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LIVER BIOPSY IN METHOTREXATE-TREATED PSORIATICS—A RE-EVALUTION

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Abstract. Two-hundred and eighty-six liver biopsies were performed in 139 psoriatics on treatment or considered for treatment with methotrexate. In 56 psoriatics included in this study both pre- and post-methotrexate biopsies were performed, the average methotrexate dose being 936 mg. None of the data showed statistically significant differences between pre- and post-methotrexate biopsies, with the exception of an increase in fatty infiltration, found when comparing all pre-methotrexate biopsies with the total number of latest post-methotrexate samples.

As expected, alcohol seemed to be significantly associated with liver fibrosis in pre-methotrexate biopsies. An earlier intake of potassium arsenite may be an important factor in some patients, although potassium arsenite alone has not been proved to be the cause of liver damage among psoriatics included in this study. While only 1 of 22 psoriatics with a total normal biopsy had been on arsenite, 6 of 18 of the same group of psoriatics who had fibrosis had been on this drug earlier.

Although no statistically significant differences related to fibrosis and cirrhosis could be demonstrated between the various groups of psoriatics it should be noted that in three cases liver cirrhosis did appear in a biopsy from a methotrexate-treated psoriatic who had no signs of fibrosis or cirrhosis in a pre-methotrexate biopsy. This incidence is low in relation to the total number of patients treated. The relatively low incidence of cirrhosis found in the present study, as in earlier studies by our group is believed to be due to the use of an intermittent dosage schedule. The study showed that early fibrosis and cirrhosis seem to appear, with very minor abnormalities in laboratory results. This finding indicates the necessity of performing liver biopsies in the control of psoriatics on long-term methotrexate therapy.

The difference between biopsies from psoriatics and liver biopsies from control patients may indicate that severity of disease may be a complicating factor in the pathogenesis of the liver damage.

Key words: Liver biopsy; Methotrexate; Psoriasis; Alcohol; Arsenite; Liver damage

We have previously published results on liver biopsies in psoriatics (10, 11, 12); these studies were performed together with various co-workers during the period 1968 to 1972. The purpose of this paper is to report the results of a follow-up on liver biopsies from some of the same patients after further treatment with methotrexate. The study includes the latest data, together with results of earlier biopsies.

MATERIAL AND METHOD

Our investigations were carried out on 286 biopsies from 139 patients with severe psoriasis treated with or considered for treatment with methotrexate. Moreover the study includes already published data (11) of control biopsies from 18 patients with Parkinson's disease considered for treatment with *l*-dopa and 42 biopsies taken from 6 to 58 hours after sudden death due to cardiac failure or traffic accidents. A number of the psoriatics had previously elsewhere received potassium arsenite for their disease, from 6 months to 48 years earlier.

The material includes pre- and latest post-methotrexate biopsies from 56 psoriatics who had received an average methotrexate dose of 963 mg, together with serial biopsies from 27 patients who had undergone from 3 to 8 biopsies with an average interval of one year.

All patients were asked to supply information upon their alcohol consumption. Generally speaking, patients with heavy alcohol consumption were not considered as candidates for methotrexate treatment. However, 11 patients with a daily alcohol intake of more than four drinks per day are included in the study. Due to the results of our examination, one of these patients did not receive methotrexate. The remaining patients could not be controlled on topical treatment and, at least for a time, received the drug. All, however, agreed upon reducing their alcohol intake.

Methotrexate was originally administered intramuscularly in weekly doses of 10 to 50 mg, occasionally with shorter or longer intervals. From 1971 most patients have been on a divided-dose intermittent oral dosage schedule over a 36 hour period (9).

Besides liver biopsies all patients have had blood controls at intervals of 1–4 weeks. The laboratory determinations for evaluating liver damage were serum glutamic pyruvic transaminase (SGPT), alkaline phosphatases (AP) and until 1973 bromsulphthalein retention (BSP).

All biopsies, including control post-mortem biopsies, were obtained by the Menghini technique (7) using a 70 × 1.9 mm needle. Sections were cut 5 μm thin and stained with haema-

Table I. *Comparison of liver biopsies from psoriatics on or considered for treatment with methotrexate with control biopsies*

