British Journal of Dermatology 1995; 133: 774–778.

Sequential liver biopsies during long-term methotrexate treatment for psoriasis: a reappraisal

M.J.BOFFA, R.J.G.CHALMERS, N.Y.HABOUBI,* M.SHOMAF* AND D.M.MITCHELL

The Skin Hospital, University of Manchester School of Medicine, Chapel Street, Salford, M60 9EP, U.K.
**Department of Pathology, Withington Hospital, Manchester, U.K.*

Accepted for publication 27 January 1995

Summary One hundred and eighty-two liver biopsies were performed over a 10-year period on patients receiving long-term, low-dose, once weekly oral methotrexate (MTX) for severe psoriasis. Forty-nine patients had two or more biopsies during continued treatment and formed the study population for our analysis. The first and last biopsies were compared to determine progression of any histological abnormalities. Liver biopsies were assessed without knowledge of the MTX dose and allocated to one of five groups according to the severity of the histological abnormalities. These were defined as: (1) normal; (2) steatosis alone; (3) inflammation without fibrosis; (4) fibrosis; and (5) cirrhosis.

The mean cumulative dose of MTX at the time of the first biopsy was 2743 mg (range 315–10,024), given over 275 weeks (range 26–738). In the interval between the first and last biopsies, patients received, on average, a further 2362 mg (range 390–7155) over 225 weeks (range 60–460).

There was improvement in the histological assessment in 12 patients, no change in 28 patients, and deterioration in nine patients. None developed cirrhosis. Liver biopsy findings prompted discontinuation of MTX in four of the 49 patients on long-term treatment. This has to be weighed against the cost and morbidity of the 124 biopsies performed in these patients. Our results suggest that, with careful follow-up, the risk of development or progression of liver disease in patients receiving long-term, low-dose, once weekly oral MTX for psoriasis is modest, and that the requirement for performing routine liver biopsies in these patients needs to be reconsidered.

Concern about possible hepatotoxicity remains an important preoccupation of physicians prescribing long-term treatment with methotrexate (MTX) for psoriasis. Although published guidelines recommend performing regular liver biopsies,[1] there is surprisingly little published data on progression of abnormalities of liver histology during continued treatment with MTX.

This paper describes our experience with psoriatic patients undergoing sequential liver biopsies during long-term treatment and reassesses the place of routine liver biopsy.

Methods

In a study carried out prospectively over a 10-year period (1984–94), 182 liver biopsies were performed on patients receiving low-dose, once weekly oral MTX for severe psoriasis. Forty-nine patients (30 male and 19 female) had two or more biopsies during continued treatment; 28 patients had two, 16 had three, and five had four biopsies; a total 124 biopsies. These 49 patients were selected for our analysis and their first and last biopsies were compared to determine whether there had been progression of any histological abnormalities.

The cumulative dose, and the duration of treatment with MTX, were calculated from the patients' clinical notes. Current and pre-MTX alcohol consumption was recorded at the time of biopsy, as weekly units of alcohol.[2]

Liver biopsies were obtained by the Menghini technique and fixed in 10% formaldehyde solution. Sections of these biopsies were stained using haematoxylin and eosin, periodic acid Schiff (PAS), before and after diastase, Perl's stain for iron, orcein for elastic tissue, hepatitis B surface antigen and metallothionein, and untoned reticulin and haematoxylin/picrosirius red for collagen. All the biopsies were assessed without knowledge of the MTX dose by two observers (M.S. and N.Y.H.) and allocated to one of five histological groups. These were defined, according to the severity of the histological abnormalities as follows: (1) normal histology; (2) steatosis (fatty change) alone; (3) inflammation (± steatosis) without fibrosis; (4) fibrosis

(± steatosis ± inflammation); and (5) cirrhosis. This classification has been reported previously;[3,4] it is more sensitive in documenting minor histological abnormalities than the method adopted by Roenigk *et al.*,[5] in which biopsies showing mild fatty change and mild portal inflammation are considered as grade 1 (normal). In our study, biopsies showing these mild changes were allocated to groups 2 and 3, respectively. Biopsies were allocated to group 4 if they showed even a mild degree of fibrosis.

The precise significance of hepatic steatosis is open to debate. It was found in post-mortem livers in 24% of 503 unselected traffic accident casualties[6] and is not generally regarded as an indicator of significant liver damage[7] or as a contraindication to MTX therapy.[1] For the purposes of our comparative analysis, examining progression of histological abnormalities, group 2 histology (i.e. steatosis alone) was not considered to be abnormal.

