Effectiveness and Toxicity of Methotrexate in Juvenile Idiopathic Arthritis: Comparison of 2 Initial Dosing Regimens

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ABSTRACT. ***Objective.*** To compare the incidence of liver toxicity and clinical response between 2 initial dosing regimens of methotrexate (MTX) for treatment of juvenile idiopathic arthritis (JIA).

Methods. Clinical and laboratory data were abstracted from the medical records of 220 children newly prescribed MTX from the same geographic region. One cohort received initial doses of MTX > 0.5 mg/kg/week ("high-dose") and one cohort received initial doses of MTX ≤ 0.5 mg/kg/week ("low-dose"). Toxicity was defined as aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) above the normal range, and positive clinical response was defined as a reduction in active joint count during the first 6 months of MTX therapy.

Results. One hundred twenty-six children were in the high-dose MTX group, 94 in the low-dose MTX group. At 6 months, the high-dose group was more likely to have an elevated AST or ALT (adjusted OR 3.89, 95% CI 1.82–8.29, $p < 0.0001$). Subjects receiving both MTX and nonsteroidal antiinflammatory drugs (NSAID) had no significant difference between groups in change of active joint count, while subjects in the high-dose group but not taking NSAID had more active joints ($p = 0.036$) at 6 months compared to the low-dose group.

Conclusion. Initial high-dose MTX was associated with an increased risk of at least one liver enzyme abnormality with no significant improvement in active joint count. This suggests that there is no apparent benefit, while the potential for liver toxicity is increased, when using higher doses of MTX at treatment inception in patients with JIA. (First Release March 1 2010; J Rheumatol 2010;37:870–5; doi:10.3899/jrheum.090826)

Key Indexing Terms:
JUVENILE IDIOPATHIC ARTHRITIS METHOTREXATE TOXICITY EFFICACY

Methotrexate (MTX) has been a cornerstone in the treatment of juvenile idiopathic arthritis (JIA) for several decades. Its effectiveness in JIA has been documented in a number of uncontrolled descriptive studies[1-5]. Current therapeutic guidelines are based on a 1992 randomized double-blind placebo-controlled trial comparing low-dose (10 mg/m^2) and very low-dose (5 mg/m^2) MTX to placebo in patients with resistant arthritis[6].

Empiric escalation of the dose of MTX in less responsive patients has occurred as experience with MTX in JIA has increased. Small noncontrolled descriptive reports have advocated the use of higher doses of MTX (25–30 mg/m^2 or 0.8–1 mg/kg/dose) in patients with JIA unresponsive to initial standard doses (10–15 mg/m^2 or 0.3–0.5 mg/kg/dose)[7,8]. However, only one study in children has attempted to compare the efficacy of high-dose (30 mg/m^2/dose) MTX with intermediate-dose MTX (15 mg/m^2/dose). No difference in efficacy or toxicity was observed, but conclusions were limited by lack of power due to the small numbers of patients who qualified for ran-

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domization[9]. Further, this study included only JIA patients who previously failed the standard low dose. Recent promotion of early and aggressive treatment of arthritis has led to empirical use of higher initial doses of MTX in an attempt to prevent later damage and disability. However, there are no objective clinical studies comparing toxicity and efficacy of initial high doses and standard doses of MTX to support this practice. Consequently, there is no consensus among practitioners on what the initial dosing of MTX should be in children with JIA.

This retrospective cohort study was conducted to compare the clinical response and incidence of liver toxicity between initial "high dose" and initial "low dose" of MTX in pediatric patients with JIA.

MATERIALS AND METHODS

Patient records of children who received care at 2 participating centers, duPont Hospital for Children (DHC) and the Children's Hospital of Philadelphia (CHOP), from January 1, 1998, to December 31, 2005, were abstracted. These centers were chosen due to their close geographic proximity and similar patient populations but with different practices with respect to initial MTX dosing regimens. This allowed a comparison of hepatic toxicity and clinical response with 2 different initial dosing regimens assumed not to be selected based on severity of disease or lack of response to treatment. Both participating sites received approval from their governing institutional review boards.

