Efficacy of folinic acid in reducing methotrexate toxicity in juvenile idiopathic arthritis

A. Ravelli¹, D. Migliavacca¹, S. Viola¹, N. Ruperto², A. Pistorio³, A. Martini¹

¹Dipartimento di Scienze Pediatriche dell’Università; ²Laboratorio di Informatica Medica; and ³Servizio di Epidemiologia Clinica e Biometria della Direzione Scientifica, Istituto di Ricovero e Cura a Carattere Scientifico Policlinico San Matteo, Pavia, Italy

Angelo Ravelli, MD; Daniela Migliavacca, MD; Stefania Viola, MD; Nicolino Ruperto, MD, MPH; Angela Pistorio, MD; Alberto Martini, MD.

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Please address correspondence and reprint requests to: Alberto Martini, MD, Clinica Pediatrica dell’Università, Istituto di Ricovero e Cura a Carattere Scientifico Policlinico San Matteo, Piazza Golgi no. 2, 27100 Pavia, Italy.

E-mail: amartini@smatteo.pv.it

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ABSTRACT

Objective
To investigate the efficacy of folinic acid in reducing the side effects associated with methotrexate (MTX) therapy in children with juvenile idiopathic arthritis (JIA) and to determine whether folate supplementation may reduce the benefit of MTX administration.

Methods
This was a retrospective, non-controlled study. Inclusion criteria were: 1) diagnosis of JIA according to the Durban 1997 criteria; 2) treatment with low to intermediate doses of MTX (10 - 20 mg/m²/week) as the sole second-line agent for at least 6 mos.; and 3) supplementation with folinic acid (2.5 - 7.5 mg) in a single weekly dose 24 hrs after MTX administration. All patients were started on folinic acid only after the development of a side effect. Exclusion criteria were: treatment with higher doses of MTX (> 20 mg/m²/week). The outcomes investigated were: hepatotoxicity (liver transaminase increase), gastrointestinal toxicity, disease flare, and clinical remission. The number of episodes per patient-year of MTX treatment of each outcome before and after folinic acid supplementation was compared by the Wilcoxon matched pairs test.

Results
A total of 43 children with JIA were included in the study. The mean duration of treatment before and after folinic acid supplementation was 1.1 years and 1.8 years, respectively. After the start of folinic acid supplementation, the mean number of episodes per patient-year of hepatotoxicity and gastrointestinal toxicity decreased from 2.30 to 0.32 (p < 0.001) and from 1.09 to 0.29 (p = 0.002), respectively. The mean number of disease flares and clinical remissions per patient-year did not change significantly.

Conclusion
In our JIA patients, folinic acid supplementation resulted in a significant reduction in the most common side effects of MTX, without affecting the clinical efficacy of the drug.

Introduction
The efficacy and safety of methotrexate (MTX) in the treatment of juvenile idiopathic arthritis (JIA) have been established in retrospective studies (reviewed in 1), in a placebo-controlled trial (2), and in clinical practice. Further evidence for the effectiveness of this drug was obtained through the demonstration that it may have a disease-modifying potential in JIA (3). Based on these data, MTX has become the therapeutic agent of choice for children with severe JIA who fail to respond adequately to the non-steroidal antiinflammatory drugs.

However, although serious toxicity is uncommon (4), mild adverse reactions occur frequently during MTX therapy and may be a source of significant discomfort or prevent many patients from obtaining benefit from the drug. Gastrointestinal symptoms and an asymptomatic elevation in hepatic transaminase levels are the most commonly observed toxic events (5).

Toxicity may be in part the result of folate deficiency, as suggested by the state of intracellular folate depletion documented in the hepatocytes and peripheral blood lymphocytes of MTX-treated patients (6). Therefore, folate supplementation has been proposed to reduce the side effects associated with MTX therapy. There has been concern, however, that folates may reduce the benefit seen with MTX if the anti-rheumatic effects of MTX are also mediated through folate antagonism. Controlled studies in adult patients with rheumatoid arthritis have indicated that supplementation with either folic or folinic acid may reduce the frequency and severity of side effects without affecting the therapeutic benefit of MTX (7, 8). A controlled trial in children with JIA has shown that the addition of folic acid does not interfere with the clinical efficacy of oral weekly MTX (9). To the best of our knowledge, the influence of folinic acid on MTX toxicity or efficacy has never been studied in JIA.

In the present study we retrospectively investigated whether the addition of folinic acid to the MTX regimen in children with JIA may lessen the frequency of adverse events or influence the clinical efficacy of the drug.
Patients and methods

Patients

We performed a retrospective review of the charts of all consecutive patients with a diagnosis of JIA according to the criteria developed by the Classification Taskforce of the Pediatric Standing Committee of the International League of Associations for Rheumatology (Durban, 1997) (10) who received low to intermediate dose MTX (10 - 20 mg/m²/week) as the sole second-line agent for at least 6 months and folinic acid supplementation. Folinic acid was given in a single weekly dose (25 - 50% of the MTX dose, corresponding to 2.5 - 7.5 mg) 24 hours after MTX dosing. Although we began to use MTX in 1986, we started to prescribe folinic acid supplementation in 1992, based on the earlier reports on the use of folates in adults with rheumatoid arthritis. Moreover, all patients were given folinic acid only after the development of a side effect. Indeed, after an adverse event had occurred, MTX was discontinued until its resolution (generally after 1 or 2 weeks) and then restarted at the same dose together with folinic acid, which was then given as chronic maintenance therapy. No patient received supplementation with folic acid. Patients treated with higher doses of MTX (>20 mg/m²/week) were excluded from this study.

