Hepatotoxicity of prolonged methotrexate therapy for rheumatoid arthritis[1]

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Sixty patients with severe rheumatoid arthritis (RA), who were being treated with methotrexate (MTX) (mean duration of therapy, 48 months; mean weekly dosage, 8.67 mg), underwent liver biopsy performed to assess hepatic toxicity. Liver biopsies of 25 comparably severe RA patients not receiving MTX served as controls. All pathologic findings were grades I and II. Fatty infiltration was present in 50% of patients treated with MTX and 44% of controls. Fatty liver occurred more frequently in older patients and in consumers of alcohol. Round-cell portal inflammatory infiltrates were present in 18% of patients treated with MTX and 20% of controls, more frequently if Sjögren's syndrome was present. No portal fibrosis (grade III) was found, but fibrous expansion of portal zones (grade II) was noted in 1 patient treated with MTX (1.7%) with Sjögren's syndrome. At these low dosages, MTX exerts a minor and clinically unimportant hepatotoxic effect during two to eight years of chronic maintenance therapy.

Index terms: Arthritis, rheumatoid, drug therapy · Methotrexate, toxicity

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Methotrexate (MTX) was apparently first used to treat rheumatoid arthritis (RA) by Gubner et al[1,2] in about 1950, but interest in cytotoxic therapy languished when the then new and promising corticosteroids became generally available. The complications of steroid therapy led Scherbel et al[3,4] to report the use of nitrogen mustard in 1957 for intractable corticosteroid-resistant RA. Scherbel and I were involved in the care of patients whose psoriatic arthropathy responded well to MTX treatment of the cutaneous lesion.[5] This experience led us to treat RA empiri-

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Table 1. Comparison of controls and patients treated with MTX

	Patients	
	Controls (25)	Receiving MTX for 24 mo (60)
Mean age (range)	50.8 yr (21–70 yr)	52.5 yr (16–76 yr)
Mean RA duration (range)	8.1 yr (1–26 yr)	9.4 yr (3–31 yr)
Female	16 (64%)	36 (64%)
Male	9 (36%)	24 (40%)
Rheumatoid factor+	21 (84%)	47 (78%)
FANA+	12 (48%)	29 (54%)*
Sjögren's syndrome	5 (20%)	16 (27%)
Nodules	8 (32%)	24 (40%)
Erosive changes	23 (92%)	52 (87%)
Polyarticular and persistent synovitis	25 (100%)	60 (100%)
Alcohol		
None to minimal	17 (68%)	41 (69%)
Moderate to heavy	8 (32%)	19 (31%)

* Not done in 6 patients.
FANA+ = fluorescent antinuclear antibody positive.

cally, using a lower dosage of MTX (5 to 12.5 mg/week) than was in use for psoriasis. In unreported studies of 1962 and 1963 without formal placebo controls, we became convinced that MTX was both effective for the suppression of RA synovitis and reasonably well tolerated. We recommended maintenance MTX therapy for severe, progressive, or complicated RA in 1971[6] when used in combination with an antimalarial agent plus a nonsteroidal anti-inflammatory drug. By 1968, others were also interested in MTX for the treatment of connective tissue disease.[7,8]

Table 2. Duration and quantity of MTX ingestion

No. Patients	Mean Age (yr)	Mean Duration of RA (yr)	MTX Therapy, Mean (Range) (mo)	MTX Ingested, Mean (Range) (mg)
18	54	7.4	28.6	905
			(24–36)	(505–1,810)
13	54	11.2	40.3	1,650
			(36–48)	(1,128–2,071)
11	52	8.5	53.3	2,023
			(48–60)	(1,358–3,946)
11	54	9.1	66.4	2,630
			(60–72)	(1,239–3,939)
7	46	10.9	77.8	3,740
			(72–94)	(1,856–4,440)

Subsequent reports have described and documented the efficacy of MTX in managing RA,[9–11] although the mode of action remains speculative. RA is considerably suppressed within the first few weeks of treatment[12–15] and tends to recur promptly upon discontinuation of MTX. Well-controlled blinded studies have amply confirmed efficacy recently and indicate a low dropout rate from adverse effects.[16,17] The dropout rate appears to be well below 10% when clinically meaningful criteria for dropout are used, and when the weekly dosage of MTX is modest (7.5 to 10 mg)[15,16,18] and if folate-depleted states are detected and managed.