Specific data collected from medical record abstraction included age, sex, ethnicity, JIA subtype, hospital of record, antinuclear antibody (ANA), rheumatoid factor (RF), and HLA-B27. At clinic visit 0 (time MTX started), 6 months, and 12 months, the patient's weight, height, dose of MTX, use of nonsteroidal antiinflammatory drugs (NSAID), use of folic acid, MTX administration route, and active joint count were recorded. Specific laboratory values recorded from the inception of MTX to 6 months and 12 months on therapy, if available, included aspartate aminotransferase (AST), alanine aminotransferase (ALT), white blood cell (WBC) count, hemoglobin (Hgb), platelets (PLT), albumin, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP). These laboratory values were recorded every 2 months on average.

Eligible subjects were identified by selecting patients diagnosed with JIA or arthritis not otherwise specified by *International Classification of Diseases*, 9th edition, codes over the 8-year period of interest. Clinical diagnosis was verified using the Edmonton 2001 International League of Associations for Rheumatology (ILAR) criteria for JIA[10]. We applied this definition to all records reviewed, regardless of the date of diagnosis. From the JIA patients identified, only those receiving their first course of MTX treatment within the study period were included. If subjects had received MTX more than once during this study period, we included only the first course of treatment in our analysis.

The "high-dose" group consisted of subjects started on MTX at doses > 0.5 mg/kg/week. The "low-dose" group consisted of subjects started on MTX at doses ≤ 0.5 mg/kg/week.

Hepatic toxicity was defined as at least one value above the normal range of either ALT or AST during the study period[11]. Only patients with at least one baseline and one followup transaminase measurement within the first 6 months on therapy (± 2 months) were included. Clinical response was defined as the change in number of active joints from baseline. The definition of an active joint included swelling not due to bony enlargement, or, if no swelling is present, limitation of motion accompanied by either pain on motion or tenderness, not due to trauma or explained by prior joint damage[12]. Only patients with at least one baseline and one or more followup clinical evaluations within the first 6 months on therapy (± 2 months) were included.

Statistical analysis. Continuous variables were summarized by the mean, median, standard deviation, and range. Categorical variables were summarized by frequencies. Bivariable analyses were conducted to evaluate the primary association of MTX dose and presence of hepatic liver enzyme elevation within the first 6 months. An odds ratio (OR) and 95% confidence interval (CI) were calculated to evaluate the strength of association as well as the precision of the estimate of effect.

Stratified analyses using the Mantel-Haenszel test for summary statistics were used to evaluate each variable of interest as a potential confounder. This identified potential confounders and effect modifiers, which were candidate variables for inclusion in the multivariable models. We specifically evaluated the following categorical variables to determine if any of these factors affected the association between MTX dose and the outcomes, liver toxicity, and clinical response: sex, hospital, concurrent medication use, use of folic acid, and MTX administration route (subcutaneous vs oral). The presence of confounding was defined by a difference of ≥ 15% between the crude OR and the summary OR. Interaction (effect modification) was assumed to be present when the test for heterogeneity between the OR for different strata was significant ($p < 0.05$).

Multivariable relative risk estimates were calculated using multiple logistic regression analysis for the toxicity outcome and multiple linear regression analysis for the response outcome. Variables found to be significant confounders or effect modifiers in the stratified analyses, in addition to the continuous variables (MTX mg/kg dose, age at MTX inception, and weight > 25 kg), were subsequently added into the regression models.

Comparison of mean and median change in active joint counts at 6 and 12-month outcomes was by the Wilcoxon rank-sum test. Multivariable linear regression analysis included confounders and effect modifiers.

A significance level of 5% and 2-sided tests were used for all analyses. Stata version 9.0 software (Stata Corp., College Station, TX, USA) was used for all statistical analyses.