	No. of Patients	Average grading: Steatosis	Nuclear variability	Periportal inflammation	Focal necrosis	Fibrosis	Cirrhosis (*n*)	Per cent with normal biopsy	Average duration of MTX-treatment (years)	Average total MTX-dose (mg)
Pre-MTX	95	1.64 ±0.08	1.91 ±0.08	1.24 ±0.05	1.34 ±0.05	1.08 ±0.03	1	15.7 (*n* = 15)		
Post-MTX	96	2.04 ±0.09	1.98 ±0.09	1.35 ±0.06	1.53 ±0.06	1.23 ±0.05	6	11.4 (*n* = 11)	2.16 ±0.16	1 164 ±98.8
Controls	60	1.33 ±0.09	1.50 ±0.08	1.12 ±0.05	1.21 ±0.06	1.12 ±0.04	2	33.3 (*n* = 20)		

toxylin-eosin and van Gieson. Fatty infiltration, periportal inflammation, nuclear variability, focal necrosis, cholestasis, fibrosis and cirrhosis were estimated. Except for cirrhosis, each histological abnormality was graded as 1 (not present), 2 (slight), 3 (moderate), or 4 (severe). Cirrhosis was interpreted as either present or absent.

RESULTS

Data on biopsies prior to treatment are shown in Tables I and II. Table I includes all pre-methotrexate biopsies together with the latest findings from all patients who had a post-methotrexate biopsy. Although there is a trend towards an increase in fibrosis and cirrhosis, only fatty infiltration was found to be significantly increased ($P < 0.05$) when comparing pre- with post-methotrexate biopsies. As in our previous studies there was a significant difference ($P < 0.05$) between liver biopsies from psoriatics and control biopsies. While 33.3% of the controls had a completely normal biopsy, only 15.7% of pre-methotrexate and 11.4% of post-methotrexate psoriasis biopsies were normal. The difference between percentages of normal pre- and post-methotrexate biopsies was not statistically significant.

When comparing biopsies from patients who had both a pre-methotrexate and at least one post-methotrexate biopsy (Table II) it should be noted that while only one patient had signs of cirrhosis in the pre-methotrexate group, 4 patients showed cirrhosis in post-methotrexate biopsies. Although not statistically significant, this finding is important. The data as a whole show a tendency towards increased liver pathology, but the difference between the groups of biopsies is at present not statistically significant.

The results of the serial biopsies appear in Table III. The parameters shown are fatty infiltration, focal necrosis, fibrosis and cirrhosis. In general, these biopsies showed little evidence of significant or progressive structural hepatic damage. Only in 3 of these patients did a cirrhosis appear in the latest biopsy which was not found in their first biopsy. In 3 patients the finding of cirrhosis led to a change of therapy. One (patient no. 51) was a

Table II. *Comparison of liver biopsies from psoriatics prior to methotrexate treatment with biopsies taken from the same patients during treatment*

	No. of patients	Average grading: Steatosis	Nuclear variability	Periportal inflammation	Focal necrosis	Fibrosis	Cirrhosis (*n*)	Per cent with normal biopsy	Average duration of MTX treatment (years)	Average total MTX-dose (mg)
Pre-MTX	56	1.70 ±0.10	1.98 ±0.10	1.23 ±0.06	1.36 ±0.07	1.09 ±0.05	1	14.2 (*n* = 8)		
Post-MTX	56	2.00 ±0.11	1.98 ±0.10	1.39 ±0.08	1.54 ±0.07	1.27 ±0.07	4	7.1 (*n* = 4)	1.41 ±0.09	963 ±82.4

Table III. *Results of serial liver biopsies in 27 methotrexate-treated psoriatics*

The pathological findings are graded 1 to 4 (grade 1 is no pathological change). The average interval between each biopsy is approximately one year

