Hepatotoxicity in Patients with Juvenile Idiopathic Arthritis Receiving Longterm Methotrexate Therapy

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ABSTRACT. ***Objective.*** To evaluate hepatotoxicity in patients with juvenile idiopathic arthritis (JIA) receiving methotrexate (MTX) therapy with doses of 20–30 mg/m^2 of body surface area.

Methods. We graded the histology of percutaneous liver biopsies from 34 patients with JIA receiving longterm (> 2.4 years) MTX therapy at the Rheumatism Foundation Hospital, Heinola, Finland, using the Roenigk classification scale. Medical records of the patients with JIA were retrospectively analyzed.

Results. Of 10 patients with MTX doses ≥ 20 mg/m^2, 4 had grade II, 5 had grade I histology, and one specimen with extensive steatosis as the only pathologic finding could not be classified. All 24 patients treated with low dose MTX had grade I histology. No specimen showed fibrosis or cirrhosis. In 2 patients with grade II histology, extensive portal tract inflammation resolved when MTX was discontinued for 6 months.

Conclusion. Aggressive medical treatment of JIA with MTX at 20–30 mg/m^2 with concomitant disease modifying antirheumatic drugs and corticosteroids may contribute to minor liver abnormalities that seem to be reversible. (J Rheumatol 2002;29:2442–5)

Key Indexing Terms:
JUVENILE IDIOPATHIC ARTHRITIS METHOTREXATE HEPATOTOXICITY

Low dose (10 mg/m^2 of body surface area) weekly methotrexate (MTX) has been established as an effective treatment for children with juvenile idiopathic arthritis (JIA)[1,2]. In patients with unsatisfactory responses to a low dose, MTX doses of 15 or 20 mg/m^2 given orally once a week have shown efficacy in short term treatment for extended oligoarticular and systemic JIA[3,4]. However, not all patients benefit from this treatment and higher doses of MTX are frequently used in patients with severe unremitting polyarticular or systemic JIA[5-7]. The efficacy of MTX at higher doses has not been established in a randomized, controlled fashion, nor has the tolerability.

One potential side effect of MTX is hepatotoxicity. Liver fibrosis or cirrhosis has been reported in adults with idiopathic arthritis receiving MTX therapy[8-10]. In pediatric JIA series, neither cirrhosis nor severe liver fibrosis has been found[11-15], but a few cases of mild fibrosis have been reported[15-17]. The low dose MTX therapy does not seem to be associated with severe hepatotoxicity[11-15]. However, with increasing use of antirheumatic treatments with higher doses of MTX and combinations of disease modifying antirheumatic drugs (DMARD), it is now necessary to pay critical attention not only to the efficacy but also to the safety issues.

We evaluated hepatotoxicity in patients with JIA receiving longterm MTX therapy in combination with DMARD. In particular, the effects of high (≥ 20 mg/m^2) weekly doses of MTX on liver histology were investigated in detail.

MATERIALS AND METHODS

Study subjects. The medical records of patients with JIA followed at the Rheumatism Foundation Hospital, Heinola, Finland, were reviewed. Between 1992 and 1997, we performed a percutaneous liver biopsy for all patients receiving longterm (> 2.4 years) MTX therapy. Thirty-four patients with JIA, 26 girls and 8 boys, were included in the study (Table 1). All patients fulfilled the Durban criteria for JIA[18]. No patient had psoriatic arthritis. Alcohol consumption was assessed by personal interview of the patients over 14 years of age. No hints indicative of alcohol consumption were observed. No patient had diabetes mellitus. During the course of the disease, all patients had taken nonsteroidal antiinflammatory drugs (NSAID) but not on the same day as MTX. Liver enzyme tests were routinely performed every 4 to 6 weeks one or 2 days before the next weekly MTX dose. Elevated levels > 2.5 times the upper limit of normal range had been recorded.

Liver biopsies. We performed liver biopsies under general anesthesia given for intraarticular injections during scheduled inpatient visits at the Rheumatism Foundation Hospital. All biopsies were done by one of 2 authors (JH or HY) with a Hepafix G17 (Medical Braun) needle. After formalin fixation, the biopsy specimens were embedded in paraffin wax, sectioned at 5 μm, and stained with hematoxylin and eosin. Informed consent was obtained from all the patients and/or parents.

Assessment of histologic grade. Pertinent histologic findings were scored as follows: Fat: 0 = no fat, 1 = occasional fatty cells, 2 = 1–10% fatty cells in the specimen, 3 = > 10% fatty cells in the specimen. Portal inflammation: 0 = none, 1 = small number of inflammatory cells in some portal tracts, 2 = inflammation in all portal tracts, 3 = extensive portal tract inflammation.

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Table 1. Characteristics of the 34 patients with JIA receiving longterm methotrexate (MTX) therapy.

