Survey on the Use of Methotrexate by Pediatric Rheumatologists in Canada

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ABSTRACT. ***Objective.*** To determine methotrexate (MTX) use and the degree to which Canadian pediatric rheumatologists adhere to the American College of Rheumatology (ACR) guidelines on monitoring for MTX toxicity.

Methods. A 20-item questionnaire was e-mailed to 37 pediatric rheumatologists in 17 centers in Canada. A total of 28 (75.7%) responded.

Results. The oral route (PO) of administration was preferred initially by 78.6% in most cases, but for more severe cases, this fell to 42.8%. Those who chose not to start PO used the subcutaneous route (SQ). When PO was initial treatment, a switch to SQ was undertaken because of dose escalation, lack of efficacy, or GI toxicity. An initial mean dose of 0.35–0.5 mg/kg/wk was prescribed by 51.8%. For 75%, the maximum dose was 1 mg/kg/wk (up to 25 mg). Complete blood count, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) were determined by 100% at baseline and in followup; albumin and creatinine by 85.7% at baseline, but by only 71.4% and 67.8%, respectively, in followup. After a change in dose, 96.3% requested blood tests at least monthly; this was extended to every 6 to 8 weeks by 78.6% when the dose was stable. Side effects of recurrent nausea and/or vomiting were reported to occur frequently. No severe toxicity, and in particular no case of cirrhosis, was reported. Prophylactic folate supplementation was prescribed by almost all physicians.

Conclusion. Most Canadian pediatric rheumatologists follow ACR guidelines to monitor for MTX toxicity in children with rheumatic diseases who were prescribed MTX. The variation in monitoring and response to toxicity raises the question whether specific pediatric guidelines should be developed. (First Release Feb 15 2007; J Rheumatol 2007;34:818–22)

Key Indexing Terms:
METHOTREXATE TOXICITY GUIDELINES

Methotrexate (MTX) has been shown to be efficacious in juvenile rheumatoid arthritis[1], and is the most commonly prescribed disease modifying antirheumatic drug (DMARD) in children with rheumatic diseases in Canada and the US[2]. Toxicity secondary to MTX has been well described and includes gastrointestinal (GI) toxicity, bone marrow suppression, and hepatotoxicity[3]. The latter issue was of such concern that the American College of Rheumatology (ACR) developed guidelines for monitoring liver toxicity in rheumatoid arthritis (RA) in 1994 and these were updated in 2002 (Table 1)[4,5]. No specific guidelines have been developed for children, and for this reason, pediatric rheumatologists have been following these ACR recommendations. However, it is not clear if these guidelines can be applied to children.

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Dr. Duffy is recipient of the Sessenwein Research Award from the Department of Pediatrics, McGill University, Montreal, Quebec, Canada.

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Accepted for publication December 15, 2006.

Modification of these screening guidelines has been suggested because they may not be cost-effective, since few side effects are observed compared to the number of tests performed[6]. Moreover, these guidelines are not followed rigidly in adults[7,8]. Yazici, *et al* reported that 22% of the 123 rheumatologists who responded to their survey monitored liver function tests (LFT) less frequently than every 2 months[7]. Fifty-nine percent of the physicians surveyed would support new guidelines monitoring LFT every 3 to 4 months. Cartwright, *et al* surveyed 1100 American rheumatologists and 3928 patients with RA, and reported that although adherence to the guidelines within the first 3 months was high, it fell to less than 50% after 12 months of treatment[8]. In an attempt to address this issue specifically in a Canadian pediatric population, Ortiz-Alvarez, *et al* reported that monitoring every 3 months is safe in the absence of specific risk factors[9].

It is clear from this literature that there are variable opinions with regard to how to monitor for hepatoxicity due to MTX, and that there is a paucity of pediatric studies. The objectives of our survey were to determine MTX use (administration, dosage, monitoring, and response to toxicity) by pediatric rheumatologists in Canada and to evaluate the degree to which Canadian pediatric rheumatologists adhere to the ACR guidelines for MTX monitoring. We hypothesized that there would be considerable variability and that this might stimulate interest in the development of specific guidelines for

Table 1. Monitoring guidelines (ACR 2002).