The primary analysis compared toxicity and clinical response between treatment groups at 6 months of therapy. Secondary analyses evaluated these variables at 12 months.

RESULTS

Of 1347 records identified by ICD-9 code, 1159 (86%) were available for review. A total of 220 subjects who met JIA criteria and were initially prescribed MTX within the designated study period were included in the analysis. The median age of all 220 subjects was 8.9 (7.9, 10.0) years at start of MTX therapy. In total 141 (64%) subjects were treated at CHOP and 79 (36%) were treated at DHC. One hundred seventy-two (78%) were female and 48 (22%) were male. As for ethnicity, 85% were Caucasian, 4% Hispanic, 10% African American, and 1% Asian. Dosing regimens for MTX included 102 (46%) by oral administration (PO) and 118 (54%) subcutaneous administration. There were 126 in the high-dose MTX group (87% from CHOP, 13% from DHC) and 94 in the low-dose group (34% from CHOP, 66% from DHC). Characteristics of the 2 groups were similar except for median initial active joint count and median age at inception of MTX treatment. The initial active joint count and the median age tended to be higher in the low-dose group compared to the high-dose group (Table 1).

Toxicity analysis. Bivariable analysis revealed 56 of 126 (44%) subjects receiving high-dose MTX had at least 1 abnormal AST or ALT value (here referred to as "toxicity") by 6 months compared to 16 of 94 (17%) subjects taking

Table 1. Clinical and demographic characteristics of patients receiving high and low-dose methotrexate (MTX).

Characteristic	High Dose, n = 126 (%)	Low Dose, n = 94 (%)
Hospital 1 (CHOP)	109 (87)	32 (34)
Hospital 2 (DHC)	17 (13)	62 (66)
Male	28 (22)	20 (21)
Female	98 (78)	74 (79)
Caucasian	105 (83)	82 (87)
Hispanic	5 (4)	3 (3)
African American	12 (10)	9 (10)
Asian	4 (3)	0
Systemic disease	29 (23)	4 (4)
Oligoarticular disease	18 (14)	10 (11)
Oligo-extended disease	13 (10)	11 (12)
Polyarticular RF+ disease	8 (6)	12 (13)
Polyarticular RF– disease	41 (33)	38 (40)
Psoriatic arthritis	10 (8)	5 (5)
Enthesitis-related arthritis	5 (4)	12 (13)
Other disease	2 (2)	2 (2)
ANA-positive	62 (49)	44 (47)
RF-positive	9 (7)	11 (12)
HLA-B27-positive	9 (7)	6 (6)
Median initial active joint count (95% CI)	5 (4, 5)	7.5 (5, 12)
Median age at start of MTX, yrs (95% CI)	6.3 (5.3, 7.3)	12.5 (10.8, 13.6)
Median dose at start of MTX, mg/kg (95% CI)	0.78 (0.72, 0.81)	0.32 (0.28, 0.35)

CHOP: Children's Hospital of Philadelphia; DHC: duPont Hospital for Children; RF: rheumatoid factor; ANA: antinuclear antibody.

low-dose MTX (OR 3.9, 95% CI 2.06–7.37, $p < 0.00001$). Other variables associated with 6-month toxicity by bivariable analyses included subcutaneous MTX administration (OR 2.04, 95% CI 1.14–3.64, $p = 0.02$) and being treated at the hospital with higher dosing preference (OR 2.6, 95% CI 1.40–4.91, $p = 0.03$). Specifically, there was no association between NSAID use and toxicity at 6 or 12 months ($p = 0.96$ and $p = 0.64$, respectively).

On stratified analysis, no significant effect modification was identified for the primary association of interest of abnormal AST or ALT. Confounding was present by MTX administration route. However, when controlling for route of administration in a multivariable logistic regression model, the incidence of toxicity remained significantly greater in the high-dose group than the low-dose group (adjusted OR 3.89, 95% CI 1.82–8.29, $p < 0.001$).

