cumulative dose, mg	4396 \pm 3140	1020–19657
Swollen joint count	2.51 \pm 3.69	0–12
Tender joint count	4.75 \pm 6.69	0–24
Leeds enthesial tender count	3.55 \pm 6.12	0–25

TABLE 2. Psoriatic disease characteristics

Ps or PSA	Ps alone	PSA alone	Both PSA and Ps	PsA
54	7	15	32	47

Biopsy results

Thirty-five (64.8%) had a normal biopsy (Roenigk Grade 1). Seven (13%) showed some early inflammatory or fatty change (Roenigk Grade 2). There were 11 (20%) who showed early mild fibrosis (Roenigk Grade 3). There were no cases of Grade 3b or 4 to suggest advanced fibrosis and no clinical evidence of liver disease.

Predictive value of LFT

LFT were available for all from the previous 12 months prior to biopsy. Most patients had been on long-term MTX and were on a stable dose. Only three patients had more than five abnormally raised transaminases in 1 year, under which circumstances the ACR guidelines recommend referral to a gastroenterologist for consideration of liver biopsy. These two consumed 20 and 40 U of alcohol, respectively, in addition to MTX. These both had normal liver biopsies. The third patient who did not drink alcohol had MTX stopped because of persistently abnormal LFT and early mild fibrosis detected on liver biopsy.

Risk factors

None of the individual risk factors alone predicted the presence of early fibrosis (Roenigk Grade 3a). The total number of known risk factors (BMI, the presence of DM, current or self-reported previous alcohol excess) was linked to the likelihood of fibrosis on liver biopsy (Table 3). No link was established between weekly dose, duration of treatment and cumulative dose of MTX.

Adverse events of liver biopsy

Post-liver biopsy abdominal pain within 2 h was present in all to varying degree. This continued up to 24 h in 21 patients. There was one serious adverse event, when one patient had to be re-admitted after a period of 3 days. A repeat abdominal ultrasound showed a small capsular haemorrhage, which settled after 24 h without transfusion. All 11 with early mild fibrosis continued to have their MTX as they did not have severe enough changes for it to be stopped according to dermatology guidelines. They will be followed up clinically and using LFT. They were monitored using LFT and in the case of dermatology patients with PIIINP as well.

Comparison of the specialist hepatic pathologist vs NHS pathology report showed that there was a disagreement between the two based on the degree of necrosis, steatosis, mild fibrosis and steatohepatitis but no disagreement on the Roenigk scale. No additional Roenigk Grade IIIb or IV was detected by specialist in liver histopathology.

TABLE 3. Significance of risk factors for hepatic fibrosis in long-term MTX treatment for psoriatic disease

	Median (Range)		Mann-Whitney U-test <i>P</i>
	No fibrosis (<i>n</i> =43)	Fibrosis (<i>n</i> =11)	
Age, years	53 (30–78)	59 (47–78)	NS
Units of alcohol/week	5 (0–40)	0 (0–42)	0.02
BMI	29 (19.3–40)	32.3 (26–46.6)	NS
Disease duration, years	28 (4–68)	24 (3–53)	NS
MTX dose, mg	15 (0.0–25.0)	15 (0.0–25.0)	NS
Duration on MTX, years	6.58 (1.3–30.0)	5.5 (2.0–10.3)	NS
Cumulative dose of MTX, mg	3839 (1020–19657)	3541 (1000–5908)	NS
Diabetic	3	3	NS
Renal impairment	3	1	NS
Number of risk factors ^a	0 (0–3)	1 (0–2)	0.01

^aThe number of risk factors for hepatotoxicity or liver fibrosis was calculated for each patient, with history of excessive alcohol consumption in the past or current consumption over the recommended weekly amount counting as one risk factor; diabetes, renal impairment or obesity counting as others.

PIIINP

PIIINP was elevated in 16 patients. There was no correlation with PIIINP, swollen joint count (Spearman correlation $P=0.99$), tender joint counts (Spearman correlation $P=0.74$), enthesial tender point score (Spearman correlation $P=0.56$) or CRP (Spearman correlation $P=0.90$). Six patients failed to have PIIINP checked. Four of those with early fibrosis had a normal PIIINP on the day of their liver biopsy; in seven patients it was elevated. As no cases of advanced liver disease were found in this cohort, it is not possible to assess the effectiveness of PIIINP in detecting liver fibrosis in PsA and MTX-induced hepatic fibrosis.