Since this treatment had proved to be empirically useful, several hundred patients with RA had received MTX between 1963 and 1973. Their rheumatoid disease had relapsed so consistently upon its discontinuation, that I perceived a need to assess the safety of chronic use of MTX. Reports from the dermatology literature in which MTX was used to treat psoriasis vulgaris had indicated a possibility of hepatic injuries including portal fibrosis and even cirrhosis.[19–22] These reports had indicated that liver biopsy was necessary to detect these changes. A study was therefore undertaken in 1973, with liver biopsy as the principal method of assessing

the long-term safety of MTX treatment of RA patients.[23]

Methods and data

The hazards of MTX therapy and of liver biopsy were discussed with RA patients who had consumed MTX for a minimum of two years of continuous therapy. It was possible to obtain a liver biopsy in 60 such patients receiving chronic MTX therapy, together with an additional 25 RA patients about to embark on MTX therapy, so that 60 patients receiving chronic therapy with MTX could be compared with 25 controls having equally severe RA, but never having been treated with MTX. Hepatic abnormalities in RA, although not satisfactorily described, have been reviewed by Weinblatt et al.[24] The alterations constituting "rheumatoid liver" must be used as the baseline, rather than "normal."

Other medications in the study were comparable, including almost invariably, a salicylate or nonsteroidal anti-inflammatory drug, an antimalarial compound, either chloroquine (≤ 4 mg/kg/day) or hydroxychloroquine (≤ 6.5 mg/kg/day). Thirteen patients were given low-dose corticosteroid therapy (prednisone, ≤7.5 mg/day). Between 1963 and 1968, no folic acid was given, but beginning in 1968, folic acid replacement was gradually added,[6] so that by the middle of 1969, all patients were receiving folic acid supplement. MTX therapy was used for seven weeks out of each eight-week cycle. Folic acid, (10 to 15 mg/day) was given during the eighth week.

The overall dropout rate during MTX therapy has remained low, estimated at 6% of all patients during the first year. This compares favorably to that of Groff et al,[14] who used prolonged therapy at a similar weekly dose, but is lower than that of Steinsson et al,[12] who used a higher weekly dose. There was no short-term dropout at these dosages in the study by Wilke et al.[9] Side effects have been limited by dividing dosage, by minimizing the weekly dose, and by giving supplemental folate. The safety record of this therapy has been gratifying with occasional mild stomatitis or macrocytosis, and rare elevations of transaminase. These manifestations have been interpreted as folate depletion and have tended to respond to intermittent folate therapy.

Allergy to MTX has not been observed. No serious bone marrow depression or macrocytic anemia and no proctitis or hepatitis have been observed at the prescribed dosage. No alteration of menstrual pattern has been seen. It is my impression that there is a modest increase in the frequency of herpes virus infection during therapy. Other infections of the type seen in immunosuppressed patients do not occur with increased frequency. Pulmonary toxicity has not been detected.

Comparison of the treated and the control groups reveals similar severity of rheumatoid disease with similarity of sex ratios, rheumatoid factor seropositivity, erosive change, persistence of synovitis, and of alcohol consumption (*Table 1*). Patients in the treated group are about three years older than those in the control group, had a few more rheumatoid nodules, and slightly more features of Sjögren's syndrome. The series of treated and control patients appears similar. These patients had severe destructive rheumatoid disease, poorly responsive to prior therapy.

Table 3. Grade classification of liver biopsy abnormalities

Grade	
I	Normal, or containing minimal to mild fatty infiltrates, minor nuclear variability, and mild portal inflammatory cell collections
II	Moderate changes containing moderate to severe fatty infiltrates, much nuclear variability, and moderate to severe portal inflammation. Portal expansion may contain centrolobular fibrosis, but lobular architecture is preserved. Scattered focal hepatocyte necrosis.
III	Sevère, containing portal fibrosis forming interlobular septa, which extend toward or connect adjacent portal tracts or central veins with one another.
IV	Cirrhosis

Table 4. Biopsy findings

	Patients			
	Controls (25)		Receiving MTX (60)	
	No.	%	No.	%
Normal	12	48	26	43
Anisonucleosis	3	12	13	22
Fatty infiltrates	11	44	30	50
No fatty infiltrates	14	56	30	50
Portal inflammation	5	20	11	18
No portal inflammation	21	80	48	80
Portal fibrosis grade II	0	0	1	1.7
Portal fibrosis grade III	0	0	0	0
Cirrhosis	0	0	0	0
Hepatic granuloma	0	0	1	1.7

Table 5. Fatty liver in 60 RA patients treated with MTX

Pathology	Grade	No. Pts	Cumulative Mean, MTX (mg)	Mean Duration of MTX Therapy (mo)	Mean Duration of RA (yr)	Mean Age of Pt (yr)
None		30	1,835	48.1	8.5	49.3
Minimal to mild	I	25	1,840	49.1	10.6	55.4
Moderate to marked	II	5	1,844	46.6	8.8	57.6
Total		60	1,837	48.5	9.4	52.5

Methotrexate administration

Table 2 lists the number of patients, age, duration of rheumatoid disease and length of MTX therapy in months, and of mean cumulative MTX ingested in milligrams. All patients received at least 24 months of MTX therapy; there were 18 patients who had taken MTX for two to three years, 13 for three to four years, 11 for four to five years, 11 for five to six years, and 7 for more than six years. Mean weekly dose was 8.67 mg (range, 2.5 to 12.5 mg). Median weekly dose was 7.5 mg.

