Monitoring Methotrexate Toxicity in Juvenile Idiopathic Arthritis

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ABSTRACT. ***Objective.*** To determine the frequency of laboratory abnormalities with methotrexate (MTX) use in patients with juvenile idiopathic arthritis (JIA); to identify potential risk factors for MTX toxicity requiring medical interventions; and to compare the frequency of liver function abnormalities in patients treated with MTX to those not treated with MTX.

Methods. Results of MTX surveillance laboratory testing (SLT) available in clinical databases were reviewed for 588 children with JIA. Information on demographics, JIA features, and factors previously associated with increased frequency of SLT abnormalities was obtained.

Results. Results of SLT performed in at least 4-month intervals were available for 138 JIA patients whose JIA was not treated with MTX, and for 198 JIA patients treated with MTX plus folic acid. On SLT of the MTX-treated patients, there were 44 of 2650 (1.7%) AST tests and 90 of 2647 (3.4%) ALT tests that exceeded 2 times the upper limit of normal (> 2 ULN) in 30 children (15%). AST or ALT tests at > 2 ULN occurred more often with systemic JIA ($p = 0.04$), macrophage activation syndrome, during infections, in systemic antibiotic use, and after intensifying JIA drug regimens. AST or ALT results at > 2 ULN were as frequent among MTX-treated children as those not treated with MTX. Renal and hematological abnormalities with MTX were uncommon.

Conclusion. Liver enzyme abnormalities > 2 ULN are rare in JIA, irrespective of MTX exposure. These data suggest that the adult standard of SLT every 4–8 weeks may not be necessary in children treated with MTX, especially if certain risk factors are absent. (J Rheumatol First Release Nov 15 2009; doi:10.3899/jrheum.090482)

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Methotrexate (MTX) is an effective treatment for rheumatic diseases, including rheumatoid arthritis (RA) and juvenile idiopathic arthritis (JIA). Due to its potential hepatotoxicity and bone marrow suppression, guidelines for monitoring MTX toxicity were proposed in 1994, by the American College of Rheumatology (ACR), for adult patients with RA[1]. These guidelines suggest that hepatic, renal, and hematological testing, i.e., surveillance laboratory testing (SLT), should be performed at the time of MTX initiation and then repeated every 4 to 8 weeks as long as MTX therapy is given[2]. Proposed risk factors for MTX-associated hepatotoxicity in RA include exposure to alcohol, presence of obesity or diabetes, older age, high cumulative MTX dose, and longer duration of MTX therapy, especially when prescribed without folate supplementation[3-5]. Similarly, risk factors for bone marrow toxicity with MTX include renal impairment, alcohol use, polypharmacy, elevated mean corpuscular volume, and the presence of extraarticular RA features[6,7].

In the absence of specific recommendations for children with JIA, many centers have adopted the ACR guidelines for monitoring MTX toxicity in RA for use in JIA. These guidelines have been implemented although they have not been formally validated in children with JIA. Further, the aforementioned risk factors for MTX toxicity are absent in the majority of patients with JIA. Indeed, to our knowledge, there has been very little evidence to substantiate hepatotoxicity or clinically significant bone marrow suppression of children treated with MTX for JIA[8-13].

Based on the above, we hypothesized that laboratory abnormalities in patients with JIA treated with MTX are rare. To test our hypothesis, we performed a medical record review with the following objectives: (1) to determine the frequency of laboratory abnormalities associated with MTX use in JIA; (2) to identify potential risk factors for MTX toxicity requiring medical interventions; and (3) to compare the frequency of liver function abnormalities in patients with

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JIA treated with MTX to those who were not treated with MTX.

MATERIALS AND METHODS

Patients. With approval from the Institutional Review Board, prospectively collected clinical database information was reviewed for 588 patients diagnosed with JIA[14], ages 20 years or younger, all followed at a tertiary children's hospital between January 2002 and July 2007. Children with JIA who regularly had SLT performed at the tertiary center were included in the study, while those patients whose SLT was ordered by their primary care physician or was done at offsite laboratories were excluded. However, the demographics and clinical characteristics of excluded patients were identified to assess whether the excluded group was similar to the included group.

