Aliment Pharmacol Ther 2004; 19: 391–399. doi: 10.1046/j.1365-2036.2004.01819.x

Monitoring methotrexate-induced hepatic fibrosis in patients with psoriasis: are serial liver biopsies justified?

G. P. AITHAL*, B. HAUGK†, S. DAS‡, T. CARD*, A. D. BURT† & C. O. RECORD†
*Queen's Medical Centre University Hospital, Nottingham, UK; †Centre for Liver Research and ‡Department of Dermatology, University of Newcastle, Newcastle upon Tyne, UK

Accepted for publication 19 October 2003.

SUMMARY

Background: Reports that up to 26% of subjects with psoriasis develop cirrhosis have led to a recommendation of serial liver biopsies after each cumulative dose of 1500 mg of methotrexate.

Aim: To evaluate the progression of liver injury in patients with psoriasis and the impact of monitoring by liver biopsy on their management.

Methods: One hundred and twenty-one liver biopsies from 66 subjects (aged 11–79 years) with psoriasis, receiving a median cumulative dose of 3206 mg of methotrexate over a period of 280.5 weeks, were evaluated.

Results: The assessment of advanced fibrosis according to the Ishak system (≥ 4) correlated perfectly with that of the Scheuer system (≥ 3) and poorly with that of the Roenigk scale (≥ 3b) (r^2 = 1.0 and 0.31, respectively). Two of 24 pre-treatment biopsies showed advanced fibrosis and both subjects were heavy drinkers. The cumulative probabilities of advanced fibrosis (Ishak ≥ 4) were 0%, 2.6%, 2.6%, 8.2% and 8.2% at cumulative doses of 1500, 3000, 4500, 5000 and 6000 mg, respectively. None of the subjects developed cirrhosis during follow-up or discontinued therapy on the basis of liver biopsy findings.

Conclusions: Advanced hepatic fibrosis with low-dose methotrexate therapy is much less frequent than previously reported. Pre-treatment or monitoring liver biopsies in accordance with the current guidelines have little impact on patient management.

INTRODUCTION

Methotrexate competitively inhibits dihydrofolate reductase, the enzyme with a key role in the S phase cell cycle.[1] Initially used in the treatment of childhood leukaemia, methotrexate is now recognized to be effective in the management of many oncological, dermatological and rheumatic diseases.[2] Methotrexate blocks the rapid epidermal cell turnover, reduces neutrophil and monocyte chemotaxis and decreases leukotriene-induced intra-epidermal penetration of granulocytes responsible for the skin lesions seen in psoriasis.[3] Methotrexate is indicated in about 20% of all patients with psoriasis and continues to be used despite the emergence of newer therapies, because of the length of experience with its use and its undoubted efficacy.[4, 5]

Although methotrexate is associated with adverse reactions, such as interstitial pneumonitis and bone marrow suppression, the potential for hepatic fibrosis and cirrhosis has remained a major concern with long-term treatment.[6] Methotrexate is metabolized into a polyglutamated form, which is retained within the cell long term.[7] This has been shown to be the major storage form of hepatic methotrexate and may be the metabolite responsible for hepatotoxicity.[8] Concern about hepatotoxicity has arisen from reports that up to 26% of patients with psoriasis develop cirrhosis on methotrexate therapy.[9] In addition, reports of abnormal histology in up to 51% of pre-treatment liver biopsies, and the suggestion that the pre-treatment abnormalities may increase the

Correspondence to: Dr G. P. Aithal, Queen's Medical Centre University Hospital, D Floor, South Block, Nottingham NG7 2UH, UK.
E-mail: guru.aithal@mail.qmcuh-tr.trent.nhs.uk

risk of further liver injury on methotrexate therapy, have led to intensive monitoring using regular liver biopsies.[10] Initial guidelines for monitoring were formulated by Roenigk and co-workers in 1972 and were revised later in 1973, 1982, 1988 and 1998.[5, 11, 12] All of these guidelines recommended baseline liver biopsy at or near the beginning of methotrexate treatment and after each cumulative dose of 1.5 g in order to detect histological abnormalities (Table 1). For the first time in 1998, pre-treatment biopsy recommendations were relaxed, indicating a baseline biopsy in high-risk individuals only.[5] These recommendations are in contrast with clinical experience, which suggests that advanced fibrosis in patients receiving long-term, low-dose, once-weekly oral methotrexate treatment for psoriasis is modest, and it has been suggested that the requirement to perform routine liver biopsies in these patients needs to be reconsidered.[13] We have evaluated the progression of methotrexate-induced liver injury in patients with psoriasis and the impact of intensive monitoring by liver biopsy on their management.