	Mean ± SD or Number	Range
Age, yrs	11.5 ± 3.0	6.2–18.0
Duration of JIA, yr	8.2 ± 3.0	3.2 –15.3
Duration of MTX therapy, yr	4.5 ± 1.7	2.4–9.8
Concomitant use of NSAID	11	
Steroid	22	
DMARD	21	
Other cytotoxic drugs	4	
Sex		
Female	26	
Male	8	
Disease onset mode		
Systemic	3	
Polyarticular	23	
Oligoarticular	8	
Disease course		
Polyarticular	34	
Antinuclear antibodies	8	
Rheumatoid factor	0	
HLA-B27	9	

Nuclear variability (anisonucleosis): 0 = none, 1 = mild to moderate, 2 = marked. Fibrosis: 0 = none, 1 = thin and short radiating septa, 2 = extensive fibrosis. The changes in the biopsy specimens were combined for grading by the Roenigk classification[19]. The histologic review with scoring and grading was done by one author (JR) without knowledge of the patient's identity or clinical history.

Statistical analysis. Correlations of liver histology with MTX doses or with elevations of liver enzymes were analyzed with Fisher's exact test. The relationship between cumulative MTX doses and the histologic score was analyzed with the permutation test.

RESULTS

Indications for liver biopsy. Altogether, 34 initial and 5 followup biopsies were performed. Two patients with MTX therapy of long duration (over 7 years) had initial biopsies after 3 years of MTX use and followup biopsies 4 years later. Two patients with extensive portal inflammation in the initial biopsies (Patients 3 and 4 in Table 2) had one or 2 followup biopsies 6 months after discontinuation of MTX.

Medical treatment. In all 34 patients, MTX was initially started with a 10 mg/m^2 dose orally. In cases of continued inflammatory activity, the MTX dose was escalated. Doses over 20 mg/m^2 were given subcutaneously. Ten patients had been treated with 20–30 mg/m^2 MTX weekly for 6 to 36 months prior to the biopsy (Table 2). In these patients, the total duration of MTX therapy was 30 to 84 months (mean 54 mo, median 58 mo), and the cumulative dose ranged from 1300 to 6200 mg (mean ± 1 SD, 3470 ± 1632 mg, median 3600 mg). At the time of the biopsy, all 10 patients were receiving DMARD and 9 of them were taking alternate day prednisolone. Six of the 10 were receiving NSAID (Table 2). During the study period, folate or folinic acid was not used on a regular basis for patients taking MTX.

During MTX treatment, of the 10 patients with > 20 mg/m^2 MTX or 24 patients with low dose MTX, 4 (40%) or 10 (42%), respectively, had elevated liver enzymes > 2.5 times the upper limit of normal range.

Histopathologic findings in liver biopsies. Liver biopsies from all 24 patients with low dose MTX were classified grade I. Of the 10 patients with > 20 mg/m^2 of MTX, 5 had grade I, 4 had grade II liver biopsy, and in one specimen the only pathologic change was extensive steatosis, and therefore it could not be classified according to the Roenigk scale. This specimen came from an overweight patient (Patient 8, Table 2) whose body mass index (BMI) was 33.8 (kg/m^2). No specimen showed fibrosis or cirrhosis.

In 2 cases with > 20 mg/m^2 MTX doses, portal inflammation was moderate to severe (Patients 3 and 4 in Table 2). In both specimens, > 10% of the specimen consisted of fatty cells. Patient 4 had been treated with MTX for over 6 years prior to the biopsy, and parenterally 30 mg/m^2 for the preceding 6 months. In the followup biopsies of both

Table 2. Drug treatment and liver biopsy findings in 10 patients with JIA receiving high dose MTX therapy.

Patient	Patient Age, yrs	MTX CD, mg	Duration of MTX, mo	Current Dose of MTX, mg/m^2	Concomitant use of Steroid*	DMARD	NSAID	Histological Findings Anisonucleosis 0–2	Portal Inflammation 0–3	Fat 0–3	Fibrosis 0–2	Grade (Roenigk)
1	9.5	1300	36	22	10	HQ	Naproxen	1	0	1	0	I
2	8.4	1500	37	27.5	5	HQ	No	1	1	1	0	I
3	9.8	1900	30	20	0	ATM	No	1	2	3	0	II
4	13.5	6200	84	30	10	ATM	No	0	3	3	0	II
5	8.8	3100	58	30	7.5	AZA	Diclofenac	1	0	2	0	II
6	18	4500	66	20	5	HQ	Naproxen	1	1	1	0	I
7	14,2	5400	64	30	20	HQ	Ketoprofen	1	1	2	0	II
8	7.7	4100	65	25	15	HQ	Naproxen	0	0	3	0	UC
9	9.7	3100	44	20	2.5	HQ	Naproxen	1	0	1	0	I
10	6.2	3600	54	30	5	ATM	No	1	0	1	0	I

*Steroid dose is alternate day dose of prednisolone. CD: cumulative dose, DMARD: disease modifying antirheumatic drug; NSAID: nonsteroidal antiinflammatory drug; HQ: hydroxychloroquine; AZA: azathioprine; ATM: intramuscular aurathiomalate; UC: unclassifiable (this case showed extensive steatosis as the only pathologic change).