Using the secondary outcome of toxicity from MTX at 12 months (determined as an abnormal laboratory value between 6 and 12 months taking MTX), bivariable analysis revealed 46 of 105 (43.8%) subjects taking high-dose MTX had at least one abnormal AST or ALT finding, compared to 13 of 81 (16%) on low-dose MTX (OR 4.08, 95% CI 2.02–8.20, $p < 0.001$). Other variables associated with 12-month toxicity on bivariable analyses included subcutaneous MTX administration (OR 2.72, 95% CI 1.44–5.16, $p = 0.002$) and hospital (OR 2.62, 95% CI 1.32–5.20, $p = 0.01$).

On stratified analysis, gender was a significant effect modifier between the association of MTX dosing group and toxicity at 12 months (test for heterogeneity $p = 0.036$). Confounding was present by MTX administration route and age at MTX inception; however, gender remained a significant effect modifier after controlling for route and age at MTX inception in a multivariable logistic regression model ($p = 0.048$). After controlling for the confounding variables of MTX route and age at MTX inception, females receiving high-dose MTX continued to have a significantly greater risk of toxicity at 12 months compared to those on low-dose MTX (adjusted OR 3.7, 95% CI 1.28–10.86, $p = 0.016$). In contrast, males receiving high-dose MTX had no increased risk of toxicity after controlling for confounders (adjusted OR 0.69, 95% CI 0.15–3.20, $p = 0.64$).

Response analysis. There was a statistically significant difference in active joint count between groups at the beginning of MTX therapy, the low-dose group exhibiting a higher number of active joints compared to the high-dose group (median joint count 7.5 in low-dose group vs 5 in high-dose group; $p = 0.0009$). By 6 and 12 months, however, there was no statistically significant difference in active joints between the 2 dosing groups. Specifically, at 6 months, the low-dose group had a median of 2 active joints (range 0–18) and the high-dose group a median 0 active joints (range 0–29) ($p = 0.06$); at 12 months, both groups had a median of 0 active joints (ranges 0–14 in the low-dose group, 0–26 in the high-dose group) ($p = 0.08$; Table 2).

Bivariable analyses at 6 months revealed that concomi-

Table 2. Active joint counts at time 0, 6 months, and 12 months.

Time	Group	Joint Count, median (95% CI)	Joint Count, mean (SD)	p
0	High dose	5 (4, 5)	7.44 (7.73)	0.0009*
	Low dose	7.5 (5.02, 11.98)	10.31 (8.31)	
6 months	High dose	0 (0)	1.77 (4.45)	0.06*
	Low dose	2 (1, 2)	2.89 (3.64)	
12 months	High dose	0 (0, 0)	1.35 (3.74)	0.08*
	Low dose	0 (0, 1)	1.36 (2.39)	

* Wilcoxon rank-sum analysis comparing median active joint counts between the 2 groups at time 0 (start of MTX), 6 months, and 12 months.

tant use of NSAID was a significant effect modifier (p = 0.035), and there was confounding by hospital, route of MTX administration, age at MTX inception, and weight > 25 kg. After controlling for confounders within a multivariable linear regression model, among subjects concurrently using NSAID there was no significant difference in the change in active joint counts between groups at 6 months. However, among subjects not taking NSAID concurrently, the low-dose group had significantly fewer active joints at 6 months than the high-dose group (coefficient –6.8, SE 3.2, p = 0.04).

Response analyses at 12 months revealed no effect modification, but showed confounding by hospital, age at MTX inception, and weight > 25 kg. A final linear regression analysis controlling for the above variables revealed no significant difference in the change in active joint counts between groups at 12 months (coefficient –1.4, SE 1.5, p = 0.34).