MATERIALS AND METHODS

Subjects

From the medical records of the Royal Victoria Infirmary, Newcastle upon Tyne, we identified patients who had undergone liver biopsy as part of the monitoring process of methotrexate treatment between 1971 and 2000. Physicians were guided by the published recommendations (Table 1) for monitoring methotrexate therapy during the study period.[5, 11, 12, 14] The case notes of the patients were traced and the following information was extracted: demographic details, full medical history including the onset and progress of psoriasis, detailed drug and alcohol history, date of onset of methotrexate treatment, weekly dosage regimen and route of administration, cumulative dose at the time of liver biopsy, duration of treatment and physical findings including body mass index, full blood count (haemoglobin, leucocytes and platelets), standard liver function tests (albumin, bilirubin, aspartate transaminase, alanine transaminase, alkaline phosphatase, γ-glutamyl transferase, hepatitis B and C serology, where available), autoantibody screen and appropriate serum metabolic profile (α1-antitrypsin, caeruloplasmin, copper, iron and ferritin).

Histological assessment

During the study period, 152 liver biopsies were attempted on 69 patients, nine of which were unsuccessful in obtaining a core of liver tissue and had to be repeated. Of the 143 samples subjected to histological

Table 1. Methotrexate in psoriasis: guidelines for monitoring[5, 12]

A. Pre-methotrexate evaluation
   1. Complete blood count
   2. Renal function: serum creatinine, blood urea nitrogen, urine analysis and creatinine clearance
   3. Liver chemistry: aspartate transaminase, alanine transaminase, alkaline phosphatase, bilirubin, albumin and hepatitis A, B and C serology test
   4. Human immunodeficiency virus antibody determination in patients at risk of acquired immunodeficiency syndrome

B. Pre-treatment liver biopsy
   If long-term methotrexate therapy is anticipated, initial liver biopsy should be performed (revision in 1998 suggested that the pre-treatment biopsy should be considered on the basis of the patient's relative risk)

C. Continuing laboratory studies
   1. Complete blood count weekly for 2 weeks, then biweekly for 1 month and then monthly
   2. Renal function studies: blood urea nitrogen and serum creatinine at 3–4-monthly intervals
   3. Liver chemistry: aspartate transaminase, alanine transaminase, alkaline phosphatase, bilirubin and albumin every 4–8 weeks (more frequent in the absence of initial liver biopsy)

D. Monitoring liver biopsy
   A liver biopsy is recommended after a cumulative dose of about 1.5 g and thereafter at 1.0–1.5 g intervals

E. Interpretation of liver biopsy
   Patients with grade 3a changes should have a repeat biopsy after 6 months
   Patients with grade 3b or 4 changes should discontinue methotrexate, except in exceptional circumstances where follow-up biopsies should be performed

assessment, 13 biopsies could not be traced from the archives for a review. In addition, nine biopsies in which samples demonstrated less than three portal tracts were considered to be too small to evaluate the degree of fibrosis and were excluded from further analysis. One hundred and twenty-one biopsies in total (from 66 patients) were examined using archival slides.

Reticulin stain was used to assess liver architecture and Van Gieson, Picromallory or Sirius Red Fast Green stain to assess fibrosis. A haematoxylin and eosin preparation was used to assess steatosis, portal inflammation and nuclear pleomorphism of the hepatocytes. In addition, the biopsies were assessed for any other histological abnormality, including iron overload using Pearl's stain, α1-antitrypsin deficiency using diastase periodic acid Schiff reaction and abnormal copper storage using Orcein stain.

The degree of portal fibrosis in each biopsy was assessed and graded from 0 to 6 using the Ishak scoring system and from 0 to 4 using the Scheuer scoring system (Tables 2 and 3). These systems for the assessment of portal fibrosis in chronic hepatitis have been described previously.[15] The Roenigk classification of methotrexate-associated liver damage was used to evaluate different histological features, such as fatty change, nuclear pleomorphism, necro-inflammatory changes and fibrosis[14] (Table 4). The individual components of the Roenigk classification were scored separately and then the final score was applied (Tables 4 and 5). All biopsies were assessed by one pathologist (BH). Each biopsy that showed any fibrosis was reviewed together with a second pathologist (ADB) and a consensus score for fibrosis was agreed. Both pathologists were blind to the clinical details of the patients. Consecutive biopsies in the same patient were compared using the Ishak system and a difference in fibrosis score of ≥1 between two biopsies was considered as progression or regression. Fibrosis scores of Ishak ≥ 4, Scheuer ≥ 3 and Roenigk ≥ 3b were considered to signify advanced fibrosis.

