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Methotrexate Hepatotoxicity in Psoriatic Patients Submitted to Long-term Therapy

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Eighty-four patients with severe psoriasis who required methotrexate (MTX) therapy have been reviewed. A total of 134 liver biopsies were performed. The lack of correlation between alcohol intake and the use of potential hepatotoxic drugs with pretreatment liver biopsies is noted. A review of 30 patients who had liver biopsies performed before and after MTX treatment showed no statistically significant difference between the histological grades before and after treatment. Nor was there any absolute correlation between the cumulative MTX doses and the histological changes of follow-up biopsies. In this group of patients, 15 (50%) developed fibrosis, which was severe in 2 patients, after 3,431 mg MTX average dose. Cirrhosis was observed in 3 patients (10%) after 1,667 mg MTX average dose. Follow-up liver biopsies are recommended for patients treated with MTX. *Key words: Cirrhosis; Fibrosis; Liver biopsy.*

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Hepatotoxicity from long-term methotrexate (MTX) therapy is well documented (1–6). Fibrosis and, less frequently, cirrhosis have been attributed to it. Recent studies, however, have shown that MTX-induced cirrhosis is nonagressive. There are reports of patients whose hepatic disease, evaluated by liver biopsies, did not deteriorate with maintenance of the treatment (7). Others (8) think that fibrotic alterations observed during MTX therapy are potentially reversible after discontinuance of the drug.

A protocol for MTX usage in psoriasis was elaborated in 1972 (9) and reviewed in 1973 (10), 1982 (11) and 1988 (12). It preconizes liver biopsy before initiating the treatment, or in

Table I. *Group 1.*

Patients sex/age	Hepatotoxic or liver disease	Alcohol	Liver biopsy pre MTX (grades)	MTX dose (mg) at follow-up biopsy	Follow-up liver biopsy (grades)
1/M/60	Hepatitis	+++	I	200	I
2/M/35	Nsaid		II	1640	II
3/F/57			III	2910	III
4/M/51	Nsaid	++	III	10650	III
5/M/30	Etretinate	+++	II	440	III
6/M/72		+	II	4435	II
7/M/55		++	I	2500	I
8/M/32		++	III	3750	II
9/F/57	Nsaid + diabetes	++	II	1700	IV
10/M/71			III	370	II
11/M/52	Nsaid + hepatitis		I	1380	III
12/M/42	Nsaid + etretinate		I	2435	III
13/M/35	Nsaid + etret. + azat.		I	3900	III
14/M/33			I	1060	II
15/M/43	Nsaid	+	I	2250	III
16/M/60	Nsaid		I	690	I
17/M/59	Nsaid + corticost.		III	3165	III
18/M/69	Cortic. + hydantoin	+++	I	1000	I
19/M/63		+	I	3690	III
20/M/45		++	I	2500	III
21/M/56	Etretinate		II	1400	III
22/F/51	Nsaid	++	II	1700	IV
23/M/44	Nsaid	+	III	4700	III
24/F/53	Corticosteroids	++	II	3800	II
25/M/51	Nsaid + diabetes	++	III	4270	III
26/M/47		+++	II	1600	IV
27/M/42	Etret. + arsenic	++	II	4000	II
28/F/48		+	II	4280	III
29/M/46		++	II	7000	II
30/M/62		++	III	3500	III

Table II. *Group 2.*

Patients sex/age	Hepatotoxic or liver disease	Alcohol	MTX dose (mg) at follow-up biopsy	Follow-up liver biopsy (grades)
31/M/56	Hepatitis	+–	3600	III
32/F/14	Etretinate		960	I
33/M/54		++–	2400	I
34/M/52	Nsaid + corticost.	+–	3000	IV
35/F/55	Nsaid + cort. + diabet		3145	III
36/M/46	Nsaid		4170	II
37/M/71	Nsaid + diabetes	+++	3000	IV
38/M/46	Nsaid	+++	6570	III
39/M/74	Nsaid + etretinate		1700	I
40/F/30	Etretinate		4335	I
41/M/38	Nsaid		1500	II
42/M/49	Nsaid		1420	II
43/M/52		+–	3500	II
44/M/63	Nsaid	+–	9360	III
45/F/44	Nsaid + etret. + cort.		7000	I
46/M/56	Etretinate	+–	3000	I
47/M/40		+–	4800	III
48/F/38	Nsaid		7460	III
49/F/11	Nsaid + etretinate		5400	I
50/M/33	Nsaid		7340	III
51/M/43			1500	I