Study procedures. Relevant information from databases and standardized medical records was exported to Excel worksheets. Patient age, gender, race, information on JIA subtype, and disease duration were obtained from a database containing prospectively collected clinical data. Additionally, the results of SLT for MTX were obtained from the laboratory database of the tertiary center, i.e., complete blood count, serum albumin, aspartate aminotransferase (AST or SGOT), and alanine aminotransferase (ALT or SGPT).

Upon identification of SLT abnormalities (see below in Data definitions), as determined by database query, the following information was extracted from the standardized medical record and/or the clinical database: (1) the action taken by the healthcare provider once the SLT abnormality was reported, including permanent or intermittent discontinuation of MTX, reduction of the weekly MTX dose, or continuation of therapy without change; (2) patient body mass index (BMI); (3) comorbidities; (4) presence of diabetes or alcohol consumption; (5) concomitant medications and their recent dosing regimens with focus on nonsteroidal antiinflammatory drugs (NSAID), immunosuppressive medications, and systemic antibiotics; (6) diagnosis of recent acute illnesses or infections; and (7) evidence for clinical diagnosis of macrophage activation syndrome (MAS). We also recorded the frequency of the laboratory abnormalities and their duration, based on abnormalities on subsequent SLT.

Data definitions. Using the local range of normal values, the following parameters were considered abnormal: white blood cell count $< 3.8 \times 10^9$/l, hemoglobin < 10 g/dl, platelet count $< 130 \times 10^9$/l, AST > 35 IU/l, ALT > 60 IU/l, serum albumin < 3.2 g/dl, and serum creatinine > 0.9 mg/dl.

Statistical analysis. Data were analyzed using SAS 9.1. Numerical variables were summarized by mean ± standard deviations (SD), and binary and categorical variables were summarized by frequency (in percentages). Statistically important differences between groups were assessed by ANOVA and chi-square test, respectively. Two-sided p values < 0.05 were considered statistically significant. As suggested, we focused on AST and ALT elevations that exceeded twice the upper limit of normal (> 2 ULN) as such changes are considered locally and by others as clinically relevant[12].

RESULTS

Patients. During the review period, there were 302 (51%) children with JIA who were treated with MTX and 286 who were not exposed to MTX (Non-MTX group) at the tertiary children's hospital. Among the 302 patients exposed to MTX, SLT data in at least 4-month intervals were available for 198 children (198/302 = 66%; MTX group). For the remaining 104 patients treated with MTX, the results of the SLT were not consistently available, as testing was performed elsewhere, and these children were excluded from subsequent assessment of laboratory abnormalities with MTX. As shown in Table 1, the MTX-treated children excluded from the study were similar to the MTX group with respect to their demographics, disease duration, age, and JIA subtypes.

AST and ALT elevations were the most common laboratory abnormalities in the MTX group. In the MTX group, a total of 2650 AST and 2647 ALT tests were performed during the study period. There were 246 (246/2650 = 9%) AST results and 371 (371/2647 = 14%) ALT results > ULN. These liver function test (LFT) elevations occurred in a total of 95 patients (95/198 = 48%) on at least one occasion during the study. Thus, more than 52% of all children in the MTX group never had any LFT abnormalities, i.e., all AST and ALT levels were within the range for normal.

Concurrent AST and ALT abnormalities were observed 83% of the time. Liver enzyme abnormalities > 2 ULN occurred with less than 3% of SLT events performed in the MTX group. Details on the frequency of AST and ALT elevations in the MTX group are provided in Table 2.

AST and ALT elevations > 2 ULN. In the MTX group, there were 30 patients with at least one SLT event in which AST or ALT levels were > 2 ULN. Among the 30 children with LFT abnormalities > 2 ULN, the average weekly dose of MTX was 13 mg (13.1 mg/m^2/week) and was administered subcutaneously in 75% of the children.