Table 2. Ishak scoring system of assessing the degree of fibrosis

Degree of fibrosis	Score
No fibrosis	0
Fibrous expansion of some portal areas ± short fibrous septa	1
Fibrous expansion of most portal areas ± short fibrous septa	2
Fibrous expansion of most portal areas with occasional portal to portal bridging	3
Fibrous expansion of portal areas with marked portal to portal and portal to central bridging	4
Marked bridging fibrosis with occasional nodules (incomplete cirrhosis)	5
Cirrhosis	6

Table 3. Scheuer scoring system of assessing the degree of fibrosis

Degree of fibrosis	Score
No fibrosis	0
Enlarged, fibrotic portal tracts	1
Periportal or portal to portal septa but intact architecture	2
Fibrosis with architectural distortion but no obvious cirrhosis	3
Probable or definite cirrhosis	4

Table 4. Scoring of the different components of the Roenigk classification of methotrexate-associated liver damage

Steatosis		Nuclear pleomorphism		Fibrosis		Portal inflammation	
None	0	None	0	None	0	None	0
Mild	1	Mild	1	Mild; fibrosis extending into acini	1	Mild	1
Moderate	2	Moderate	2	Moderate/severe	2	Moderate	2
Severe	3	Severe	3	Cirrhosis	3	Severe	3

Statistical analysis

Continuous variables were summarized as the mean ± S.E.M. or median (range) when they were not normally distributed and categorical variables as frequencies and percentages. Cumulative methotrexate doses received by patients at the time of each liver biopsy and the grades of liver fibrosis on biopsy were compared between biopsies using Spearman's rank correlation. Pearson's correlation was used to estimate the linear relationship between advanced fibrosis as assessed by the Ishak, Scheuer and Roenigk systems. The cumulative probability of developing advanced fibrosis was calculated using the Kaplan–Meier method. Analyses were carried out using Stata 7 (Stata Corporation, TX 77845, USA).

Table 5. Grading of methotrexate-induced liver injury based on the Roenigk system

Fatty change	Nuclear pleomorphism	Fibrosis	Necro-inflammation	Grade
Mild/none	Mild/none	None	± Mild portal inflammation	1
Moderate/severe	Moderate/severe	None	Moderate/severe portal inflammation Moderate/severe hepatocellular necrosis	2
±	±	Mild (fibrosis extending into acini)	±	3a
±	±	Moderate/severe	±	3b
±	±	Cirrhosis	±	4

RESULTS

Demographic details

Sixty-nine patients (35 females and 34 males) with psoriasis, aged 11–79 years (median, 50 years) at the time of initiation of methotrexate therapy, had liver biopsies performed in the study period. At the time of introduction of methotrexate therapy, 20 patients (29%) had one or more recognized risk factors for methotrexate-induced liver injury. Documentation of alcohol consumption (current or past) was in the case notes of 61 of the 69 patients (88.5%) and, of those in whom there was no record of alcohol intake, six of the eight were below the age of 25 years (median age, 20 years). Eleven patients consumed excess alcohol (> 21 units for males and > 14 units for females per week), one of whom was also obese. The presence or absence of a past history of diabetes was recorded in 42 of the 69 patients (60.8%), and the median age of those in whom there was no record of diabetes was 33 years. One patient had diabetes mellitus and eight patients were either overweight or obese (body mass index > 25). The maximum weekly dose of methotrexate was ≤ 15 mg in 54 patients (78%), 17.5–20 mg in 11 (16%) and > 20 mg in four (6%). During the median cumulative follow-up period of 280.5 weeks (4–1225 weeks), patients received a median cumulative dose of 3206 mg (30–15 312 mg). The demographic details are shown in Table 6.

Table 6. Details of patient demographics and methotrexate treatment

Female/male	35/34
Age (median) (years)	11–79 (50)
Risk factors	11 (16%): excess alcohol 8 (12%): obesity 1 (1%): diabetes mellitus
Maximum weekly dose (mg)	54 (78%): ≤ 15 11 (16%): 17.5–20 4 (6%): > 20
Cumulative dose during study period (median) (mg)	30–15 312 (3206)
Follow-up (median) (weeks)	4–1225 (280.5)

Liver function tests

As the guidelines for the monitoring of methotrexate hepatotoxicity are set out on the basis of liver biopsy findings, data on liver enzymes were not used in the decision-making process. There was no correlation between the grades of histological change and any of the liver function tests. The data on the liver function tests are not presented in detail.

Histological assessment

Of the 143 biopsies performed, 121 (85%) were available for evaluation. This included 24 pre-treatment biopsies and 97 performed whilst on methotrexate therapy.