Patient no.	Sex	Age[a]	Fatty infiltration biopsy no.								Focal necrosis biopsy no.								Fibrosis biopsy no.								Cumulative dose (mg)
			1	2	3	4	5	6	7	8	1	2	3	4	5	6	7	8	1	2	3	4	5	6	7	8	
14	♂	21	1	2	1	1	1	1	1	1	2	2	2	1	2	1	1	1	1	1	1	1	1	1	1	1	6 420
3	♂	66	3	2	3	3	3	3			2	2	2	1	2	2			1	1	2	1	3[c]	3[c]			3 955
5	♀♂	51	2	2	3	3	3				2	1	1	2	1				1	1	1	1	1				2 180
23[b]	♂	30	1	1	1	1	2				1	1	1	2	1				1	1	1	1	1				4 750
51	♀	19	1	1	1	1	3				1	1	2	2	3				1	1	1	1	2[c]				3 600
1	♀	65	2	2	2	2					1	1	1	2					1	1	1	1					1 015
28	♂	40	1	1	1	2					1	1	1	1					1	1	1	1					2 155
37	♂	55	3	3	3	4					1	1	1	2					1	1	1	2					1 275
48	♂	65	3	3	3	3					2	2	2	2					1	2[c]	2[c]	2					970
55	♀	76	4	4	4	4					2	1	2	2					1	1	1	1					2 035
56	♀	60	2	2	2	2					2	2	2	2					1	1	2	1					1 300
71	♀	33	2	3	4	3					1	1	2	2					1	1	2	1					1 750
88	♂	60	3	2	3	3					1	1	2	2					3[c]	1	2[c]	3[c]					1 440
118	♂	54	4	3	3	3					2	2	3	3					2[c]	2[c]	3[c]	3[c]					790
7	♀	46	2	2	2						2	1	1						1	1	1						1 300
15	♂	27	1	1	1						1	1	1						1	1	1						1 140
33	♂	63	3	3	3						2	1	1						1	1	1						1 750
43	♂	10	2	2	2						1	1	1						1	1	2						1 230
46	♂	60	2	1	1						1	1	1						1	1	1						1 400
47	♂	55	2	1	3						2	3	2						1	2[c]	2[c]						1 360
57	♂	62	1	2	2						1	2	2						2	1	1						1 510
58[b]	♂	57	2	3	3						1	1	2						1	1	1						2 600
60	♂	52	2	2	3						1	1	1						1	1	1						2 160
62	♂	53	1	1	1						1	1	1						1	1	1						520
63[b]	♂	37	1	1	1						2	1	1						1	1	1						780
72[b]	♂	62	2	2	3						1	1	2						1	1	1						1 010
78[b]	♂♀	54	1	2	2						1	2	3						1	1	2						1 090
119	♀	57	1	3	3						1	2	2						1	1	1						580

[a] Age at first biopsy.
[b] Previous arsenite potassium treatment.
[c] Cirrhosis.

19-year-old girl with a universal severely infiltrated psoriasis. Treatment was changed to hydroxyurea.

In the remaining patients with cirrhosis the dosage was reduced to a minimum. It should be noted that in most cases of cirrhosis there were relatively few signs of pronounced active inflammation (Table IV). The serial biopsies as a whole showed no (or almost no) changes in relation to nuclear variability and periportal inflammation.

Table IV. *Findings in the latest post-methotrexate biopsy showing cirrhosis*

The figures are graded 1 to 4

Patient no.	Steatosis	Nuclear variability	Periportal inflammation	Focal necrosis	Fibrosis
3	3	4	1	2	3
47	3	3	2	2	2
48	3	2	1	2	2
51	3	3	3	3	2
88	3	4	1	2	3
118	3	4	3	3	3

Tables V and VI show liver pathology in relation to alcohol consumption. The pattern of alcohol consumption does not differ from alcohol intake in non-psoriatics (6). In pre-methotrexate biopsies, fibrosis was significantly increased in patients with the highest alcohol intake ($P < 0.05$). Following methotrexate, this difference disappeared.

Table VII shows a trend towards a worsening liver pathology when patients had been treated with both methotrexate and arsenite. While only one (5%) of the 22 psoriatics in this group with a normal biopsy had been on potassium arsenite, 6 of 18 (33%) of the same group who had fibrosis had been on this

Table V. *Pre-methotrexate biopsy findings in relation to alcohol consumption*

Drinks per day	No. of patients	Average grading					Cirrhosis (*n*)
		Steatosis	Nuclear variability	Periportal inflammation	Focal necrosis	Fibrosis	
< 1	78	1.55 ±0.08	1.88 ±0.08	1.21 ±0.05	1.28 ±0.05	1.02 ±0.03	1
1–3	9	1.89 ±0.30	1.67 ±0.23	1.22 ±0.15	1.44 ±0.18	1.22 ±0.15	0
⩾ 4	8	2.25 ±0.31	2.38 ±0.38	1.63 ±0.26	1.75 ±0.25	1.50 ±0.19	0

Table VI. *Post-methotrexate biopsy findings in relation to alcohol consumption*

Drinks per day prior to methotrexate	No. of patients	Average grading					Cirrhosis (*n*)
		Steatosis	Nuclear variability	Periportal inflammation	Focal necrosis	Fibrosis	
< 1	76	2.00 ±0.10	1.97 ±0.09	1.37 ±0.07	1.57 ±0.06	1.28 ±0.06	6
1–3	10	1.90 ±0.28	1.70 ±0.30	1.20 ±0.13	1.10 ±0.10	1.00 ±0.00	0
⩾ 4	10	2.70 ±0.26	2.40 ±0.34	1.60 ±0.22	1.70 ±0.21	1.20 ±0.13	0
				Biopsies with		Biopsies with	