While LFT > 2 ULN resolved on subsequent testing in 24 of the 30 children (80%) in the MTX group, these abnormalities persisted on the subsequently ordered laboratory testing in the remaining patients. Of these 6 children, 2 had systemic JIA and MAS; 2 children had trisomy 21; one adolescent had autoimmune hepatitis after initiation of infliximab; and one child was obese.

Among the 24 patients (male:female = 5:19) with transient LFT > 2 ULN , there were 6 children (6/24 = 25%) with systemic JIA and 18 (75%) with other forms of JIA (Table 3). Liver enzyme abnormalities > 2 ULN were significantly more common with systemic JIA than other JIA subtypes (6/24 vs 18/156; chi-square = 4.3, DF = 1, p = 0.04).

Among the 24 patients, there were 47 events with single nonsequential LFT elevations > 2 ULN. Actions taken by healthcare professionals in response to these SLT abnormalities were as follows: MTX was discontinued temporarily in 38% (18/47) of such episodes; the dose was reduced in 13% (6/47) of the episodes, while MTX therapy was continued without dose adjustment during 49% (23/47) of such events.

There were no important differences in the mean disease duration, age, BMI, or duration of MTX treatment between children with and those without LFT elevations > 2 ULN. Groups were similar with respect to patient race, ethnicity, or types of JIA medications. Folic acid was prescribed to all the patients, including those with LFT elevations > 2 ULN.

Frequency of renal and hematological abnormalities on SLT. In addition to LFT elevations, abnormalities in other SLT components, i.e., complete blood count, blood urea nitrogen, and serum creatinine, were reported rarely and occurred less frequently than LFT abnormalities[12].

Table 1. Characteristics of the study populations.

	Patients Treated with MTX†		Patients not Treated with MTX, Laboratory Testing Available, n = 286
	Laboratory Testing Available, n = 198	No Laboratory Testing Available, n = 104	
Age, yrs, mean (SD)	12.0 (4.9)	11.9 (5.4)	13.0 (4.7)
Disease duration, yrs, mean (SD)	4.9 (4.0)	4.8 (5.0)	4.7 (2.9)
Race, no. (%)			
African American	7 (4)	3 (3)	20 (7)
Caucasian	175 (89)	98 (94)	250 (87)
Other	6 (3)*	—	6 (2)
Unknown	6 (3)	3 (3)	10 (3)
Gender, no. (%)			
Male	42 (21)	25 (24)	98 (34)
Female	155 (79)	79 (76)	188 (66)
JRA onset type, no. (%)			
Pauciarticular	57 (29)	25 (24)	183 (64)
Polyarticular	116 (59)	67 (65)	73 (26)
Systemic	24 (12)	11 (11)	29 (10)
JIA subtypes, no. (%)			
Enthesitis related	1 (0.5)	1 (1)	4 (1)
Extended oligoarticular	20 (10)	13 (13)	14 (5)
Persistent oligoarticular	38 (19)	11 (10)	159 (56)
Polyarticular RF–	100 (51)	58 (57)	70 (25)
Polyarticular RF+	13 (7)	9 (9)	7 (2)
Psoriatic	1 (0.5)	—	2 (1)
Systemic	24 (12)	11 (10)	29 (10)

† None of the differences between methotrexate-treated patients that were included in the study and those who were excluded because of surveillance laboratory testing reached statistical significance. * 2 multiracial African American/Caucasian, 1 American Indian, 1 Alaska native, 2 Asian.

Table 2. Frequency of liver enzyme testing and proportion of abnormalities detected*.

Test Value	AST, no. (%)	ALT, no. (%)
Any value > ULN	246 (9.0)	371 (14)
> 1.5 × ULN	65 (2.5)	124 (4.7)
> 2 × ULN	40 (1.5)	77 (2.9)
> 2 × ULN**	17 (0.6)	33 (1.2)
Total no. of tests	2650 (100)	2647 (100)

* All patients were supplemented with folate. ** Excluding patients with MAS (3 patients), genetic abnormalities (3 patients), obesity (1 patient), and autoimmune hepatitis (1 patient). ULN: upper limit of normal; local normal ranges of AST are 35 IU/l and ALT 60 IU/l.