At baseline
CBC, creatinine, LFT, alkaline phosphatase, chest radiograph within previous year, hepatitis B and C serology in high-risk patients
In followup
CBC, creatinine, LFT monthly for the first 6 mos; every 1–2 mos thereafter
For minor elevations in AST/ALT < 2 × normal, repeat testing in 2–4 wks
For moderate elevations in AST/ALT > 2 × normal but < 3 × normal, closely monitor with LFT every 2–4 wks and dosage reduction as necessary
For persistent elevations in AST/ALT > 2–3 × normal, discontinue MTX and perform liver biopsy as necessary

LFT: AST, ALT, albumin. ACR: American College of Rheumatology; LFT: liver function test; CBC: complete blood count; AST: asparate aminotransferase; ALT: alanine aminotransferase; MTX: methotrexate.

MTX monitoring in children. In addition, we were interested to see if pediatric rheumatologists recommended varicella vaccination prior to MTX administration, since varicella is a common childhood disease and children taking MTX may have a worse course because of the immunosuppression from MTX.

MATERIALS AND METHODS

A 20-item questionnaire was developed by one author (GC). The questionnaire was distributed to other pediatric rheumatologists (RS, CD) and was modified following their input. This questionnaire focused on determining MTX use (including route of administration and dosage), the monitoring of MTX toxicity, the specific side effects observed, the prescription of folate supplementation, and the use of the varicella vaccine. The list of pediatric and adult rheumatologists caring for children with rheumatic diseases in all centers across Canada was obtained through the Canadian Pediatric Rheumatology Association list of members with the approval of the executive committee. The survey was sent by e-mail to a total of 37 physicians, located in 17 centers. Responding physicians were directed to complete the survey questionnaire and to return it within one month. They were not explicitly directed to review patient charts to enhance the accuracy of their response. Thus it was deemed that the respondents would provide information based on recall, rather than actual data.

RESULTS

Twenty-eight of 37 physicians (75.7%), from 14 of the 17 centers, responded. Their responses are described below.

Route of administration of MTX. The oral route (PO) was preferred by 78.6% of the pediatric rheumatologists at commencement of treatment. However, this route was preferred by only 42.8% in more severe cases (as defined by the physician surveyed, such as JIA-systemic arthritis, severe JIA-polyarthritis, or juvenile dermatomyositis). In all cases when PO was not the preferred route, the subcutaneous route (SQ) was chosen. No one used the intramuscular route. During treatment, a switch from PO to SQ was undertaken if indicated: e.g., for dose escalation, lack of efficacy, or GI toxicity.

Dose of MTX. The mean dose at commencement of treatment was 0.35-0.5 mg/kg/week (equivalent to 10–15 mg/m^2) for 51.8% of physicians surveyed, with a maximum dose of 1 mg/kg for 79.2% (Table 2). The maximum dose used was 25 mg for 72.7%, 30 mg for 18.2%, and if the child's weight was above 50 kg, the maximum dose was 32.5 mg for 4.5%.

Table 2. Dose of methotrexate (MTX) at commencement of treatment and maximum dose.

MTX Dose at Commencement, mg/kg	
0.2	7.4%
0.35–0.5	51.8%
0.5–0.6	37.1%
1	3.7%
Maximum Dose of MTX, mg/kg	
0.5	8.3%
0.8	4.2%
1	79.2%
1.2	8.3%

In response to the question, "How rapidly is methotrexate increased to your maximum dose?", 25% indicated that the dose was increased progressively every 2 weeks, while for an additional 25%, the dose was increased progressively every month. For 15.6%, the need for dose escalation was based on the patient's response, while an additional 15.6% answered that their maximum dose was given immediately. The remainder indicated other intervals. In general, when a progressive approach was adopted the dose was increased by increments of 2.5 to 5 mg.

Monitoring for MTX toxicity. The investigations undertaken by the respondents at baseline and in followup are summarized in Table 3. CBC, AST, ALT were completed by 100% at baseline as per ACR guidelines. However, the type and frequency of followup investigations varied considerably. The frequency with which blood tests were undertaken is shown in Table 4. As recommended, blood tests were undertaken by 96.3% within 1 month following a change in dose. When the dose was stable for at least 3 months, 78.6% undertook blood tests every 4 to 8 weeks. Responses to the question "What result is abnormal for you?" are summarized in Table 5, showing considerable variability among respondents. Similar variability was observed with the answers to the question "What do you do with an abnormal result", as shown in Table 6.