the first months after it has been initiated, and follow-up biopsies after 1.5 gm intervals of cumulative MTX doses if there are no alterations in liver chemistry values or risk factors. If there are significant alterations in these parameters, it is recommended that follow-up liver biopsies are performed at 1.0 gm intervals of cumulative MTX doses. The purpose of the present work was to review MTX hepatotoxicity in a population of psoriatic patients submitted to long-term treatment with this cytotoxic drug.

PATIENTS AND METHODS

A review of the medical records between 1965 and 1990 was performed in the Department of Dermatology at the Hospital de Santa Maria, in Lisbon, concerning all psoriatic patients treated with aminopterin and MTX.

The data of 84 patients were examined focusing on the disease evolution time, type of cutaneous lesions, previous treatments, MTX cumulative doses, laboratory data and liver histology, before and during the treatment, and history of hepatic disease and risk factors, such as diabetes, alcohol abuse and use of retinoids, nonsteroid antiinflammatory drugs, barbiturates and arsenic.

Sixty-three patients were males (75%) and 21 females (25%). The ages ranged from 11 to 79 years old (average 49.5). Thirty-five patients had extensive psoriasis, refractory to standard topical therapy, 30 had arthropathic psoriasis, 8 pustular psoriasis and 11 erythrodermic psoriasis. The diseases evolution time ranged from 1 month to 67 years (average 18.4 years).

All patients had previously been given topical treatments. Fifty-three had had combined treatments: 11 had made UVB phototherapy, 8 had been treated with PUVA, 5 with REPUVA and 4 had been submitted to localized superficial X-ray therapy. Ten patients had received systemic corticosteroids, 15 patients etretinate. The MTX cumulative doses, at the moment of the last liver biopsy, ranged from 200 to 10,650 mg, the average dose being 3,374 mg.

Past medical history included hepatitis in 4 patients and diabetes in 8.

Alcohol intake was considered high when there was a consumption equal or higher than 80 gm of ethanol per day, moderate when it did not exceed 60 gm and mild when it did not exceed 40 gm per day. Forty-eight patients (57.1%) referred alcohol intake, 42 being males (66.6% of the men) and 6 females (28.6%). According to the criteria previously mentioned, habits were considered severe in 15 patients, moderate in 23 and mild in the remaining 10 patients.

Forty-nine patients (58.3%) used potentially hepatotoxic drugs, some of them having taken more than one. The nonsteroid antiinfammatory drugs had been used by 34, systemic corticosteroids by 10 and etretinate by 15. Seven patients used other drugs like immunosuppressors, arsenic or diphenylhydantoin.

Concerning laboratory data, special attention was paid to full blood cell count, liver and renal function tests.

Liver biopsy specimens were obtained by the percutaneous Menghini technique, using the Jamshidi needle. Sections were stained with hematoxylin-eosin, Masson trichrome and reticulin stains. All biopsy specimens were reviewed by the same pathologist. The histological parameters were classified in 4 grades (12): grade I, normal, fatty infiltration, portal inflammation, nuclear morphology – mild alterations; grade II, fatty infiltration, portal inflammation, necrosis, nuclear morphology – moderate and severe alterations; grade III, fibrosis (septum formation); grade IV, cirrhosis.

The patients were divided into three groups, depending on the moment of the liver biopsies in relation to the treatment (Tables I–III): group 1, 30 patients with biopsies before and during MTX treatment; group 2, 21 patients with biopsies during the treatment only; group 3, 33 patients with pretreatment biopsies only.

The groups were compared by the χ^2 test modified for small series (13).

RESULTS

The laboratory data were normal in all patients before taking MTX. In 19 patients (22.6%) significant abnormalities were found during therapy. From these, 17 had alterations in liver chemistry values, which normalized after discontinuing MTX. The remaining 2 patients had bone marrow depression after cumulative doses of 390 and 3,600 mg.