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patients, when MTX was discontinued for 6 months the portal inflammation resolved.

Statistical analysis. MTX doses > 20 mg/m^2 were correlated with grade II histology of the liver biopsies (Fisher's exact test, p = 0.003). Higher cumulative MTX doses were also associated with grade II histologic score (permutation test with exact 2 sided p = 0.005). In the 4 patients with grade II histology, the median cumulative MTX dose was 4250 mg, whereas in the patients with grade I histology, the median cumulative MTX dose was 1600 mg. Elevated liver enzymes > 2.5 times the upper limit of normal range any time during MTX treatment were not associated with the histologic grade (Fisher's exact test, p = 0.63). One of the 4 patients with grade II liver histology had highly elevated transaminases.

DISCUSSION

Our study provides for the first time an analysis of the liver histology in patients with JIA treated with high doses of MTX (> 20 mg/m^2), and allows insights into the possible hepatotoxicity of this treatment. This retrospective study provides evidence that higher MTX doses may increase the risk for histopathologic liver changes. However, these changes seem to be reversible, because regardless of high doses of MTX, cumulative doses up to 6 g, and the use of MTX in combination with other DMARD, we did not find any case of fibrosis or cirrhosis.

The 10 patients treated with higher doses of MTX represent patients with prolonged polyarticular disease course. All patients were treated with various combinations of DMARD and oral and intraarticular corticosteroids. Steatosis was a common finding in many liver biopsies. It is possible that longterm use of corticosteroids and active inflammatory disease *per se* may also have contributed to the liver changes. However, resolution of portal inflammation in 2 patients when MTX was discontinued support the idea that MTX contributed to the liver changes. It has been suggested that concurrent use of hydroxychloroquine might protect the liver against MTX toxicity[20]. The limited numbers of patients taking various combination therapies and the absence of fibrosis preclude any meaningful statistical evaluation of hepatotoxicity. Thus, we were unable to show protective effects or additive toxicities in patients receiving DMARD. Because folic acid was not used at the time of the study, the putative hepatoprotective effects of this drug[21] could not be assessed either.

Currently, it is not known whether minor liver changes in patients with JIA treated with MTX would progress to significant histopathology later in life. In sequential liver biopsies of adult patients with idiopathic arthritis during MTX therapy, results regarding the progression of fibrosis have been conflicting[22]. Most probably, other confounding factors, e.g. alcohol use, preexisting liver disease, and obesity, especially when associated with diabetes mellitus, may contribute to hepatotoxicity. Such factors were not evident in our series, except for mild to moderate obesity in a small number of patients (data not shown). Obesity is also recognized as a contributing factor to the development of hepatic steatosis that frequently progresses to liver fibrosis[23]. However, there are no reports on MTX causing extensive hepatic steatosis. Thus, most probably, in one patient in this study obesity was the major factor in the development of hepatic steatosis. In 7 other patients with moderate obesity in our series, no significant liver abnormalities were observed (data not shown).

Retrospective studies of patients with JIA have shown that short term hepatic toxicity (transaminase elevations) does not occur more frequently with higher than with low dose MTX treatment[5-7]. These findings do not, however, exclude the possibility of longterm hepatotoxicity due to MTX treatment because single abnormal transaminase levels may not be sensitive markers for significant hepatotoxicity. A recent study suggested that serial liver enzyme abnormalities in JIA patients taking MTX therapy might be associated with histopathologic liver changes[15]. Due to the retrospective nature of our study, the frequency of elevated transaminases could not be accurately assessed. Because serial liver enzyme abnormalities might reflect recurrent hepatocyte damage and result in formation of scar tissue and fibrosis, Hashkes, *et al*[15] suggested that biopsy should be considered for patients with JIA if 40% or more of the biochemical liver tests were abnormal in the course of a year.

Our results support the consensus that liver biopsies merely because of longterm MTX therapy are not indicated, and that the potential for severe hepatotoxicity of low dose MTX is minimal in JIA[11-15,24]. However, our results also imply that treatment of JIA with high doses of MTX with DMARD and corticosteroids may contribute to portal inflammation and steatosis of the liver, changes that are potential risk factors for liver fibrosis. Larger prospective studies are needed to define the appropriate guidelines for monitoring of patients with JIA receiving aggressive antirheumatic drug therapy.

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