Pre-treatment histology. Twenty-four patients had pre-treatment liver biopsies, 18 of which showed no evidence of fibrosis (17 with Roenigk grade 1 changes and one with Roenigk grade 2 changes). Four patients had less than advanced fibrosis (Ishak grades 1–3), all of whom had recognized risk factors (two with excess alcohol intake and two with obesity). Two additional patients had advanced fibrosis (Ishak grade 4), both of whom consumed excess alcohol (66-year-old female who drank 40–80 units/week and 60-year-old male who drank 140 units/week).

Table 7. Relationship of the cumulative dose of methotrexate to the degree of fibrosis at consecutive biopsies in patients who had more than one biopsy during methotrexate therapy

	Cumulative dose (mean ± S.E.M.) (mg)	Ishak grade (mean ± S.E.M.)
Biopsy 1 ($n = 27$)	1582 ± 557	0.48 ± 0.18
Biopsy 2 ($n = 27$)	4128 ± 745	0.96 ± 0.22
Biopsy 3 ($n = 15$)	5601 ± 917	0.94 ± 0.36
Biopsy 4 ($n = 8$)	6950 ± 1144	1.0 ± 0.6
Biopsy 5 ($n = 3$)	7587 ± 1254	2.0 ± 1.5
P value	< 0.0001	0.09

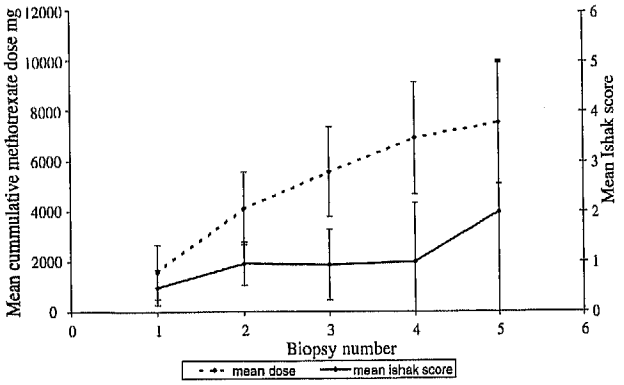

Figure 1. Relationship between the degree of fibrosis (Ishak score) and the cumulative methotrexate dose at the time of liver biopsy in 27 patients without advanced fibrosis prior to treatment.

Relationship of cumulative dose to hepatic fibrosis. Excluding two patients who showed advanced fibrosis prior to methotrexate therapy, 27 patients had more than one monitoring biopsy during the study period. The cumulative methotrexate doses in these patients at the time of liver biopsy and the degree of fibrosis as assessed by the Ishak scale are summarized in Table 7 and illustrated in Figure 1. Although there was a significant increase in the mean cumulative dose received by patients between biopsies ($P = 0.0001$), there was not a similar increase in fibrosis score ($P = 0.09$) when assessed for trend using Spearman's rank correlation. Similarly, no significant correlation was found between dose and Ishak grade ($r = 0.052$; $P = 0.65$).

Trend in hepatic fibrosis on methotrexate therapy. Overall, nine of the 27 patients (33%) who had more than one biopsy during treatment showed net progression (increase in fibrosis by one or more Ishak grades). Six of these progressed by one Ishak grade and three progressed into advanced fibrosis at cumulative

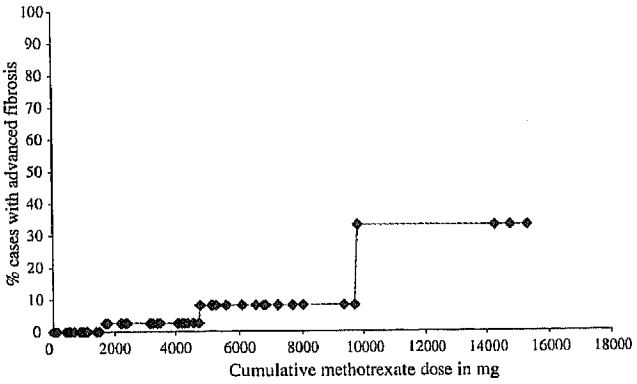

Figure 2. Cumulative probability of developing advanced fibrosis (Ishak ≥ 4) whilst on methotrexate therapy.

methotrexate doses of 4770, 9810 and 1718 mg. Three of the 27 subjects (11%) showed a net improvement in fibrosis. Two improved by one Ishak grade and one improved from Ishak grade 4 to Ishak grade 2 (patient who reduced alcohol intake whilst on methotrexate therapy).