A deterioration in the liver histology was defined as a change from groups 1 or 2 to groups 3, 4 or 5, from group 3 to groups 4 or 5, or from group 4 to group 5. Similarly, an improvement in the liver histology was defined as a change from groups 5, 4 or 3 to groups 2 or 1, from groups 5 or 4 to group 3, or from group 5 to group 4.

Results

The mean cumulative dose of MTX at the time of the first liver biopsy was 2743 mg (range 315–10,024), given over 275 weeks (range 26–738). In the interval between the first and last biopsies, patients received, on average, a further 2362 mg (range 390–7155) (interval MTX dose) over 225 weeks (range 60–460). The mean average weekly MTX dose was 10·5 mg (range 3·9–19·2).

The number of patients in each histology group at the time of the first biopsy was as follows: group 1, 18 patients; group 2, 7; group 3, 13; group 4, 11; group 5, 0. The corresponding figures for the last biopsy were 14, 12, 13, 10 and 0 patients, respectively (Fig. 1). None of the patients developed cirrhosis.

There was an improvement in the histological group in 12 patients, no change in 28 patients, and a deterioration in nine patients. Figure 2 shows the mean cumulative MTX dose and histology score for patients in these three categories. Table 1 gives further details, including mean age, alcohol consumption, duration of treatment and the MTX dose received. Patients showing improvement had a higher mean cumulative, interval and weekly MTX dose, than those whose liver histology remained unchanged or deteriorated.

Overall, there was no significant correlation between a change in the histological group and either the dose of MTX received, between biopsies, or the cumulative dose

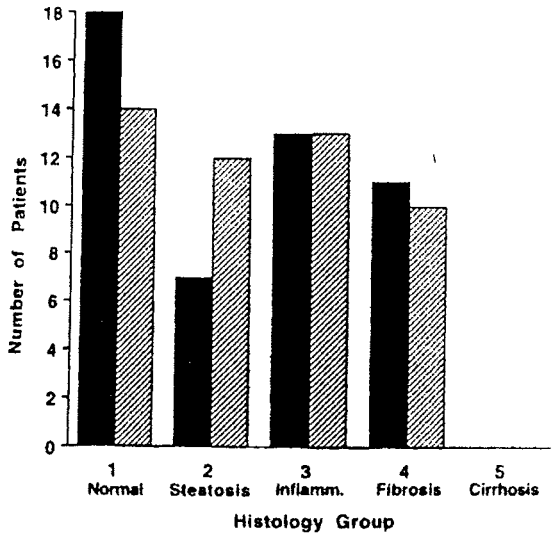

Figure 1. Number of patients in each histology group at the time of the first (■) and last (▨) biopsies.

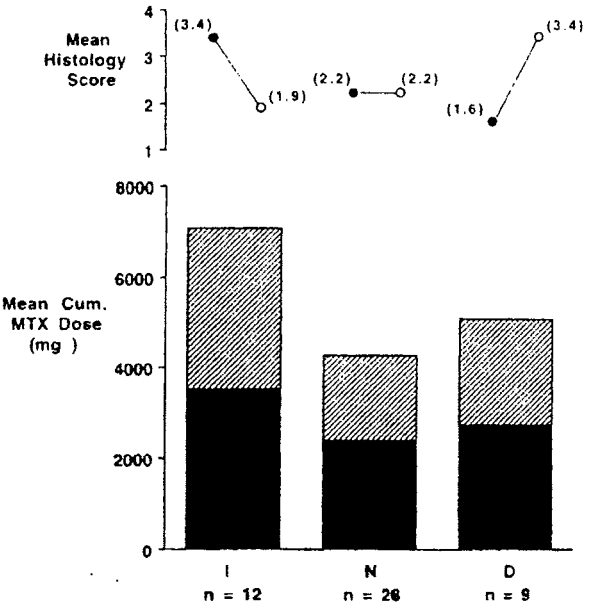

Figure 2. The mean cumulative methotrexate dose and the histology score at the time of the first (■●) and last (▨○) biopsies in patients showing an improvement (I), no change (N), or a deterioration (D) in their liver histology.