Respondents reported that recurrent nausea and/or vomiting occurred frequently, while hepatotoxicity, blood dyscrasias, infectious diseases, and mouth ulcers were uncom-

Table 3. Percentages of respondents who do the following investigations for methotrexate monitoring.

Investigation	At Baseline, %	In Followup, %
CBC*	100	100
AST*	100	100
ALT*	100	100
Bilirubin*	42.8	21.4
γ-glutamyl transferase	39.3	28.6
Alkaline phosphatase*	32	21.4
Albumin*	85.7	71.4
Total protein	32	3.6
Urea	78.6	50
Creatinine*	85.7	67.8
Chest radiograph*	32	NA
Hepatitis serology*	64.3	NA
Varicella serology	71.4	NA
PPD testing	32	NA

* ACR guideline item. PPD: purified protein derivative. NA: not applicable.

mon. Overall, few pediatric rheumatologists reported that they discontinued MTX because of side effects. No one recommended routine liver biopsy, but 46.4% of the respondents would recommend a liver biopsy as per ACR guidelines for persistent elevation in AST/ALT. No cirrhosis or other severe toxicity was reported.

Folate supplementation. All respondents except one prescribed folate supplementation to their patients at initiation of MTX, most often as folic acid as opposed to folinic acid. The most common dose was 1 mg daily, and this was increased for side effects such as nausea up to 5 mg daily.

Varicella vaccine. Of all respondents, 46.4% would recommend the varicella vaccine prior to initiating MTX. An interval of 3 to 8 weeks after vaccination was chosen before commencement of MTX. There was no specific question on varicella titers or previous varicella disease, and respondents did not comment on these issues.

DISCUSSION

MTX is the most commonly used DMARD for the treatment of pediatric rheumatic diseases. Although no specific guidelines on its use or for the monitoring of its toxicity in children have been published, pediatric rheumatologists have been using those published for adults with RA by the ACR[4]. Our survey shows, however, that while pediatric rheumatologists in Canada follow these ACR guidelines, there is considerable variation in the degree to which they adhere to these guidelines. Moreover, despite the extent of monitoring for toxicity, few side effects are actually reported.

In our survey, 78.4% use MTX PO initially; however, they either commence or switch to SQ in cases of more severe disease, when a higher dose is used, when there is lack of efficacy, or when GI toxicity occurs. Respondents vary considerably with regard to the approach taken with each of these scenarios. While the mean dose administered is 0.35–0.5 mg/kg once a week for 51.8%, and the maximum dose is 1 mg/kg for 79.2%, 72.7% would not increase the dose beyond 25 mg once weekly. In regard to the frequency of undertaking laboratory investigations for the monitoring of MTX toxicity, ACR guidelines are followed rigidly for some investigations such as CBC, AST, and ALT, but not for others such as albumin and creatinine. However, there is variability in following the guidelines in regard to response to abnormal laboratory results. For a minor elevation of AST/ALT, 30% of the physicians surveyed choose not to repeat blood tests within 2–4 weeks despite recommendations, while in contrast, 3.4% will stop MTX for that same result. However, 89.3% will stop MTX for AST/ALT elevation more than 3 times the upper normal limit (Table 6). Despite this intensive monitoring, few side effects are noted by the physicians. The main side effect reported by respondents was nausea and/or vomiting. No serious toxicities were reported and, in particular, no case of cirrhosis. Respondents infrequently stopped MTX because of side effects, other than for nausea and/or vomiting.

Recently, the need to modify the ACR guidelines for monitoring of liver toxicity in adults has been discussed since few side effects are reported compared to the number of tests per-

Table 4. Frequency of blood tests recommended by respondents to monitor for methotrexate toxicity.