The total number of reviewed biopsies was 134, with 10 patients having 2 follow-up biopsies, 3 patients having 3 follow-up biopsies and one patient having 5 follow-up biopsies.

In group 1, constituted by 30 patients with biopsies both

Table III. *Group 3.*

Patients sex/age	Hepatotoxic or liver disease	Alcohol	Liver biopsy pre MTX (grades)
52/M/64		+++	I
53/F/46		++	I
54/M/38			III
55/M/68		++	III
56/M/70		+++	I
57/M/38		+++	I
58/M/79			II
59/F/62			I
60/M/60		+++	I
61/M/69		++	II
62/F/46			I
63/M/38		++	I
64/M/26		+	III
65/M/42	Etretinate + cortic.	+++	II
66/F/49	Etretinate + cortic.		III
67/M/30	Nsaid		I
68/F/63	Corticosteroids		III
69/M/67		+	III
70/F/41	Nsaid		III
71/M/37	Nsaid	+++	II
72/M/54	Nsaid + diabetes	+	III
73/M/44	Nsaid + etretinate		III
74/M/59	Etretinate	+	III
75/M/38	Nsaid		III
76/M/72	Hepatitis + diabetes	+++	III
77/F/28	Nsaid		I
78/F/45	Diabetes	+	I
79/M/43	Nsaid	++	I
80/M/64		+++	I
81/M/55			I
82/F/21	Nsaid		I
83/F/72	Diabetes		II
84/M/49	Nsaid + cortic.		I

Table IV. *Group 1.*

Pre MTX liver biopsy			Follow-up liver biopsy			
%	Grades	Patients	%	Grades	Patients	MTX (mg) average
36.7	I	11	13.4	I	4	200–2,500 1,098
36.7	II	11	26.6	II	8	370–7,000 3,257
26.6	III	8	50.0	III	15	440–10,650 3,431
00.0	IV	0	10.0	IV	3	1,600–1,700 1,667

before and during MTX treatment, 11 patients (36.7%) were in grade I, 11 (36.7%) in grade II and 8 (26.6%) in grade III, before beginning treatment. In follow-up biopsies, 4 patients (13.4%) were in grade I, 8 (26.6%) in grade II, 15 (50.0%) in grade III and 3 (10.0%) in grade IV.

The 4 patients who maintained the grade I (nos. 1, 7, 16, 18) had cumulative doses from 200 to 2,500 mg (average 1098 mg).

In one patient (no. 14) the histological picture, after 1,060 mg, was grade II. The other 6 (nos 11, 12, 13, 15, 19, 20) changed to grade III after MTX cumulative doses between 1,380 and 3,900 mg (average 2693 mg).

From 11 patients with grade II histological changes in pretreatment liver biopsies, 5 (nos. 2, 6, 24, 27, 29) maintained the same grade in follow-up biopsies, after cumulative doses between 1,640 and 7,000 mg (average 4,175 mg). Three patients (nos. 5, 21, 28), with cumulative doses of 440, 1,400 and 4,280 mg, respectively, changed to grade III. The remaining 3 patients (nos. 9, 22, 26) changed to grade IV – cirrhosis- after MTX doses of 1,700, 1,700 and 1,600 mg.

Six out of 8 patients, with histological grade III in pretreatment liver biopsies (nos. 3, 4, 17, 23, 25, 30), maintained the same grade after MTX cumulative doses between 2,910 and 10,650 mg (average 4,866 mg). In 2 patients (nos. 8, 10) the histological findings improved-to grade II-after MTX cumulative doses of 3,750 and 370 mg, respectively.

In group 2, constituted by 21 patients with liver biopsies during MTX treatment only, 8 (38.1%) were in grade I, 4 (19.1%) in grade II, 7 (33.3%) in grade III and 2 (9.5%) in grade IV. The MTX cumulative doses ranged from 960 to 7,000 mg (average 3,287 mg) in patients with grade I, from 1,420 to 4,170 mg (average 2,648) in patients with grade II, from 3,145 to 9,360 mg (average 6,039 mg) in patients with grade III and after 3,000 mg in the 2 patients with grade IV.