Advanced fibrosis on methotrexate therapy. When the three different scales used in the histological assessment were compared, the assignment of advanced fibrosis according to the Ishak scale (≥ 4) correlated perfectly with that using the Scheuer scale (≥ 3) ($r^2 = 1.0$), but poorly with that based on the Roenigk scale (≥ 3b) ($r^2 = 0.31$). The cumulative probabilities of developing advanced hepatic fibrosis (Ishak ≥ 4 or Scheuer ≥ 3) on methotrexate therapy were 0%, 2.6%, 2.6%, 8.2% and 8.2% at cumulative doses of 1500, 3000, 4500, 5000 and 6000 mg, respectively (Figure 2). In the small number of patients receiving more than 10 g of methotrexate, 32% developed advanced fibrosis (Figure 2).

Clinical outcome

Nine of the 153 attempts at percutaneous biopsy were unsuccessful in yielding a core of liver tissue, and had to be repeated under ultrasound guidance. Six procedures (4%) were complicated, including two biliary leaks, two with significant and prolonged pain, one with bleeding and one who developed a seizure immediately following the procedure (concluded to be related to vasovagal syncope). Nine biopsies (6%) were considered to be inadequate (less than three portal tracts). During the follow-up period, 10 of the 69 patients (14%) withdrew from methotrexate therapy. Indications for withdrawal were thrombocytopenia in two and toxic epidermolysis,

squamous cell carcinoma, pulmonary fibrosis, gastrointestinal intolerance, non-compliance and lack of efficacy in one each. Methotrexate was stopped in one patient because of raised liver enzymes (without liver biopsy at the time), and another patient who suffered a biliary leak following a biopsy requested withdrawal from methotrexate to avoid further liver biopsies.

During follow-up, five of the 69 patients (7%) died. The causes of death were determined in four (myocardial infarction, left ventricular failure, chronic obstructive airways disease, brain tumour). The cause of death could not be traced in one, but the patient did not have any symptoms or signs of liver disease at his last follow-up whilst on methotrexate therapy. During the study period, none of the patients developed symptoms or signs of decompensated liver disease and there were no withdrawals from therapy based on liver biopsy findings.

DISCUSSION

Methotrexate-induced liver injury in patients with psoriasis has remained an important concern since its first description.[16] Initial reports of the development of cirrhosis in 11–26% of patients receiving long-term methotrexate therapy[9, 17–20] led to the recommendation of serial liver biopsies to monitor the progression of liver injury. Despite a better understanding of the risk factors and the use of safer dosage schedules, the reported frequency of methotrexate-induced cirrhosis has varied widely (between 0% and 10%) in more recent studies.[21, 22] Such uncertainty has led to a continued emphasis on an intensive monitoring regime, and the guidelines for monitoring methotrexate therapy have changed little over the last three decades.[5, 11, 12, 14] We have systematically evaluated, for the first time, the degree of methotrexate-induced hepatic fibrosis using validated and widely accepted systems, such as the Scheuer and Ishak scales. In contrast with previous reports, only three of 69 patients in our group developed advanced fibrosis over a mean follow-up period of 6.5 years and none developed cirrhosis. During the study period, 143 liver biopsies were performed, but none of the patients were withdrawn from methotrexate therapy on the basis of histological findings; hence, monitoring with liver biopsy, as recommended by the guidelines, had no impact on the clinical management of patients in our group.

Although monitoring for methotrexate-induced hepatotoxicity is based on liver biopsy findings, and recommendations to discontinue therapy are determined on the basis of the degree of fibrosis, published studies have varied widely in the methods used for histological evaluation. In the majority of reports, there is either a lack of information regarding the method used for histological assessment,[9, 23] or an *ad hoc* system without previous validation has been used.[17, 18, 21, 22, 24, 25] Almost all such studies have only described the frequency of fibrosis or cirrhosis in patients on methotrexate therapy, with no assessment of the degree of fibrosis. Some studies have used the Roenigk classification in the histological assessment.[26–28] The Roenigk classification was developed by the Psoriasis Task Force, led by dermatologists, and is based on clinical observations; it has since been recommended by the American Academy of Dermatology guidelines for monitoring methotrexate-induced liver injury.[5, 11] However, the Roenigk grading system is subjective, including some features (such as nuclear pleomorphism) of unclear significance and insensitive to small changes, particularly when assessing fibrosis.[29] Although scoring appears to take into account changes such as steatosis and inflammation, their presence or absence has no impact on the allocation of more advanced grades (Tables 4 and 5). The Roenigk scale has never been validated or used in the evaluation of any other liver disease. For the first time, we have compared the Roenigk scale with the Scheuer and Ishak scoring systems, which are well established in the detailed histopathological assessment of portal fibrosis in chronic hepatitis. Our findings demonstrate that the assessment of advanced fibrosis according to the Roenigk scale correlates poorly with that using either the Scheuer or Ishak system. The Roenigk scale classifies all those with more than minimal fibrosis as advanced fibrosis (grade 3b), and hence overestimates the degree of histological change. This may have contributed to the reports of a high frequency of advanced fibrosis due to methotrexate.[28] Adherence to such a system of assessment and reporting may lead to unnecessary withdrawal from effective therapy.