Further secondary analyses. Fourteen of the 220 subjects crossed over from one dosing group to the other within the 12-month timeframe. In the low-dose group, 4 subjects increased their dose to > 0.5 mg/kg, all by the 6-month visit. The remaining 10 subjects were in the high-dose group initially and decreased their dose to < 0.5 mg/kg, 3 by the 6-month visit and 7 by the 12-month visit. Repeat analysis as described above was conducted with the removal of these 14 patients from the analysis. No substantive difference was noted in results. Additionally, since systemic-onset JIA is often associated with transaminase elevation due to disease activity, repeat analysis was conducted with the removal of the systemic JIA subgroup from all analyses (4 subjects in low-dose group, 29 in high-dose group). No substantive difference was noted in results. Specifically, with removal of the systemic JIA patients from the analysis, final logistic regression at 6 months still revealed the high-dose group remained at higher risk for liver enzyme elevation (OR 3.4, 95% CI 1.50–7.72, p = 0.003). The final linear regression at 12 months continued to reveal no significant improvement in active joint count (coefficient –0.54, SE 1.7, p = 0.75).

Although the frequency and extent of AST or ALT elevations were significantly less in the low-dose group, increased transaminase levels were moderate (i.e., < 2 times normal) and reversible in the majority of patients in both groups. Within the high-dose group (n = 126), there were 748 sampling instances (average 5.9 laboratory results per patient over 12 months). Ninety-nine of 748 (13%) AST values were elevated above normal range. Within this group of elevated AST values, 90% were 1 to 2 times normal, 5% were 2 to 3 times normal, and 5% were ≥ 3 times normal range. One hundred nineteen of 748 (16%) ALT laboratory values were elevated above the normal range. Within the group of elevated ALT values, 77% were 1 to 2 times normal, 9% were 2 to 3 times normal, and 13% were ≥ 3 times normal range.

In the low-dose group (n = 94), there were 597 sampling instances (average 6.4 blood draws per patient over 12 months). Twenty-four of 597 (4%) AST values were elevated above normal range. Within this group of elevated AST values, 100% were 1 to 2 times normal range. Thirty-four of 597 (6%) ALT values were elevated above the normal range. Within the group of elevated ALT values, 94% were 1 to 2 times normal, 3% were 2 to 3 times normal, and 3% were ≥ 3 times normal range.

The subgroup of patients with severely elevated (≥ 3 times normal) transaminases were overwhelmingly in the high-dose group. In 11 patients, there were 21 sampling instances with an AST or ALT value ≥ 3 times normal. Of the 11 patients, one was in the low-dose group and this patient had a single ALT value of 3.1 times the normal range. Among the 10 remaining patients, 20 samplings resulted in AST or ALT values 3 times normal. The ranges of the results were from 3.1 to 21 times the normal range.

No patient in the low-dose group discontinued MTX due to hepatic toxicity in the 12-month interval evaluated. Five of 126 (4%) patients in the high-dose group discontinued MTX due to hepatic toxicity. AST or ALT elevations in these 5 patients ranged from 2.5 to 21 times the normal range and all elevations occurred within the first 6 months of therapy. All 5 patients were taking folic acid and NSAID concurrently. Three of the 5 patients had systemic-onset JIA and 2 had RF-negative polyarticular JIA. No concurrent illness was identified for these 5 patients and both AST and ALT returned to normal after discontinuation of MTX.

DISCUSSION

The most notable observation from this study was that the higher initial MTX dose did not confer any therapeutic advantage. Indeed, at 6 months, among subjects not concurrently taking NSAID, the high-dose group had less improvement in active joint count than the low-dose group. Patients reported to be taking NSAID in addition to MTX had no significant difference in active joint counts at 6 months. This suggests a possible additive antiinflammatory effect of NSAID and MTX. At 12 months, there also was no difference in active joint counts between the high-dose and the low-dose MTX groups.