Assessment of toxicity and efficacy outcomes

The effect of folinic acid on MTX toxicity was evaluated in each patient by comparing the number of episodes of hepatotoxicity and gastrointestinal toxicity before and after folinic acid supplementation. Hepatotoxicity was defined as an increase in serum liver transaminases above the normal limit, which normalised after temporary MTX discontinuation. Liver enzymes were checked monthly in all patients. Gastrointestinal toxicity was defined as the occurrence of anorexia, nausea, vomiting, diarrhoea, or abdominal complaints that were related to the MTX dosage and which diminished or disappeared thereafter. Due to the difficulties in assessing reliably the frequency of gastrointestinal symptoms in children, the data on the number of episodes of gastrointestinal toxicity in this study refer to the number of visits during which this side effect was reported.

The influence of folinic acid on the clinical efficacy of MTX was evaluated in each patient by assessing the frequency of episodes of disease flare and clinical remission before and after folinic acid supplementation. A disease flare was defined as a worsening of arthritis that required an increase in the dose of MTX and/or the initiation or increase in the dosage of prednisone therapy. Clinical remission was defined according to the following criteria: duration of morning stiffness not exceeding 15 min., no fatigue, no active arthritis for at least 2 consecutive months, and ESR < 20 mm/hour [based on the American College of Rheumatology criteria for clinical remission of adult rheumatoid arthritis (11)].

Statistical analysis

The mean number of episodes, per patient-year of MTX treatment, of hepatotoxicity, gastrointestinal toxicity, disease flare and clinical remission before and after folinic acid supplementation was compared by the Wilcoxon matched pairs test.

Results

Of the 96 patients with JIA who received MTX between 1986 and 1998, 43 fulfilled the inclusion criteria. Thirteen were boys and 30 were girls. At the beginning of MTX therapy, their ages ranged from 1.2 to 16 years and the duration of JIA from 0.5 to 8 years. The disease onset subtype was systemic in 13 patients, polyarticular in 10 patients (all rheumatoid factor negative), and oligoarticular in 20 patients (all with a polyarticular course: i.e., extended oligoarticular patients).

Table I. The number of episodes of toxicity and efficacy outcomes before and after folinic acid (FA) supplementation. The frequency of each outcome is expressed as the mean (± SD) number of episodes per patient-year of methotrexate treatment.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Before FA supplementation</th>
<th>After FA supplementation</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatotoxicity</td>
<td>2.30 ± 3.43</td>
<td>0.32 ± 0.71</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Gastrointestinal toxicity</td>
<td>1.09 ± 2.26</td>
<td>0.29 ± 0.61</td>
<td>0.002</td>
</tr>
<tr>
<td>Disease flare</td>
<td>0.30 ± 0.59</td>
<td>0.36 ± 0.79</td>
<td>ns</td>
</tr>
<tr>
<td>Clinical remission</td>
<td>0.17 ± 0.44</td>
<td>0.19 ± 0.52</td>
<td>ns</td>
</tr>
</tbody>
</table>

Discussion

The results of our retrospective analysis suggest that folinic acid supplementation reduces the frequency of MTX side effects in JIA patients without influencing the therapeutic benefit.

To our knowledge, only two studies focusing on folate supplementation in JIA patients receiving MTX have been reported. In a double-blind, placebo-controlled, crossover trial of 13 weeks duration, Hunt et al. (9) examined the effects of folic acid 1 mg/day on the efficacy of MTX to control disease activity in 19 children with JIA. With the exception of one patient who flared during the first 2 weeks while taking placebo, for the remaining 18 patients there was no statistically significant difference in disease activity indicators with folic acid treatment compared to placebo. No case of abnormal transaminase levels was observed in either the folic acid or the pla-
One advantage of folinic acid in the treatment regimen is that it requires only one administration once weekly, the day after taking MTX. This simpler regimen is more likely to lead to adherence to treatment in the child or adolescent with JIA who is already taking several other pills.

In conclusion, our findings indicate that low dose folinic acid supplementation in JIA patients is effective in lessening the most common side effects of MTX treatment, including elevated liver transaminase values. Since the frequency of liver biochemical abnormalities was recently found to be associated with the Roenigk grade and the presence of liver fibrosis (13), this suggests that folate administration be considered for all children with JIA who are receiving MTX. It remains to be established which form of folate is more cost effective as a preventive agent and whether folate supplementation should be prescribed routinely to all children taking MTX or only to those who develop side effects.

References