Table 1. Details of patients having sequential liver biopsies

Patient group	First biopsy			Interval MTX		Average weekly MTX dose (mg)	Last biopsy				
	Cumulative MTX								Cumulative MTX		
	Dose (mg)	Weeks	Histology score	Dose (mg)	Weeks		Age* (years)	Alcohol† (U/week)	Dose (mg)	Weeks	Histology score
I ($n = 12$; M = 8, F = 4)	3548	312	3·4	3534	301	11·7	55·0	3·7 (8·2)	7082	613	1·9
N ($n = 28$; M = 19, F = 9)	2400	251	2·2	1865	190	9·8	53·5	4·0 (5·6)	4265	441	2·2
D ($n = 9$; M = 3, F = 6)	2736	302	1·6	2342	233	10·1	55·8	1·3 (2·1)	5078	535	3·4

Patients groups: I = improvement, N = no change, D = deterioration in liver histology: M = Male, F = Female. Numerical values are means for each patient group. *Age at time of last biopsy. †Stated average alcohol consumption (units/week) at time of last biopsy (pre-MTX alcohol consumption in parenthesis). Interval MTX dose = total dose received between first and last biopsies. MTX = methotrexate.

of MTX at the time of the last biopsy (Spearman correlation coefficients, 0·23, $n = 49$, $P = 0·06$ and 0·11, $n = 49$, $P = 0·23$, respectively).

There was no significant correlation between the liver histology group and either the cumulative MTX dose or the duration of treatment at the time of the last biopsy (Spearman correlation coefficients, −0·013, $n = 49$, $P = 0·46$ and −0·036, $n = 49$, $P = 0·40$, respectively).

In summary we found that, during continued treatment with MTX, more patients showed an improvement than showed a deterioration in their liver histology grading, and there was no significant correlation between the MTX dose received and a change in the histological group: patients showing an improvement had, on average, received more MTX than those showing a deterioration or in whom there was no change. None of the 49 patients developed cirrhosis. Of the 11 patients with fibrosis on the first biopsy, none showed deterioration; five showed significant improvement with no evidence of fibrosis on the last biopsy. Five patients, whose initial liver biopsy was completely normal (i.e. group 1), progressed to inflammation or fibrosis. Liver biopsy findings prompted discontinuation of MTX therapy in four of the 49 patients who underwent sequential biopsies.

Discussion

Bone marrow suppression, particularly in older patients, is undoubtedly the most hazardous potential adverse effect of MTX therapy.[8] Of the 24 fatalities associated with MTX treatment for psoriasis reported to the United Kingdom Committee On Safety of Medicines between 1969 and 1993, myelosuppression was given as the cause of death in 19 cases (personal communication). In only three of the other cases could death be attributed to hepatotoxicity (hepatic failure in one case, hepatic cirrhosis in one case, and gastrointestinal haemorrhage in one case). Nevertheless, concern about possible hepatotoxicity and controversy about which tests to employ for monitoring the hepatic status remain important to physicians prescribing MTX long-term.

The first case of hepatic fibrosis, attributed to MTX, in a psoriatic patient, was reported in 1964.[9] Further reports of hepatic injury, including cirrhosis, in psoriatic patients receiving MTX, followed. MTX was seen as an effective treatment for psoriasis, and its use increased rapidly. By 1974 it was the most commonly prescribed systemic therapy for severe psoriasis in the U.S.A.[10]

Concerns about hepatotoxicity may have been heightened by a recent publication[11] describing three disastrous cases of cirrhosis and liver failure, leading to liver transplantation, in patients receiving largely unsupervised MTX treatment for psoriasis. One patient received 9·5 g MTX in a 5-year period. Another received combined oral and intramuscular MTX (30 mg/week and 25 mg every 2 weeks, respectively) for 12 years (approximately 26 g cumulative MTX dose). Liver biopsies were not performed. A third patient self-medicated herself with a personally obtained supply of MTX for 6 years. Although no information was given about other potential aetiological factors, such as alcohol

consumption, hepatitis B and C status, and other drug history, it is reasonable to accept that MTX contributed to the liver failure in these patients.

Percutaneous liver biopsy has been considered the only reliable method for assessing MTX-associated liver damage, despite many attempts to find suitable alternatives for monitoring patients on long-term therapy. Several studies have found a poor correlation between liver biopsy findings and the results of conventional liver enzyme tests.[12] To varying degrees, dynamic and other liver function tests,[4] and imaging techniques including ultrasound,[3] magnetic resonance[13] and radionuclide scanning,[3] have also proved unsatisfactory. The current guidelines of the *Ad Hoc* Committee on Methotrexate of the American Academy of Dermatology[1] recommend performing a liver biopsy at or near the beginning of treatment with MTX, and periodically after every 1–1·5 g cumulative dose during continued treatment. These guidelines are variably followed in clinical practice.[14,15]

In addition to the purely economic considerations and the inconvenience of the hospital admission required, the procedure of liver biopsy is not entirely without risk.[16,17] According to a confidential postal questionnaire,[14] British consultant dermatologists collectively recalled five deaths as a result of liver biopsies on the estimated 10,000 psoriatic patients treated by them with MTX during their consultant careers.