Conclusions

Reports from case studies having routine serial liver biopsies for psoriasis treated with long-term MTX have an incidence of hepatic fibrosis of 13–34% and cirrhosis of 0–20% [4]. Our cohort was selected from patients on long-term MTX for PsA ($n=47$) and psoriasis ($n=7$) under the routine follow-up in outpatients with other risk factors for hepatotoxicity. Sixteen (30%) had insulin-dependent diabetes, obesity, or both; eight (15%) continue to drink above the recommended weekly number of units of alcohol despite advice to the contrary; and six (11%) of these admitted to drinking excessively in the past. Despite this, our study shows a prevalence of mild and clinically insignificant fibrosis of 20% and no clinical liver disease or cirrhosis. In only one patient with persistently abnormal LFT and early mild fibrosis was MTX therapy stopped by the consultant.

Although sampling error is up to 33% on liver biopsy, it is unlikely to have resulted in the absence of cirrhosis in our cohort [10]. In our study no link could be made between MTX dosing, duration, cumulative dose or disease duration and hepatic fibrosis confirming other studies. Histological appearances were similar to published results from patients with psoriasis who have never had MTX [16]. This calls into question whether much older reports of MTX hepatotoxicity have actually been cases of NASH or alcoholic cirrhosis. Previous studies in which liver biopsies demonstrated improvement whilst continuing MTX therapy may suggest that these factors, rather than MTX, are important in determining the risk of early hepatic fibrosis [17]. The sample size in this study is too small to demonstrate an effect of each individual risk factor. We have shown, however, that mild liver fibrosis appears to be more likely the greater the total number of pre-disposing factors for hepatotoxicity and is independent of MTX dose.

This study is reassuring to rheumatologists and dermatologists treating patients with MTX. It suggests that using ACR

rheumatology guidelines developed for RA is also safe in MTX treatment for PsA and not safe for liver biopsy, at least for a mean of 5 years and support the view that the significant hepatic fibrosis is unlikely if serial LFT are kept within the normal range. This is regardless of the combination of individual risk factors of hepatic fibrosis, as 30% of our group were obese or diabetic or both and may have had NASH. Our patients who have regular liver monitoring once in 3 months may also have effective monitoring for alcohol-induced liver fibrosis and NASH.

One observation in this study was that patients claimed to consume less alcohol when warned about the toxicity on the liver, and when alanine aminotransferase was elevated, whilst blood tests were more frequent and concerns about liver function were conveyed albeit in the short term. Whilst LFT often improved during a period of more intense monitoring, the cause being temporarily reduced alcohol consumption is an assumption and not one that guarantees long-term safety or abstinence (no data were collected on alcohol consumption specifically during the study); however, advice given in the clinic on the basis of abnormal liver tests to cut down on alcohol consumption may well be heeded as continued MTX treatment requires normal LFT. This may be one mechanism in which those with early fibrosis tend to consume or claim to consume significantly less alcohol in our study.

Oral folic acid supplementation with MTX protects from gastro-intestinal side effects and LFT abnormalities and may have a protective effect against serious liver disease in our cohort compared with the higher incidence found in older studies [18, 19]. Whilst serial PIIINP monitoring has been used to reduce the frequency of liver biopsy in cutaneous psoriasis, it is frequently elevated in PsA. It did not, however, correlate with tender or swollen joint counts, enthesial tender points or the presence of hepatic fibrosis in this study. PIIINP may lead to more patients receiving liver biopsy who have active arthritis and disease activity and is unreliable in the presence of PsA. Whilst retrospective studies of NASH have suggested that progressive liver fibrosis can occur in the context of normal LFT [11], our study provides valuable evidence which supports the view that following the ACR guidelines for monitoring long-term MTX is a safe way of preventing liver cirrhosis in PsA and if LFT are normal then serial liver biopsies are not indicated.

Rheumatology key messages

- Monitoring PsA using ACR guidelines for RA appears safe.
- PIIINP is not useful in monitoring MTX in PsA possibly due to inflammation in the joint.

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