The fact that the frequency of hepatic fibrosis increases with increasing cumulative dose of methotrexate is well established. Even in patients without other risk factors, increasing the methotrexate dose results in the progressive deposition of matrix proteins and collagen (types III and IV) in the liver.[30] However, the risk of hepatic fibrosis related to specific dosage regimens has received less attention and is not mentioned in the guidelines.[5]

Methotrexate given in three divided doses weekly may have been associated with a greater risk of hepatic fibrosis, but this regimen is now rarely used.[31] Small doses given daily or every other day produced up to a four-fold increase in the incidence of fibrosis or cirrhosis compared with larger doses given once weekly.[18, 19, 32] Indeed, hepatic injury can be produced in rats only when methotrexate doses are given daily, but never on weekly therapy even at higher doses.[33, 34] A review of previous studies indicates that the frequency of cirrhosis is lower (0–4%) in groups receiving maximum weekly doses of ≤ 20 mg[21, 24, 27, 30] than in those receiving higher maximum weekly doses (3–26%).[9, 10, 28, 35, 36] In our group, 65 of the 69 patients (94%) received a single weekly dose of 20 mg or less of methotrexate, consistent with the observation that most patients maintain adequate control of psoriasis on this regimen.[21] We believe that the low-dose regimen adopted is an important reason for the low frequency of advanced fibrosis in our group.

In addition, our findings emphasize the role of excess alcohol consumption as a risk factor for methotrexate-induced fibrosis. Both of our patients who had advanced fibrosis on pre-treatment biopsies were heavy drinkers and the only patient to develop advanced fibrosis on a relatively low cumulative dose (1718 mg) consumed excess alcohol (40 units/week). Hence, it could be argued that the recognition of risk factors and the use of a safer dosage regimen could be the key to the prevention of methotrexate-induced liver fibrosis, rather than intensive monitoring with serial liver biopsies.

We acknowledge that the retrospective nature of this study could have resulted in the under-reporting or under-recording of risk factors such as excess alcohol. It should be noted that the minority of patients (11.5%) for whom information on alcohol consumption was not available were in the age group unlikely to have alcohol-induced liver disease. In addition, any underestimation of these risk factors in our group would only strengthen our conclusion that methotrexate-induced fibrosis is less frequent than has been reported previously. However, it is possible that patients considered to be at high risk for hepatic fibrosis could have been excluded from methotrexate therapy. Therefore, we are unable to estimate the impact of various risk factors in this retrospective study. Similarly, this study did not assess the compliance of physicians with the monitoring guidelines.

Despite published recommendations to discontinue methotrexate therapy in subjects who develop advanced fibrosis, treatment may need to be continued in those with severe psoriasis that cannot otherwise be controlled. All three of our patients who developed advanced fibrosis opted to continue methotrexate therapy following detailed discussion regarding the benefits and risks of continued treatment. None developed any evidence of progression of liver disease during the study period. This is in keeping with previous studies in which continued methotrexate therapy following the development of liver fibrosis did not adversely affect the long-term outcome.[3, 9, 21, 37] Zachariae and Sogaard reported 25 patients with histologically proven cirrhosis who were maintained on methotrexate; follow-up biopsies 1–13 years later showed less advanced fibrosis in 14 patients.[37] Three patients in our group showed apparent improvement in the degree of fibrosis whilst on methotrexate. Although sampling errors could account for some of these observations, our findings are consistent with the suggestion that methotrexate-induced liver injury progresses very slowly.

Methotrexate is also used extensively in rheumatoid arthritis and inflammatory bowel disease. The American College of Rheumatology recommends monitoring liver biopsy if five of nine aspartate transaminase determinations in a 12-month period are above the upper limit of normal or if there is a decline in serum albumin to less than normal levels in the setting of well-controlled rheumatoid arthritis.[38] In a recent study of 32 patients with inflammatory bowel disease receiving > 1500 mg of methotrexate, there was little evidence of hepatotoxicity and surveillance liver biopsies were not recommended.[39] In this population, only one patient fulfilled the American College of Rheumatology criteria for liver biopsy and the one patient with Roenigk grade 3b fibrosis did not meet these criteria. Nevertheless, in a leading article, liver biopsy was recommended in patients with persistently abnormal laboratory values.[40]

