The Role of Subcutaneous Administration of Methotrexate in Children with Juvenile Idiopathic Arthritis Who Have Failed Oral Methotrexate

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ABSTRACT. ***Objective.*** To describe the outcome of patients with juvenile idiopathic arthritis (JIA) treated with subcutaneous (Sc) methotrexate (MTX) after failing oral MTX (either because of inefficacy or toxicity) in a clinic population.

Methods. The study cohort was identified from our clinical database, and consisted of 61 children with JIA treated with MTX between 1988-2001. All patients fulfilled International League Against Rheumatism (ILAR) criteria for JIA and had disease duration of ≥ 6 months and 3 or more active joints before institution of MTX. All patients had a core set of outcome variables assessed at baseline and at 3 months after achieving both maximum oral and SC MTX. Outcome variables included physician global assessment of disease activity, number of active joints, number of joints with limited range of motion, duration of early morning stiffness, and erythrocyte sedimentation rate (ESR). Improvement was defined as at least 30% improvement from baseline in 3 of 5 variables in the core set, with no more than one of the remaining variables worsening by more than 30%.

Results. A total of 61 patients, 43 females and 18 males with JIA were studied. The disease subtypes were systemic 8, polyarticular 25 (12 rheumatoid factor positive), oligoarticular 14, enthesitis related arthritis 5, and unclassified 4. Thirty-one patients were switched to SC MTX, 13 of whom had not improved, and 18 who had improved, but had nausea (11) or insufficient clinical improvement (7). After 3 months of SC MTX treatment, 76% of patients were classified as improved and 23% as not improved. Toxicity on SC MTX was less than on oral MTX.

Conclusion. Our results suggest that for patients failing oral MTX either because of inefficacy or toxicity, the use of SC MTX has a high likelihood of success with more than 70% of patients achieving clinically significant improvement, without clinically significant toxicity. (J Rheumatol 2004;31:179–82)

Key Indexing Terms:
JUVENILE IDIOPATHIC ARTHRITIS METHOTREXATE TREATMENT

Methotrexate (MTX) is an effective agent in the treatment of juvenile idiopathic arthritis (JIA) and has become now the most commonly used disease modifying antirheumatic drug (DMARD) for this condition[1-10]. Although MTX is widely used to treat children with arthritis, its optimal dose and route of administration remain uncertain. A commonly used initial dose is 10 mg/m^2 in a single weekly dose[6] with doses up to 30 mg/m^2 being used subsequently[10]. The route of administration of MTX in children with arthritis is not standardized and varies according to patient's and treating physician's preference. In most of the reported studies in children with JIA, MTX has been given orally; however, some investigators have chosen the parenteral route[11]. The oral route is generally preferable because of its ease of administration; however the parenteral route (intramuscular or subcutaneous, SC) has the potential advantages of greater absorption and high drug bioavailability[12-15]. In our clinic practice we start oral MTX at a dose of about 10 mg/m^2 weekly in combination with oral folic acid 1 mg daily, and increase the dose as needed on clinical grounds until either benefit is obtained or side effects occur. Evidence suggests that bioavailability with oral dosing often does not increase significantly beyond 20 mg/m^2 per week[13]; therefore if there is no benefit at about this dose, we switch to SC MTX. There is however little or no published data to show that switching to SC administration is clinically effective in children with JIA who have failed oral MTX. Our objective was to examine retrospectively what proportion of children with JIA who had failed or were intolerant of oral MTX improved after changing to SC dosing.

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MATERIALS AND METHODS

Patients. We identified all children with JIA who were treated with MTX from 1988-2001. A chart review of all 61 patients who met inclusion criteria was undertaken. The data collected included the following variables: age, sex, age at diagnosis, disease subtype, disease duration, initial and maximum MTX dose, time to response to MTX, and observed adverse effects of MTX such as liver toxicity (enzymopathy), lymphopenia, mucocutaneous manifestations, and gastrointestinal side effects.

Variables collected to assess outcome and clinical improvement were (1) physician global assessment of disease activity (PGDA) scored on a 4 point scale (1 = inactive, 2 = mild activity, 3 = moderate activity, 4 = severe activity); (2) number of joints with active arthritis; (3) number of joints with limited range of motion (defined for each joint as a loss of at least 5° in any articular movement); (4) duration of early morning stiffness in minutes; and (5) erythrocyte sedimentation rate (ESR).