A liver biopsy in an NHS hospital in the U.K. was estimated in 1992 to cost £588.[18] Unit drug costs for MTX are, however, modest. Based on 1994 (U.K.) prices,[19] 1 year's supply of MTX (15 mg/week) costs £34. This compares with an estimated £412 for once weekly photochemotherapy with 8-methoxypsoralen and UVA,[18] £401 for acitretin (25 mg/day)[19] and £1905 for cyclosporin (200 mg/day).[19] Even taking into account the cost of liver biopsies, MTX treatment is relatively inexpensive. If liver biopsies could be dispensed with in patients on long-term treatment, MTX would represent an even more cost-effective treatment for severe psoriasis.

Little has been published on the progression of liver histology abnormalities during continued treatment with MTX, although improvement of even advanced changes has been demonstrated after withdrawing the drug.[20] Zachariae and Sogaard[21] reported 25 patients with histologically proven cirrhosis, who were maintained on MTX because of severe psoriasis which could not be controlled otherwise. Liver biopsies, done from 1 to 13 years after cirrhosis was diagnosed, showed no progression in most of the cases and, in 14 patients, cirrhosis was not apparent in the latest biopsy. It has been suggested that a single abnormal liver biopsy does not necessarily indicate disease which will progress during continued treatment. Our results confirm this and, in our series, more patients showed an improvement than a deterioration during continued treatment.

Published recommendations on the use of MTX imply that hepatic damage is related to the cumulative dose received. In our patients, however, there was no significant correlation between biopsy findings and the cumulative dose or duration of treatment. Those showing an improvement in liver histology had, on average, received more MTX than those who showed a deterioration or no change. None of the 49 patients developed cirrhosis during long-term treatment. Overall, our results suggest that, long-term, low-dose, once weekly MTX may be significantly less hepatotoxic than previously stated.

During the study period, none of our patients required an average dose of more than 20 mg MTX weekly to maintain adequate control of their psoriasis. Biopsy findings did not correlate with the mean weekly MTX dose received. Nevertheless, the average weekly MTX dose may still be an important factor in determining whether hepatic damage occurs and it is certainly possible and, indeed, probable, that higher doses may be more hepatotoxic.[11]

Several studies have suggested an increased risk of hepatotoxicity in psoriatic patients who drink alcohol regularly during MTX treatment.[12] In our practice, patients with a history of high alcohol consumption were generally not treated with MTX and patients on long-term treatment were advised to minimize alcohol intake. Although we did not demonstrate a correlation between the stated alcohol consumption and the likelihood of histological deterioration, alcohol is a well known hepatotoxin and it would seem prudent to continue to advise alcohol restriction during long-term treatment with MTX.

Overall, in only four of the 49 patients who had sequential biopsies, was it felt necessary to stop MTX therapy as a result of the liver biopsy findings. One patient (K.L.) admitted to previous alcohol abuse and continued to consume 12 units of alcohol weekly during MTX treatment. Although there was no deterioration in the liver histology grade, both his biopsies showed fibrosis and it was felt wise to stop MTX because the patient was suspected of concealing his true alcohol consumption. The liver biopsy in another patient (R.H.) showed deterioration from steatosis to fibrosis, accom-

panied by elevated liver enzyme levels. Although the possibility of continued MTX was considered, the patient was unwilling to have further liver biopsies and, therefore, MTX was stopped. In the two other patients (S.D. and R.K.), fibrosis was present in both biopsies and the referring dermatologist considered it prudent to withdraw MTX treatment. The psoriasis in both patients subsequently proved difficult to control with alternative therapies.

Further analysis shows that, of the 11 patients with fibrosis on the first biopsy and who continued to receive MTX, none showed a deterioration in their liver histology grade. Five showed significant improvement, with no evidence of fibrosis on the last biopsy. This suggests that fibrosis alone need not necessarily be a contraindication to continued MTX therapy.

The liver biopsy findings prompted discontinuation of MTX in only four of our patients on long-term treatment. This has to be weighed against the cost and morbidity of the 124 biopsies performed in these patients. Our study has shown that, with careful follow-up, the risk of development or progression of hepatic disease in patients receiving long-term, low-dose, once weekly MTX for psoriasis, is modest. In patients where there is doubt about previous alcohol consumption or hepatitis, we feel that a liver biopsy near the start of treatment may be justified, primarily to exclude hepatic pathology not apparent on simple enzyme tests. If, however, the initial biopsy is normal or shows only mild fibrotic changes, then it would appear there is little to be gained from repeating liver biopsies routinely during long-term treatment with MTX.