Although liver biopsy is generally a safe procedure, when performed for monitoring purposes in those who are otherwise asymptomatic, the benefits should be balanced against the potential risks. Six of 153 attempted liver biopsies (4%) were complicated, including two biliary leaks, two with severe significant and prolonged pain, one with bleeding and one who developed a seizure immediately following the procedure. These results are similar to the published data from a nation-wide audit wherein 1.7% of the procedures were

complicated with bleeding, with 0.13–0.33% procedure-related deaths.[41] In addition, the prospective audit reported 12% post-biopsy pain requiring opiate analgesia.[41] Because of the retrospective nature of our study, pain as a complication is likely to have been under-reported. Considering both the 4% complication rate as well as the probability of advanced fibrosis of $<2.6\%$ at a cumulative dose of up to 4000 mg, the potential risks of monitoring liver biopsy outweigh its benefits. The probability of advanced fibrosis increases to 8.2% at 5000 mg and the performance of a liver biopsy at this stage is justified.

Hence, we conclude that the frequency of development of advanced hepatic fibrosis on methotrexate therapy for psoriasis is small in low-risk subjects on a low, single-weekly dosage regimen. Intensive monitoring with serial biopsies, as recommended by the published guidelines, has no impact on clinical management and should be reviewed. On the basis of the findings in this study, we suggest the following recommendations for liver biopsy in patients requiring or receiving long-term methotrexate therapy. These recommendations apply to those on doses of methotrexate up to 20 mg per week. Those on higher weekly doses may be at higher risk, but this could not be assessed by this study as the number of such patients was small.

(a) Before methotrexate therapy, patients with clinical evidence of liver disease or abnormal liver function tests should be evaluated and investigated by a hepatologist, and all risk factors for liver disease determined.
(b) Liver biopsy should be undertaken after careful consideration of current hepatological guidelines for this procedure,[42] especially the risk–benefit ratio in individual patients.
(c) Pre-treatment liver biopsy is no longer justified in individuals with no additional risk factors (such as excess alcohol intake). In patients who have received a cumulative methotrexate dose of 5 g, liver biopsy should be considered, as the likelihood of detection of advanced fibrosis is greater than the risks of liver biopsy.

ACKNOWLEDGEMENTS

We are grateful to all the dermatologists in Newcastle upon Tyne, both past and present, who have been responsible for the care of these patients during the past 25 years.

REFERENCES

1 Bertino J. The mechanism of action of the folate antagonists in man. Cancer Res 1963; 23: 1286.
2 Jolivet J, Cowan KH, Curt GA, *et al.* The pharmacology and clinical use of methotrexate. N Engl J Med 1983; 309: 1094–104.
3 Zachariae H. Methotrexate side effect. Br J Dermatol 1990; 122: 127–33.
4 Bergstresser PR, Screiber SH, Weinstein GD. Systemic chemotherapy for psoriasis: a national survey. Arch Dermatol 1976; 112: 977–81.
5 Roenigk HH Jr, Auerbach R, Mailbach H, Weinstein G, Lebwohl M. Methotrexate in psoriasis: Consensus Conference. J Am Acad Dermatol 1998; 38: 478–85.
6 Tang H, Neuberger J. Review article: methotrexate in gastroenterology — dangerous villain or simply misunderstood? Aliment Pharmacol Ther 1996; 10: 851–8.
7 Nair MG, Baugh CM. Synthesis and biological evaluation of poly-gamma-glutamyl derivatives of methotrexate. Biochemistry 1973; 12: 3923–7.
8 Kremer JM, Galivan J, Streckfuss A, *et al.* 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.
9 Zachariae H, Kragballe K, Sogaard H. Methotrexate induced liver cirrhosis. Studies including serial liver biopsies during continued treatment. Br J Dermatol 1980; 102: 407–12.
10 Nyfors A, Poulsen H. Liver biopsies from psoriatics related to methotrexate therapy. Findings in 123 consecutive non-methotrexate treated patients. Acta Pathol Microbiol Scand, Sect A 1976; 84: 253–61.
11 Roenigk HH, Mailbach H, Weinstein GD. Guidelines on methotrexate therapy for psoriasis. Arch Dermatol 1972; 105: 363–5.
12 Roenigk HH, Auerbach R, Mailbach HI, *et al.* Methotrexate in psoriasis: Revised Guidelines. J Am Acad Dermatol 1988; 19: 145–56.
13 Zachariae H. Liver biopsies and methotrexate: a time for reconsideration? J Am Acad Dermatol 2000; 42: 531–4.
14 Roenigk HH, Auerbach R, Mailbach HI, *et al.* Methotrexate Guidelines: Revised. J Am Acad Dermatol 1982; 38: 478–85.
15 Brunt EM. Grading and staging the histopathological lesions of chronic hepatitis: the Knodell Histology Activity Index and beyond. Hepatology 2000; 31: 241–6.
16 O'Rourke RA, Eckert GE. Methotrexate-induced hepatic injury in an adult. Arch Intern Med 1964; 113: 191–4.
17 Dahl MGC, Gregory MM, Scheuer PJ. Liver damage due to methotrexate in patients with psoriasis. Br Med J 1971; 1: 625–30.
18 Podurgiel BJ, McGill DB, Ludwig J, *et al.* Liver injury associated with methotrexate therapy for psoriasis. Mayo Clin Proc 1973; 48: 787–92.