Frequency of Blood Tests	After a Change in Dose		When the Dose is Stable at Least 3 mos	
q wk	1	96.3%	0	
q 2 wks	10		0	
q mo	15		9	
q 4–6 wks	0		1	78.6%
q 6 wks	0		1	
q 6–8 wks	0		3	
q 2 mos	1		8	
q 2–3 mos	0		3	21.4%
q 3 mos	0		3	
NA	1		0	

NA: not applicable.

formed. Yazici, *et al*, who recently reviewed the safety of MTX in 248 patients with RA, noted permanent discontinuation occurred in 18.5%, 56.5% of which were for adverse effects but only 7.7% for laboratory abnormalities[10]. Kent, *et al* reviewed 481 patients with RA who had undergone 2323 person-years of MTX monitoring with 17,849 laboratory measurements[11]. These authors showed that while 63% of patients had at least one episode of elevation in AST, 83% of those had an elevation less than 2 times normal, 12% between 2 and 3 times normal, and only 5% above 3 times normal. Leukopenia was observed in 11% of the patients and 1.8% had thrombocytopenia. MTX was stopped definitively in 4.6% and temporarily in 14%, mainly due to elevation in AST. Risk factors associated with these side effects were obesity, hyperlipidemia, and a lack of folate supplementation. Pediatric rheumatologists invariably prescribe folate supplementation in association with MTX and this might have a role in reducing hepatotoxicity[11].

Some authors have also suggested that children may have a better tolerance to MTX toxicity[4,12]. Graham, *et al* published a series of 62 children in whom MTX was well tolerated overall[12]. While nausea was reported frequently, blood dyscrasias and hepatotoxicity were noted infrequently. Only 9 patients had elevated transaminases and none of these patients had to discontinue MTX. More recently, Lahdenne, *et al* reported the results of liver biopsies in 34 children receiving MTX[13]. None had significant changes in liver histology and the changes noted were reversible. Ortiz-Alvarez, *et al* published their experience with MTX toxicity in Vancouver[9]. The conclusion was that MTX had mild side effects. The probability of developing a side effect at 3 months post-MTX in those without other risk factors did not differ from chance alone. Therefore, they recommended monitoring blood tests every 3 months. This is contrary to the recommendations stated by Ramanan, *et al*, who recommended monitoring every 2 weeks until a stable dose is reached, then every month for 6 months, and every 6 weeks thereafter[14].

We also included a question on varicella vaccination, as this is important for children receiving MTX. Varicella vaccination should be proposed in children who are candidates for MTX until varicella vaccine becomes part of the routine childhood vaccination program. The concern here is that children taking MTX may be immunocompromised and therefore may have a more severe clinical course if infected with varicella. As well, hepatotoxicity can be a significant problem in these cases. In regard to varicella vaccination, we have to determine when it should be given and the interval needed between the vaccine and initiation of MTX.

Our survey and the few pediatric studies published to date suggest that specific guidelines for the monitoring of MTX toxicity in children should be developed. Moreover, few side effects are reported that are based on abnormal laboratory test results and thus the current guidelines lead to overtesting. The variation in monitoring and response to abnormal laboratory results among pediatric rheumatologists in Canada suggests that there is a need for appropriate guidelines for children. Thus, a task force should be established to deal specifically with this issue in an evidence-based fashion.

Table 5. Test result limits that physicians surveyed considered to be abnormal.

Result	%
AST/ALT	
> 1 and < 2-fold upper normal limit	57.1
> 2-fold upper normal limit	96.4
> 3-fold upper normal limit	100
Albumin	
< 35 g/l	52
< 30 g/l	100
White blood cell count	
$< 4 \times 10^9$/l	42.8
$< 3 \times 10^9$/l	92.8
Other	7.2
Platelets	
$< 150 \times 10^9$/l	74
$< 100 \times 10^9$/l	96.2
Other	3.8

ACKNOWLEDGMENT

We thank all the members of the Canadian Pediatric Rheumatology Association who contributed to this survey.

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Table 6. Response to abnormal result.

Abnormal Result	Action		
	Do Nothing, %	Repeat Blood Tests*, %	Stop MTX and Repeat Tests, %
AST/ALT < 2 × normal	27.6	69	3.4
AST/ALT > 2 < 3 × normal	0	57.1	42.9
AST/ALT > 3 × normal	0	10.7	89.3
Albumin	16.7	61.1	22.2
White blood cells	0	68.8	31.2
Platelets	0	63	37

* All blood tests were repeated within 1 month.

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