Among the 198 patients in the MTX group, there were 13 (6%) and 2 (1%) patients with transient serum creatinine levels > 0.9 mg/dl and > 1.5 mg/dl, respectively. There were 4 (2%) patients with serum albumin levels < 3.2 mg/dl, all diagnosed with MAS. Ten (5%) patients had transient leukopenia of < 3.5×10^9/l, and 2 (1%) children of < 3.0×10^9/l; the latter 2 were diagnosed with MAS. Anemia with hemoglobin < 10 g/dl was observed in 4 (2%) of the patients. Two of the 4 patients with anemia had MAS, one had iron deficiency anemia, and one was diagnosed with a bleeding gastric ulcer. No child in the MTX group had thrombocytopenia of less than 130,000/l.

Results of SLT in children with JIA not exposed to MTX. Compared to the MTX group, there was a higher frequency of patients with extended or persistent oligoarticular JIA in the non-MTX group (MTX: 58/198 = 29% vs non-MTX: 173/286 = 61%; chi-square = 16, DF = 1, $p < 0.0001$), reflecting the use of MTX in JIA patients with more severe phenotypes.

Comparing both groups for LFT abnormalities, we found that any AST but not ALT abnormalities were significantly more common in the MTX group than the non-MTX group. Of note, all LFT abnormalities in the non-MTX group were transient (Table 4). Conversely, any LFT elevations > 2 ULN were as frequent in the MTX group as in the non-MTX group.

Adherence to liver biopsy recommendations of the ACR guidelines. The ACR guidelines recommend a liver biopsy be performed in MTX-treated adults with RA if the SLT shows AST elevation > ULN on 6 of 12 monthly laboratory tests, or 5 of 9 tests if SLT is done less often. In our cohort, there were 11 patients who met the ACR guidelines for a liver biopsy (Table 5). However, only 2 of these patients underwent liver biopsy. Both patients had persistent AST and ALT elevations > 2 ULN: the first patient had autoimmune hepatitis that appeared to be secondary to infliximab treatment; this patient had been treated with MTX for 5 years, and LFT abnormalities resolved only with discontinuation of infliximab, but not when MTX was stopped. The second patient was markedly obese and, on liver biopsy, was found to have steatosis with mild hepatic fibrosis. This child had had mild LFT elevation even before initiation of MTX but LFT abnormalities resolved with MTX discon-

Table 3. Documented interventions, comorbidities, and illnesses during episodes of liver enzyme elevations transiently greater than 2 times the upper limit of normal in 24 children treated with methotrexate (MTX).

Clinical Information	Details	No. of Events†
Acute infectious Illness	Fever	3
	Otitis media	6
	Viral syndrome (upper respiratory infection, rash)	10
Biologic therapy	Infliximab, etanercept	15
	Anakinra	2
Antibiotics/antiviral medications	Amoxicillin, azithromycin, acyclovir	7
Comorbidities	Obesity	4
	Hashimoto thyroiditis	1
Increase in medications	Increase in infliximab	2
	NSAID started or increased	5
	Increase in MTX dose	1
Timing of safety laboratory investigation	Within 3 days of MTX dose	7

† 6 of the 24 children had more than one event. NSAID: nonsteroidal antiinflammatory drugs. For additional details see Tables 1 and 2.

Table 4. Number of AST and ALT laboratory abnormalities in patients not treated with methotrexate (MTX).

	Patients Treated with MTX, n = 198			Patients not Treated with MTX, n = 286			
Test	Total	Mean	SD	Total	Mean	SD	p*
AST							
Any value > ULN	246	1.2	2.4	138	0.5	1.7	< 0.003
> 1.5 × ULN	65	0.3	1.3	38	0.1	0.9	0.04
> 2 × ULN	40	0.2	1.2	23	0.1	0.7	0.7
ALT							
Any value > ULN	371	1.9	4.0	150	0.5	2.2	0.9
> 1.5 × ULN	124	0.6	1.8	73	0.3	1.4	0.2
> 2 × ULN	77	0.4	1.5	40	0.1	1.0	0.3

* Two-sided unpaired t-test. ULN: upper limit of normal. For additional details see Tables 1 and 2.