19 Millward-Sadler GH, Ryan TJ. Methotrexate-induced liver disease in psoriasis. Br J Dermatol 1974; 90: 661–7.
20 Shapiro H, Towbridge J, Lee J, *et al.* Liver disease in psoriasis — an effect of methotrexate therapy? Arch Dermatol 1974; 110: 547–51.
21 Boffa MJ, Chalmers RJ, Haboubi NY, *et al.* Sequential liver biopsies during long-term methotrexate treatment for psoriasis: a reappraisal. Br J Dermatol 1995; 133: 774–8.
22 Themido R, Loureiro M, Pecegueiro M, *et al.* Methotrexate hepatotoxicity in psoriatic patients, submitted to long-term therapy. Acta Derm Venereol 1992; 72: 361–4.
23 Lanse SB, Arnold GL, Gowans JDC, *et al.* 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.
24 Robinson JK, Baughman RD, Auerbach R, *et al.* Methotrexate hepatotoxicity in psoriasis: consideration of liver biopsies at regular intervals. Arch Dermatol 1980; 116: 413–5.
25 Mitchell D, Smith A, Rowan B, *et al.* Serum type 3 procollagen peptide, dynamic liver function tests and hepatic fibrosis in psoriatic patients receiving methotrexate. Br J Dermatol 1990; 122: 1–7.
26 Reese LT, Grisham JW, Aach RD, *et al.* Effects of methotrexate on the liver in psoriasis. J Invest Dermatol 1974; 62: 597–602.
27 Van Dooren-Greebe RJ, Kuijpers ALA, Mulder J, *et al.* Methotrexate revisited: effects of long-term treatment in psoriasis. Br J Dermatol 1994; 130: 204–10.
28 Malatjalian DA, Ross JB, Williams CN, *et al.* 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.
29 West SG. Methotrexate hepatotoxicity. Rheum Dis Clin North Am 1997; 23: 883–915.
30 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.
31 Zanolli MD, Sherertz EF, Hedberg AE. Methotrexate: anti-inflammatory or anti-proliferative? J Am Acad Dermatol 1990; 22: 523–4.
32 Dahl MGC, Gregory MM, Scheuer PJ. Liver damage due to methotrexate in patients with psoriasis — comparison of different dose regimens. Br Med J 1972; 1: 654.
33 Hall PD, Jenner MA, Ahem MJ. Hepatotoxicity in a rat model caused by orally administered methotrexate. Hepatology 1991; 14: 906–10.
34 Kaplan MM. Methotrexate hepatotoxicity and the premature reporting of Mark Twain's death: both greatly exaggerated. Hepatology 1990; 12: 784–5.
35 Nyfors A. Liver biopsies from psoriatics related to methotrexate therapy: 3. Findings in post-methotrexate liver biopsies from 160 psoriatics. Acta Pathol Microbiol Scand, Sect A 1977; 85: 511–8.
36 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.
37 Zachariae H, Sogaard H. Methotrexate-induced liver cirrhosis: a follow-up. Dermatologica 1987; 175: 178–82.
38 Kremer JM, Alarcon GS, Lightfoot RW Jr, *et al.* Methotrexate for rheumatoid arthritis: suggested guidelines for monitoring liver toxicity. American College of Rheumatology. Arthritis Rheum 1994; 37: 316–28.
39 Te H, Schiano T, Kuan SF, *et al.* Hepatic effects of long-term methotrexate use in the treatment of inflammatory bowel disease. Am J Gastroenterol 2000; 95: 3150–6.
40 Balfour Sartor R. Editorial. N Engl J Med 2000; 342: 1664–6.
41 Gilmore IT, Burroughs A, Murray-Lyon IM, *et al.* Indications, methods and outcomes of percutaneous liver biopsy in England and Wales: an audit by the British Society of Gastroenterology and Royal College of Physicians of London. Gut 1995; 36: 437–41.
42 Grant A, Neuberger J. Guidelines on the use of liver biopsy in clinical practice. Gut 1999; 45; Suppl. IV.