There are inherent limitations associated with any retrospective cohort study. However, we designed and implemented this study to minimize the influence of such limitations. Quality of data is always a concern when obtained from medical records that are primarily created for patient care. For this reason we selected primary outcome variables for measures of toxicity and efficacy that are objective as well as consistently and routinely recorded in the medical record. There is the potential for selection bias based on disease severity, patient demographics, or treatment site. However, the 2 treatment cohorts were virtually identical with respect to demographic and diagnostic characteristics at baseline, with the exception of age and active joint count. The significance of an older median age in the low-dose group is not clear. However, the greater active joint count in the low-dose group at baseline would be expected to bias toward greater efficacy of the higher dose, the opposite of what we observed. Bias due to diagnostic misclassification was minimized by using the ILAR criteria for diagnosis of JIA and having the same investigator abstract all charts (MLB). To avoid misclassification of MTX treatment group, we required clear and unambiguous documentation of MTX prescription in the medical record. The dose per kilogram of MTX was accurately calculated based on the weekly dose of MTX and the weight recorded at each clinic visit. Controlling statistically for weight > 25 kg also corrected for misclassification bias that may have occurred with mg/kg dosing in larger children. We could not evaluate patient adherence to prescribed dose and assumed the patient took the medication as prescribed. Bias related to use of transaminase elevations as an indicator of hepatotoxicity could have occurred, since there are potential causes of liver enzyme abnormalities in children other than MTX toxicity. However, given the close geographic proximity and demographic homogeneity of the 2 patient populations, the risk of common alternative causes of liver enzyme elevation, such as viral infections, would be expected to be equal between the 2 groups and bias towards the null. Further, the chronology and size of the difference in transaminase elevations between the high and low-dose groups strongly indicates an association with MTX dose.

Route of MTX administration was found to be a confounding variable in the toxicity analysis and 6-month response analysis. This could be explained by the fact that the majority of patients receiving subcutaneous dosing were in the high-dose group (86%). Additionally, subcutaneous dosing likely would result in higher bioavailability, at least at higher doses, and could potentially result in higher serum or intracellular levels of MTX, thereby potentially increasing the risk for toxicity. We did not obtain MTX serum or intracellular polyglutamate concentrations in this subgroup of patients; however, after controlling for route of administration in the final multivariable regression models, results remained significant for toxicity and nonsignificant for response.

Although transaminase elevations in most patients from both dose groups were modest, they did reflect some degree of hepatocellular toxicity, albeit reversible. Pediatric liver biopsies after cumulative doses of MTX in JIA have not shown hepatic fibrosis or cirrhosis. However, changes in histology were noted, and their significance was unclear[13-15]. Further discussions have arisen to debate the need for such frequent toxicity monitoring in children, noting the risks for significant transaminase or hematologic abnormalities are no greater than by chance alone[16]. This small degree of transaminase elevation might be acceptable in the majority of patients in the absence of other evidence of toxicity if there were a significant therapeutic benefit from the initial higher MTX dose. However, in the absence of therapeutic benefit, it is difficult to argue for subjecting patients to any real or potential toxicity attributed to the higher initial dose. This is not to say that patients who require higher doses to achieve clinical response should not have them if they derive clinical benefit without significant toxicity; however, our results do not support starting all patients with JIA at a higher initial dose.

An interesting and unexpected observation was that gender was an effect modifier, i.e., females had a significantly higher risk of toxicity than males. This has not been reported previously and could be due to the relatively small male cohort in the study. However, it raises several hypothetical possibilities, including hormonal interactions or differences in MTX pharmacokinetics between males and females. These and other possibilities merit further investigation.

This is the first and largest cohort study to directly compare toxicity and effectiveness of high and low initial dosing regimens of MTX in patients with JIA. In the absence of comparable prospective randomized studies, our results provide the best available information to guide initial dosing of MTX in children with JIA. There appears to be no clinical advantage to starting MTX at a higher initial dose in all patients, although an individual patient who does not respond to an initial low dose may require higher doses to control continued active disease. Nevertheless, our observation that the initial higher dose MTX regimen increases toxicity, but offers no therapeutic advantage, makes confirma-

tion of these findings with an adequately powered prospective, controlled trial imperative; these findings have profound implications for safe and effective use of MTX in clinical practice.

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