Finally in group 3, constituted by 33 patients with pretreatment liver biopsies only, 16 (48.5%) had histopathological findings of grade I, 5 (15.2%) of grade II and 12 (36.3%) of grade III.

It is important to note that in the 42 grade III liver biopsies, the histological findings disclosed moderate to severe fibrosis, only in 3 patients (nos. 5, 13, 31).

DISCUSSION

MTX is an efficient therapy in the treatment of severe forms of psoriasis. Hepatic fibrosis and cirrhosis are the major problems related to its long-term administration (1–6). Some risk factors, like patient age (14), abnormalities in renal function (11), obesity and diabetes (1, 15) and alcohol intake (2), increase the incidence of hepatotoxicity from MTX. In this study, 26% of the patients in group 1 (previous and follow-up biopsies) and 36% of group 3 (previous biopsy), had mild grade III liver alterations (liver fibrosis) before beginning treatment, which compares with the figures reported by Weinstein et al. (22%) (1), Reese et al. (20%) (4) and Newman et al. (18%) (8). However, there was no correlation between the observed alterations and the amount of alcoholic beverages consumed, or the use of potentially hepatotoxic drugs. For that reason, the pretreatment liver biopsy is essential for therapeutic decision, since there is not a significant correlation between liver function tests and histological findings (1, 2, 4, 5, 7, 8, 15). According to some authors (13, 16) the tendency to fibrosis and cirrhosis is higher in patients whose pretreatment liver biopsies have abnormal histological findings. In group 1 there was no statistically significant difference in paired observations of the same patient between the histological grades before and after the treatment-previous and fol-

low-up biopsies (13). There was no significant correlation between the cumulative MTX doses and the histological grade of the follow-up biopsies (13).

However, the difference is significant (13) when comparing the percentages of the different grades in the whole group in previous and follow-up liver biopsies (Table IV).

The risk of developing fibrosis and cirrhosis with increased MTX cumulative doses is not unanimously accepted by all authors. Roenigk et al. (15) think that there is no correlation between MTX total dose and liver histological findings. On the other hand, Zachariae et al. (6), who reported 13.5% of cirrhosis after 2,200 mg MTX average dose and 25.6% with a cumulative dose superior to 4,000 mg, support the idea that there is a cirrhosis-increasing risk with the cumulative dosage. Also Nyfors (17), who found 24% of patients with fibrosis and 21% with cirrhosis after 4,000 mg MTX average dose, thinks that fibrosis and cirrhosis frequency increases considerably with cumulative doses between 2,000 and 4,000 mg MTX and, for that reason, defends the need of follow-up biopsies at those levels.

We agree with the great majority of authors that liver biopsies are recommended in follow-up of MTX-treated patients. However, Miller et al. (18) support the view that follow-up liver biopsies can be lengthened if ultrasound scans remain normal. Zachariae et al. (19, 20) concluded that serial measurements of serum PIIINP (aminoterminal propeptide of type III procollagen) is a valuable non-invasive test for liver function in MTX-treated patients. Normal levels of PIIINP allow a reduction in the follow-up liver biopsies. For O'Connor et al. (21) the high sensitivity of the liver function tests may reduce the follow-up liver biopsies in the absence of abnormal results.

In our series we observed a great individual variability between the MTX cumulative dosage and the histological findings in posttreatment biopsies. In group 1, 15 patients maintained the same level of liver histological changes after 3,413 mg MTX average dose, while in 13 patients there was a worsening of the liver biopsy after 2,180 mg MTX average dose; in 2 patients there was even an improvement of the histological findings after MTX doses of 370 and 3,750 mg. There was no absolute correlation between liver alteration level in posttreatment biopsy and MTX cumulative dosage. The occurrence of liver disease seems to depend mostly on individual susceptibility that cannot be anticipated.

MTX, when used according to internationally established criteria (12), carefully weighting the risk/benefit relation and informing the patients about its interactions, especially with regard to alcohol intake, is a valuable drug in the treatment of severe psoriasis.

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