Response to oral MTX treatment was evaluated in all patients by comparing the values of these 5 variables after 3 months on maximal doses of oral MTX with the values at the time of institution of oral MTX. We did not include a measure of functional outcome such as the Child Health Assessment Questionnaire (CHAQ) or a parental assessment of well being in our outcome measures, as suggested by Giannini, *et al*[16] as these measures had not been routinely performed in our clinic.

For patients who switched to SC MTX, response to MTX was assessed by comparing these variables after 3 months of maximum doses of SC MTX with the values obtained after 3 months of maximum oral MTX. This baseline was chosen for the SC MTX group as most children were switched from oral to SC at about this time point.

Improvement was considered to have occurred when patients had at least 30% improvement from baseline in 3 of the 5 variables assessed, with no more than one of the remaining variables worsening by more than 30%.

Inclusion criteria. All patients fulfilled ILAR criteria for the diagnosis of JIA[17]. All patients had disease duration of at least 6 months, and at least 3 active joints (defined as the presence of swelling or limitation of movement with either pain on movement or tenderness) before institution of MTX. All patients had to have been treated for at least 3 months with at least 10 mg/m^2 per week oral MTX (if tolerated). All patients received oral folic acid at the dose of 1 to 2 mg orally daily.

Exclusion criteria. Patients were excluded if MTX was used primarily to treat other disease manifestation such as uveitis, if they had poor compliance with MTX based on the physician's assessment, or if they were lost to followup.

Statistical analysis. Descriptive statistics were used to summarize the demographic data. The Wilcoxon test or paired t test were used to assess the outcome variables before and after treatment.

RESULTS

There were 61 patients, 18 males and 43 females. The disease subtypes were systemic 8; polyarticular 25 (12 rheumatoid factor positive); oligoarticular 14; enthesitis related arthritis 5; and unclassified 4. Mean age at onset of JIA was 11.4 years (standard deviation, SD, ± 2, range 1.6-16), and mean disease duration was 10.9 months (± 18.4, range 2-99). Mean age at time of treatment with oral MTX was 11.9 years (± 4.3, range 3-20).

Forty of these 61 patients (66%) fulfilled the criteria for improvement after oral MTX (mean maximum oral dose was 13.8 mg/m^2 per week, range 5-20). Thirty-one patients were subsequently switched to SC MTX (mean maximum dose: 15.4 mg/m^2 per week, range 5-20). These included 13 patients whose arthritis had failed to improve by the defined criteria. The other 18 children had fulfilled criteria for improvement, but were switched to SC MTX because of persistent nausea (n = 11) or insufficient clinical improvement as judged by the pediatric rheumatologists (n = 7) (Figure 1).

Thirty of these 31 patients had adequate data to assess outcome. Twenty-three of the 30 patients (77%) who were switched to SC MTX fulfilled the defined criteria for improvement when compared to the values obtained after 3 months of maximum dose oral MTX. Seven patients failed to improve.

Improvement ≥ 30% was calculated separately for each outcome variable: PGDA 25/31 (80.6%); active joints 24/31 (77.4%); number of joints with limited range of movement 16/30 (53.3%); early morning stiffness 14/29 (48.3%); and ESR 23/27 (85.2%). There was a statistically significant difference in each of these variables before and after SC MTX ($p < 0.05$ for each variable).

A total of 15 patients had toxicity related to oral MTX (11 with nausea and 4 with raised serum liver enzyme levels). Nine of the 11 patients with nausea had complete resolution of their symptoms after switching to SC MTX; the other 2 patients continued to have nausea, but this was less severe, and they were able to continue with SC MTX. All 4 children with raised liver enzymes were able to remain on oral MTX as the abnormalities resolved after temporary discontinuation of oral MTX.

Four children had transient toxicity related to SC MTX (liver enzyme abnormalities, or mild lymphopenia), requiring temporary discontinuation of SC MTX in 2 patients, which did not recur when it was reinstituted.