Table VII. *Findings in arsenite-treated psoriatics*

	All biopsies	Normal biopsies	fibrosis	cirrhosis
Pre-MTX *n* = 95	28/95 = 29 %	3/28 = 11 %	1/7 = 14 %	1/1 = 100 %
Post-MTX *n* = 96	22/96 = 23 %	1/22 = 5 %	6/18 = 33 %	2/6 = 33 %

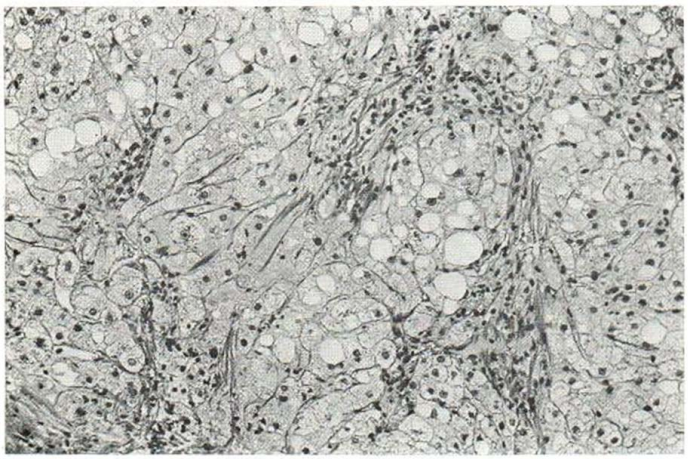

Fig. 1. Liver biopsy with active cirrhosis, collagenous fibres, moderately destroyed liver cell parenchyma and steatosis. Note the lymphocytic infiltrations.

Table VIII. *Laboratory findings in methotrexate-treated psoriatics with liver cirrhosis*

Patient no.	SGPT[a] units	AP[b] units	BSP (%)
3	8.0	5.4	4.0
47	3.0	5.7	4.0
48	8.0	5.0	4.0
51	8.0	4.6	4.0
88	9.0	4.0	3.0
118	9.0	5.9	13.7

[a] Normal values ⩽30 units.
[b] Normal values 0–10 units.

drug earlier. Although none of these findings are statistically significant they should be noted as well as the fact that the one pre-methotrexate biopsy with cirrhosis was from a patient treated with potassium arsenite. The same concerned another patient who developed cirrhosis during methotrexate treatment (Fig. 1). It should also be noted that one patient previously treated with potassium arsenite showed signs of multifocal liver cancer (11).

The relation between laboratory results in patients with cirrhosis can be seen in Table VIII. This Table indicates that cirrhosis can appear with no or very small abnormalities in laboratory results.

None of the liver biopsies showed signs of cholestasis

DISCUSSION

The high incidence of pathological liver biopsies in psoriatics is in agreement with previous reports in the literature (2, 5) as well as with our own earlier data (10, 11, 12). Although most changes were of a mild nature, in contrast to our earlier findings, cirrhosis and fibrosis now appeared in a number of biopsies.

With the exception of an increase in fatty infiltrations the differences between the pre- and post-methotrexate biopsies were not statistically significant, but it should be noted that fibrosis and cirrhosis were found in patients who had none of these signs in their pre-methotrexate biopsies. The percentage is still very small in relation to the great number of psoriatics treated, and it is by no means comparable to the data reported elsewhere (1, 4). This is probably due to the fact that all patients had been on an intermittent dosage schedule, which seems less toxic to the liver (8).

A history of increasing alcohol consumption correlated significantly with liver fibrosis in pre-methotrexate biopsies, but not in post-methotrexate samples, where other factors seem to influence the data.

Previous treatment with potassium arsenite may be another factor having an influence on the hepatic status (3). As in our earlier studies on psoriatics, these new data do not prove that liver pathology in general could be attributed to this drug, but the high percentage of previously arsenite-treated patients among methotrexate-treated psoriatics with fibrosis should be noted.

Our data should further stimulate the use of liver biopsy in the control of psoriatics treated with methotrexate. Liver function tests alone seem not to be reliable indicators of early hepatic fibrosis or cirrhosis. We recommend a biopsy with approximately one year's interval between the first two or three biopsies. Later the intervals may well be increased in accordance with the age of the patient and the findings in earlier biopsies. With an intermittent dosage schedule, liver damage in the form of fibrosis or cirrhosis seems to appear at a slower rate than with a daily orally administered dosage schedule.

We propose that the differences between biopsies from psoriatics and liver biopsies from control patients make it likely that the severity of psoriasis itself may be an additional complicating factor in the pathogenesis of liver damage among methotrexate-treated patients.

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