Acknowledgments

We thank Sister B.Young and the staff of the Programmed Investigation Unit, Manchester Royal Infirmary, for the dedication and efficiency which made this study possible, and Ms Sally Hollis of the Statistics and Computing Unit, Hope Hospital, Salford, for performing the statistical analyses.

References

1 Roenigk HH Jr, Auerbach R, Maibach HI *et al.* Methotrexate in psoriasis: revised guidelines. *J Am Acad Dermatol* 1988; 19: 145–56.

2 Paton A, Saunders JB. ABC of alcohol: Definitions. *Br J Med* 1981; 283: 1248–50.

3 Mitchell DM, Johnson RJ, Testa HJ *et al.* Ultrasound and radionuclide scans—poor indicators of liver damage in psoriatic patients treated with methotrexate. *Clin Exp Dermatol* 1987; 12: 243–5.

4 Mitchell D, Smith A, Rowan B *et al.* Serum type III procollagen peptide, dynamic liver function tests and hepatic fibrosis in psoriatic patients receiving methotrexate. *Br J Dermatol* 1990; 122: 1–7.

5 Roenigk HH Jr, Auerbach R, Maibach HI *et al.* Methotrexate guidelines—revised. *J Am Acad Dermatol* 1982; 6: 145–55.

6 Hilden M, Christoffersen P, Juhl E *et al.* Liver histology in a 'normal' population—examination of 503 consecutive traffic casualties. *Scand J Gastroenterol* 1977; 12: 593–7.

7 Powell EE, Cooksley WGE, Hanson R *et al.* The natural history of nonalcoholic steatohepatitis: A follow-up study of forty-two patients for up to 21 years. *Hepatology* 1990; 11: 74–80.

8 Al-Awadhi A, Dale P, McKendry RJ. Pancytopenia associated with low dose methotrexate therapy. A regional survey. *J Rheumatol* 1993; 20: 1121–5.

9 O'Rourke RA, Eckert GE. MTX-induced hepatic injury in an adult. *Arch Intern Med* 1964; 113: 191–4.

10 Bergstresser P, Schreiber S, Weinstein G. Systemic chemotherapy for psoriasis: A national survey. *Arch Dermatol* 1976; 112: 977–81.

11 Gilbert SC, Klintmalm G, Menter A *et al.* Methotrexate-induced cirrhosis requiring liver transplantation in three patients with psoriasis. *Arch Intern Med* 1990; 150: 889–91.

12 Weinstein G, Roenigk HH, Maibach HI *et al.* Psoriasis–liver MTX interactions. Cooperative study. *Arch Dermatol* 1973; 108: 36–42.

13 Rademaker M, Webb JAW, Lowe DG *et al.* Magnetic resonance imaging as a screening procedure for methotrexate-induced liver damage. *Br J Dermatol* 1987; 117: 311–6.

14 Carmichael AJ, Motley RJ, Finlay AY *et al.* Methotrexate-associated hepatic complications and monitoring protocols in UK dermatology. *Br J Dermatol* 1992; 127 (Suppl. 40): 18.

15 Peckham PE, Weinstein GD, McCullogh JL. The treatment of severe psoriasis—A national survey. *Arch Dermatol* 1987; 123: 1303–7.

16 Piccinino F, Sagnelli, Pasquale G *et al.* Complications following percutaneous liver biopsy—A multicentre, retrospective study on 68,276 biopsies. *J Hepatol* 1986; 2: 165–73.

17 Creswell SN, Burrows D. Liver biopsies in psoriatics. Complications and evaluation. *Int J Dermatol* 1980; 19: 217–9.

18 Cork M. Economic considerations in the treatment of psoriasis. *Dermatol Pract* 1993; Jan/Feb: 16–20.

19 *British National Formulary*, 27. British Medical Association and Royal Pharmaceutical Society of Great Britain, 1994.

20 Newman M, Auerbach R, Feiner H *et al.* The role of liver biopsies in psoriatic patients receiving long-term MTX treatment—improvement in liver abnormalities after cessation of treatment. *Arch Dermatol* 1989; 125: 1218–24.

21 Zachariae H, Sogaard H. MTX-induced liver cirrhosis—a follow up. *Dermatologica* 1987; 175: 178–82.