Table 5. Patients with juvenile idiopathic arthritis qualifying for liver biopsy per ACR guidelines.

Comorbidities/Potential Risk Factors	No. of Patients	Liver Biopsy Done
Macrophage activation syndrome — chronic	1	No
Infliximab-induced autoimmune hepatitis	1	Yes
Severe obesity	1	Yes
Chronic or recurrent sinusitis or otitis media treated with antibiotics	4*	No
Safety laboratory surveillance within 3 days of MTX intake	2*	No
Congenital abnormality: tetralogy of Fallot, abdominal pain with collapsed gall bladder	1	No
Congenital abnormality: jejunal atresia with microcolon, short-gut syndrome with multiple antibiotics	1	No
Total patients	11	

* One patient fulfilled both features and was counted only in the methotrexate (MTX) laboratory category. For additional details see Tables 1 and 2.

tinuation. The remaining 9 patients did not undergo liver biopsy and were found to have one or more coexisting congenital or comorbid conditions (Table 5) that could have contributed to the abnormalities.

DISCUSSION

Since the first reports of MTX use in JIA 13 years ago[15], there have been many studies supporting its efficacy in JIA[16-18]. To date, besides nonsteroidal antiinflammatory drugs (NSAID), MTX remains by far the most commonly prescribed medication for JIA treatment. Despite its ubiquitous use in pediatric rheumatology clinics, unanswered questions remain about the most appropriate approach for monitoring MTX safety, especially with respect to the fre-

quency of SLT. Many providers currently perform SLT in JIA at the frequency recommended by ACR guidelines for adult RA[1]. Although MTX often is prescribed at similar absolute doses in JIA and RA, the applicability of the guidelines to children may be controversial, as children often lack the risk factors considered when recommending SLT at 4 to 8 week intervals for adults.

When following the ACR guidelines, transient LFT elevations were common in our cohort but generally resolved within less than 4 weeks, as reported in previous studies[12,13]. Similar to our study, transient LFT abnormalities appeared to be unrelated to the use of NSAID, patient sex, age, disease duration, or disease activity.

The frequency of LFT abnormalities in our study was similar to that in a prospective study by Ortiz-Alvarez, *et al* of children with JIA treated with comparable weekly doses of MTX[19]. Conversely, Lahdenne, *et al* report LFT elevations > 2.5 ULN in 42% of children in a cohort of JIA patients treated with somewhat higher MTX doses at 20 to 30 mg/m^2/week and without routine folic acid supplementation[12]. Despite the higher frequency of SLT abnormalities, none of the patients reported by Lahdenne, *et al* developed liver fibrosis or cirrhosis, and all LFT abnormalities resolved during the study period[12].

We found fewer than 3% of total LFT performed in our cohort to be highly abnormal (> 2 ULN), and 85% of the MTX-treated children never appeared to have any highly abnormal SLT findings. It is especially intriguing that LFT abnormalities > 2 ULN were equally frequent among children with JIA whose therapy did not include MTX. It is unlikely that the non-MTX group was exposed to JIA medications with more hepatic side effects than the MTX group, as the non-MTX group had less severe disease than the MTX group. Further, although AST elevations are thought to be more specific for MTX-related toxicity[1], ALT elevations were more common in our cohort, raising the possibility that the observed ALT abnormalities were due not only to MTX use but possibly to other factors pertaining to children with JIA.

One consideration when developing a suitable monitoring scheme for MTX safety in JIA may be to determine the influence of the current SLT approach in terms of change of medical therapies for those children with laboratory abnormalities. Even in patients with LFT elevations > 2 ULN, the MTX regimen was continued without modifications during almost half these episodes. None of the transient LFT elevations > 2 ULN led to permanent discontinuation of MTX, and even persistent LFT elevations resulted only rarely in performance of the recommended liver biopsy.