DISCUSSION

Our study shows that in children with JIA who have an inadequate response to oral MTX, or who develop toxicity to oral MTX, approximately 75% will get substantial benefit from switching to SC MTX. One probable explanation for the increased efficacy of SC MTX may be inadequate absorption of MTX via the oral route. Oral absorption of MTX is known to vary widely between individuals[12,18-22]. Wallace, *et al* have shown a 20-fold variance in 1 h serum MTX levels at oral dosages between 0.11-0.6 mg/kg per week in children with juvenile rheumatoid arthritis (JRA)[19]. Dupus, *et al* showed that oral bioavailability of MTX is greater in the fasting state in children with JRA[21]. It is known[13] that in some individuals, saturation of oral absorption may occur at doses as low as 12 mg/m^2. Jundt, *et al* found that the relative bioavailability of low dose MTX is less with oral than with parenteral administration in adults with RA[20].

The apparent beneficial effect of switching from oral to SC MTX in our patients who failed to respond to oral MTX may be best explained by the increased bioavailability of SC MTX. It is also possible that there is improved adherence to MTX therapy when it is given by SC injection than when taken orally.

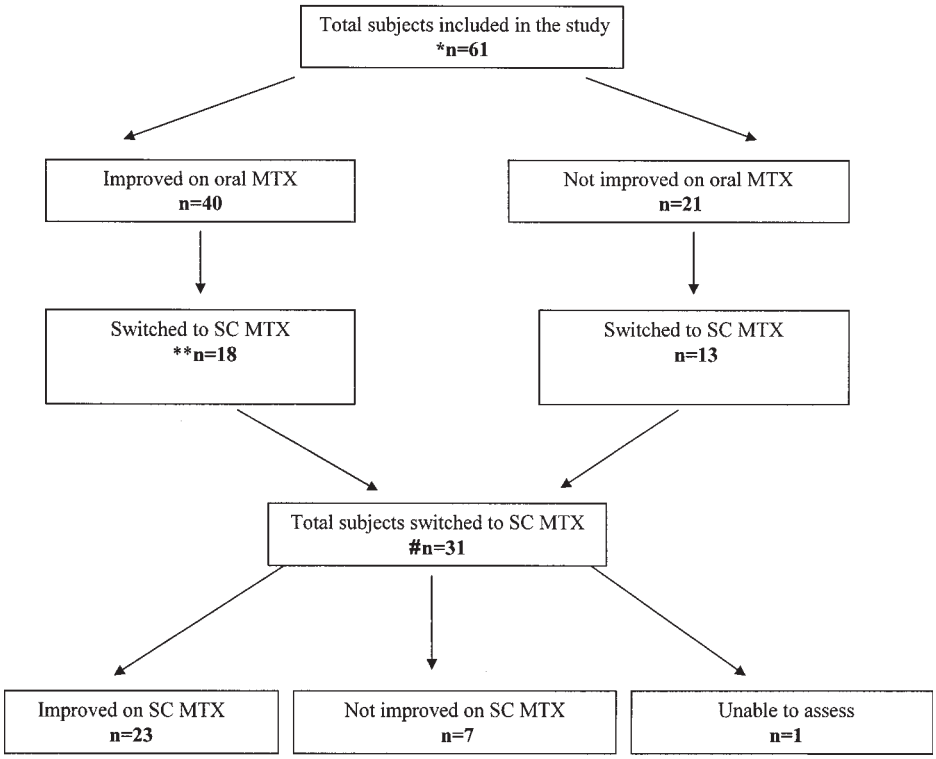

Figure 1. Flow diagram showing the outcome of patients treated with methotrexate. * 15 patients had toxicity on oral MTX; 11 with nausea and 4 with elevated liver enzymes. **Patients were switched to SC MTX because of persistent nausea (n = 11) or insufficient clinical improvement (n = 7). #4 patients had elevated liver enzymes or lymphopenia.

It is perhaps surprising that MTX toxicity (particularly nausea) was less marked in some patients once switched to SC MTX. The explanation for this is not immediately apparent.

Our study has the limitations of being retrospective in design. As we had not routinely obtained parental global assessment of well being or CHAQ assessments in all patients included in this study, we were unable to use the American College of Rheumatology pediatric core set[16], a validated definition of improvement, and this might have affected our evaluation of how many children improved with MTX therapy. Nevertheless we believe that as each child acts as his/her own control, the results of this study are fairly robust and that the majority of children with JIA who are inadequately responsive to oral MTX will improve significantly without increased toxicity after switching to SC MTX.