Sixty patients (mean age, 52.5 years) had RA a mean duration of 9.4 years. The mean exposure of each patient to MTX therapy was 48.5 months (range, 24 to 94 months) with a mean cumulative dose of 1,837 mg per patient (range, 505 to 4,440 mg). Total MTX consumption in this series was 110,263 kg in 2,903 months.

Standard laboratory tests consisted of complete blood count with differential count, and 18-channel automated blood chemistry profile at intervals of three and six months in the clinically stable patient. Liver-spleen scans were not obtained.

Table 6. Fatty liver biopsy results: alcohol use by RA patients and controls

	Patients			
	Controls		Received MTX	
Pathology	No.	%	No.	%
Nondrinkers				
Lack fat	11	65	24	59
Have fat	6	35	17	41
Drinkers				
Lack fat	3	37	6	31
Have fat	5	63	13	69
Total	25		60	

Sulfobromophthalein excretion was measured in selected patients only.

Biopsy

Liver biopsy specimens were obtained percutaneously by standard needle biopsy techniques using Menghini or Vim-Silverman needles. The specimens were fixed and stained by standard methods with hematoxylin-eosin and Masson trichrome. Pathologists examined the biopsy material without knowing whether the biopsy was done before or after MTX therapy. Liver biopsy findings were classified according to the 1973 "methotrexate guidelines"[25] in which liver findings are graded I–IV in degree of severity. *Table 3* presents the histopathologic classification as used in this study, slightly modified from Roenigk et al.[25] Normal, plus minor or normal variations, are grade I, ascending in severity to cirrhosis, grade IV. This system differs from the 1972 "methotrexate guidelines"[26] by assigning one less numerical grade to each category. The entirely normal specimen was then grade I. Minor variations were grade II. Here, they are combined in grade I. The definitions and details of histologic interpretation follow those of Nyfors.[27]

Dermatologists have concluded that grade II liver changes, even fibrous expansion of the portal zone, is an indication for repeat liver biopsy in the future, but not an indication to discontinue MTX therapy. Grade III changes (fibrosis, formation of fibrous septa between liver lobules), however, are regarded as a contraindication for further MTX therapy. In the present study, all liver biopsies in both the MTX and the control groups fell within grades I and II; although 1 MTX-treated patient had a minor expansion of the portal tract with fibrous tissue, no septum formation was detected.

Table 4 shows that portal inflammation occurred in about 20% of severe RA patients, with no difference in the MTX and untreated groups. Fatty infiltration of the liver occurred in about 50% of the MTX-treated group and about 44% of the control patients. These observations seem to parallel the literature reports closely, for liver changes observed in RA before MTX therapy.[28,29] A single case of scattered, noncaseating, hepatic granulomata was observed, which had disappeared a year later at repeat biopsy. Expansion of the portal zone with fibrous tissue (grade II) was observed in one MTX-treated patient, but did not reveal interlobular fibrous septum

Table 7. Portal inflammatory infiltrates (PI)

Pathology	Grade	MTX Cumulative Mean Dose (mg)	Mean Duration of MTX Therapy (mo)	No. Pts	Mean Duration of RA (yr)	Mean Age of Pt (yr)
None	I	1,690	45	48	9.7	52.4
Minimal PI	I	3,070	69	3	8.3	48
Mild PI	I	2,220	63.5	6	7.2	50.5
Marked PI	II	1,915	53	2	12	65
Fibrosis	II	2,838	57	1	7	56
Total		1,837	48.5	60	9.4	52.5

formation. This patient was a 56-year-old man with RA of seven years' duration, who consumed MTX for 57 months, for a cumulative total of 2.8 g. He had well-developed Sjögren's syndrome and chronic peptic ulcer disease. On follow-up, biopsy was not repeated in this patient, but no evidence of progressive hepatic disease was observed.

Fatty liver

Fatty infiltrates in the liver did not appear to correlate with MTX therapy, although 6% more of the MTX-treated group had steatosis than of the controls. The cumulative mean MTX dose was the same for all categories of none, minimal and mild (grade I), and moderate and marked (grade II) fatty infiltration. Fatty infiltration occurred more frequently in older patients (*Table 5*) and in consumers of alcohol (*Table 6*). Sixty-nine percent of alcohol drinkers had some degree of fat in the liver, while only 41% of nondrinkers had fatty infiltrates.