Besides the statistical significance of the more common occurrence of transient SLT abnormalities with systemic JIA, other factors — acute infections, antibiotic use, intensification of JIA regimen, and blood draws shortly after MTX dosing — appeared to be more frequent during times of LFT elevations. However, possibly due to our limited sample size, none of these variables by themselves constituted a statistically significant risk factor for transient LFT elevations > 2 ULN. Similarly, age, disease duration, and MTX duration were all found to be unrelated to SLT abnormalities. Thus, further study is required to evaluate the relevance of these proposed candidate risk factors for SLT abnormalities in RA when assessing MTX toxicity in children with JIA.

Concerns of liver toxicity arise in cases of persistent (as opposed to transient) LFT abnormalities, which we observed mostly in patients with chromosomal (trisomy 21) or congenital abnormalities, systemic JIA, particularly in the setting of MAS, and obesity. Elevated BMI has been identified as a risk factor for LFT elevation in both adult and pediatric populations[9,20]. One of our patients with rheumatoid factor-positive polyarticular JIA developed autoimmune hepatitis on a regimen that included MTX and infliximab. Although previously reported[21], the relevance of this case with respect to SLT for MTX therapy will need further investigation.

The major purpose of following the ACR guidelines for MTX is to identify patients at risk of developing liver damage in order to allow clinicians to discontinue MTX in a timely fashion. If liver enzyme elevations persist, then a liver biopsy is recommended by the guidelines to objectively assess potential liver compromise. However, liver biopsies in patients with persistent liver enzyme elevations were not performed as often as they should have been, had the ACR guidelines been followed strictly. This may have been because of physician preference, or known coexisting conditions, but also because research suggests that there is rarely, if ever, significant liver fibrosis in JIA patients who are exposed to MTX[8-12].

Our study has certain limitations. Given that all data were collected at a single center, treatment decision on review of SLT may be different at other centers. However, the 7 pediatric rheumatologists at this tertiary center make individual decisions on patient management, and previous research suggests that their treatment approaches are similar to those employed at other US pediatric rheumatology centers[22]. In addition, MTX is given in our clinic at doses of 10 to 20 mg/m^2/week, much in agreement with the most effective dosing, based on the results of a recent clinical trial[17]. Laboratory monitoring is done in 1 to 4 month intervals at our center. Thus, LFT abnormalities that could occur between testing timepoints of SLT will not have been observed, which may underestimate the frequency of liver enzyme elevations. We do not think that the employed frequency of SLT has changed the findings of our study importantly with respect to the safety of MTX, as persistent LFT elevations, e.g., LFT abnormalities of clinical relevance, would have been identified nonetheless, albeit at a somewhat later time. Given the lower frequency of SLT testing in the non-MTX group, the comparison with the MTX group,

in terms of LFT abnormalities, has likely provided a conservative estimate.

Our study is not suited to provide recommendations about the optimal frequency of SLT for MTX in JIA. Further prospective studies in larger patient groups will be necessary. We are confident that our findings will be helpful in delineating risk factors that may be included in such future recommendations. Further investigations will also be necessary as to whether withholding or reducing MTX doses is warranted with LFT elevations, or whether watchful waiting suffices. Nonetheless, given this gap in knowledge and the potential clinical (rather than only laboratory) pathology, it appears prudent to monitor children and adolescents with JIA more closely during times of acute infection, with or without fever, and after altering the JIA drug regimen.

The recent change in the ACR 2008 recommendations for the use of nonbiologic and biologic disease modifying antirheumatic drugs in RA acknowledges that SLT every 4 to 8 weeks in adults may be unnecessarily frequent[23]. The transient and infrequent occurrence of LFT abnormalities > 2 ULN in JIA in our study supports the notion that frequent laboratory monitoring, as recommended for adults in accord with earlier guidelines, might not be necessary, and that updated recommendations for MTX monitoring in JIA are needed, although the potential for alcohol exposure among adolescents may need to be considered, as does the increasing frequency of childhood obesity. In the interim, infections, especially when treated with systemic antibiotics, presence of systemic JIA, and increase of JIA therapy, as well as MTX use in children with congenital abnormalities and obesity, may warrant closer laboratory surveillance.

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