REFERENCES

1. Truckenbrodt H, Hafner R. Methotrexate therapy in juvenile rheumatoid arthritis: a retrospective study. Arthritis Rheum 1986;29:801-6.
2. Speckmaier M, Findeisen J, Woo P, et al. Low-dose methotrexate in systemic onset juvenile chronic arthritis. Clin Exp Rheumatol 1989;7:647-50.
3. Rose CD, Singsen BH, Eichenfield AH, Goldsmith DP, Athreya BH. Safety and efficacy of methotrexate therapy for juvenile rheumatoid arthritis. J Pediatr 1990;117:653-9.
4. Halle F, Prieur AM. Evaluation of methotrexate in the treatment of juvenile chronic arthritis according to the subtype. Clin Exp Rheumatol 1991;9:297-302.
5. Ravelli A, Neirotti G, Viola S, Giaccari MC, Guidi T, Martini A. Low dose methotrexate therapy for seronegative juvenile rheumatoid arthritis. Riv Ital Pediatr 1991;17:315-9.
6. Giannini EH, Brewer EJ, Kuzmina N, et al. Methotrexate in resistant juvenile rheumatoid arthritis. Results of the USA-USSR double-blind, placebo-controlled trial. N Engl J Med 1992;326:1043-7.
7. Wallace CA, Sherry DD. Preliminary report of higher dose methotrexate treatment in juvenile rheumatoid arthritis.J Rheumatol 1992;19:1604-7.
8. Lepore L, Pennesi M. Treatment with low-dose methotrexate in intractable juvenile chronic arthritis. Pediatr Med Chir 1992;14:509-12.
9. Corona F, Bardare M, Cimaz R, Rognoni MG. Methotrexate in juvenile chronic arthritis. Clin Exp Rheumatol 1993;11:346-7.
10. Reiff A, Shaham B, Wood BP, Bernstein BH, Stanley P, Szer IS. High dose methotrexate in the treatment of refractory juvenile rheumatoid arthritis. Clin Exp Rheumatol 1995;13:113-8.
11. Ravelli A, Gerloni V, Corona F, et al. Oral versus intramuscular methotrexate in juvenile chronic arthritis. Italian Pediatric Rheumatology Study Group. Clin Exp Rheumatol 1998;16:181-3.
12. Teresi ME, Crom WR, Choi KE, Mirro J, Evans WE. Methotrexate bioavailability after oral and intramuscular administration in children. J Pediatr 1987;110:788-92.
13. Balis FM, Mirro JU, Reaman GH, et al. Pharmacokinetics of

subcutaneous methotrexate. J Clin Oncol 1988;6:1882-6.
14. Brooks PJ, Spruill WJ, Parish RC, Birchmore DA. Pharmacokinetics of methotrexate administered by intramuscular and subcutaneous injections in patients with rheumatoid arthritis. Arthritis Rheum 1990;33:91-4.
15. Hamilton RA, Kremer JM. Why intramuscular methotrexate may be more efficacious than oral dosing in patients with rheumatoid arthritis. Br J Rheumatol 1997;36:86-90.
16. Giannini EH, Ruperto N, Ravelli A, Lovell DJ, Felson DT, Martini A. Preliminary definition of improvement in juvenile arthritis. Arthritis Rheum 1997;40:1202-9.
17. Petty RE, Southwood TR, Baum J, et al. Revision of the proposed classification criteria for juvenile idiopathic arthritis: Durban, 1997. J Rheumatol 1998;25:1991-4.
18. Kearney PJ, Light PA, Preece A, Mott MG. Unpredictable serum levels after oral methotrexate in children with acute lymphoblastic leukemia. Cancer Chemother Pharmacol 1979;3:117-20.
19. Wallace CA, Bleyer WA, Sherry DD, Salmonson KL, Wedgwood RJ. Toxicity and serum levels of methotrexate in children with juvenile rheumatoid arthritis. Arthritis Rheum 1989;32:677-81.
20. Jundt JW, Browne BA, Fiocco GP, et al. A comparison of low methotrexate bioavailability: oral solution, oral tablet, subcutaneous and intramuscular dosing. J Rheumatol 1993;20:1845-9.
21. Dupuis LL, Koren G, Silverman ED, Laxer RM. Influence of food on the bioavailability of oral methotrexate in children. J Rheumatol 1995;22:1570-3.
22. Wallace CA, Sherry DD. A practical approach to avoidance of methotrexate toxicity. J Rheumatol 1995;22:1009-12.