Portal infiltration

Infiltration of the portal zone with round cells was seen frequently. Although one might expect an increase of such biopsy evidence of cellular inflammation to precede fibrosis, no trend could be detected in this data to indicate that this had occurred (*Table 7*). The numbers of patients were too small to indicate whether alcohol use influences portal infiltration. The data did not suggest that increased cumulative MTX dosage is a factor increasing portal infiltration. Advancing age, however, may be a factor in portal infiltrates. In addition, Sjögren's syndrome appears to be a factor in increasing portal infiltrates.

Anisonucleosis and anisocytosis

Liver cells or liver nuclei were of unequal size in 12% of the control patients and 22% of those treated with MTX. This is definitely a feature of folate deficiency, as might be expected from the clinical manifestations in folate-depleted states (*Table 8*).

Liver function tests

Serum glutamic-oxaloacetic transaminase (SGOT) was occasionally, mildly and transitorily elevated in 10 patients, including the man with portal fibrosis. Lactic dehydrogenase elevation did not parallel SGOT consistently. No increase in alkaline phosphatase was detected. Sulfobromophthalein retention greater than 5% appeared to correlate with fatty liver change. Enzyme elevation may be a clue to MTX-induced liver disease, but is probably not a reliable one.

Discussion

In these 60 RA patients, the mean weekly dose of MTX was 8.67 mg (median dose, 7.5 mg). This is roughly a third of the dose at which the experience in treating psoriasis vulgaris with MTX was obtained. The results of this study appear to confirm the clinical impression that low-dose MTX therapy (≤ 12.5 mg/wk) administered between two and eight years' time, used as suppressive therapy for chronic RA, has relatively minor harmful effects on the liver, histopathologically. DiBartolomeo et al[30] reported almost identical results at a similar cumulative

Table 8. Anisocytosis-anisonucleosis in liver biopsy

	Patients	
	Controls (25)	Received MTX (60)
Equal cells	22 (88%)	47 (78%)
Aniso.	3 (12%)	13 (22%)

Aniso. = anisocytosis-anisonucleosis.
Alcohol consumption (one third of each group) did not influence anisocytosis.

MTX dose (1.6 g). A possibility that concurrent salicylate therapy might amplify toxicity could not be controlled in this study, but the potential interaction of salicylates with high-dose MTX therapy appears not to be clinically significant at the low dosages used. The possibility that alternating cotherapy with folic acid may ameliorate MTX hepatotoxicity was uncontrolled in this study and remains unproved.

How often should liver biopsy be performed during MTX maintenance therapy? Current practice in psoriasis management, reviewed by Hanno et al,[31] recommends repeat liver biopsy at some specified cumulative MTX dose (e.g., 1,500 mg) or at an arbitrary time interval. Data from the present study obtained at weekly doses roughly one third those often employed for psoriasis do not appear to support a rigid prescribed schedule for repeat biopsy. Probably, baseline liver biopsy should be done before MTX use. This study does not clarify a threshold of toxicity, either for cumulative dose or for duration of therapy.

It may be reasonable to follow a conservative rule, i.e., to perform repeat liver biopsy every fourth or fifth year in the absence of alcohol abuse, marked folate depletion, or sustained elevation of hepatic transaminases, when the weekly dose is between 5 and 12.5 mg. It is also probably reasonable to perform repeat biopsy at shorter intervals when the weekly dose approaches 25 mg of MTX for sustained periods of time. These biopsies were all performed in 1973 and 1974, three years after consolidating the MTX dose for an entire week within a single 24-hour period. The previous Monday-Wednesday-Friday regimen has been shown to carry greater risk of liver damage.[4,19]

Although these data have been published in abstract form,[23] the growing popularity of MTX therapy for RA provoked the submission of this additional information.

Conclusions

Long-term (mean, 4 years), low-dose (mean, 8.7 mg/wk) MTX maintenance therapy for RA had a minor and clinically unimportant hepatotoxic effect in this series of 60 patients. A single case of grade II portal fibrosis without septum formation was observed, but liver disease was nonprogressive during a follow-up period of four years.

Most of the hepatic histopathology in this series appeared to be related to the severity of RA, to advancing age, to concomitant Sjögren's syndrome, and to alcohol consumption.

Since therapy with MTX appeared to be reasonably safe during this study, the effects of cotherapy with other agents, folate in particular, require additional study. Still longer-term therapy must be studied to determine the magnitude and clinical significance of lower levels of toxicity. Also, follow-up studies of patients treated with MTX in whom portal fibrosis develops are needed to determine whether this lesion may be progressive and how serious it may be.

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