Efficacy of Subcutaneous Methotrexate in JIA Patients Who have Failed to Improve with Oral Methotrexate

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Abstract
Objective: To determine the efficacy of subcutaneous methotrexate in patients with juvenile idiopathic arthritis (JIA) who failed to improve with oral methotrexate according to American College of Rheumatology 30 (ACR 30) improvement criteria.

Design: Interventional Study.

Setting: Rheumatology follow up clinic, Department of paediatrics, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh, during the period from July 2006 to December 2008.

Methods: Twenty five patients who failed to improve with oral methotrexate were switched to subcutaneous methotrexate. Dose of methotrexate were same in both oral and subcutaneous route, at a dose of 10 mg/m²/week as a single dose.

Results: According to ACR 30 criteria 76% patients improved after switching over to subcutaneous route. Among the core set variables active arthritis had the highest percentage of improvement and laboratory criteria (ESR) showed lowest improvement.

Conclusion: From this study it may be concluded that subcutaneous methotrexate could be effective in patients with JIA who failed to improve with oral methotrexate.

Introduction
Methotrexate is the most commonly used disease modifying anti-rheumatic drug (DMARDs) for rheumatoid arthritis¹. However, some patients are intolerant to oral MTX despite folate supplementation and some patients do not respond adequately². The route of administration of MTX in children with juvenile idiopathic arthritis (JIA) 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 route³. Several studies reported that parenteral administration of MTX is more effective than oral⁴,⁵.

Some studies had been done for comparing the efficacy and tolerance of subcutaneous and intramuscular methotrexate. These studies found that subcutaneous route was more convenient, less painful and easier to administer than intramuscular route, though efficacy of both the routes, were similar⁶,⁷. It has been shown that while there is parenteral administration of MTX, there is 10 to 12% increased absorption compared with oral preparation⁴, ⁵, ⁸. This study was performed to evaluate whether the JIA patients who had inadequate response to oral MTX or were intolerant to oral MTX would improve after switching over to subcutaneous (S/C) route.

Materials and Methods
This was a interventional study done in the paediatric rheumatology follow up clinic, department of paediatrics, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, during the period of July 2006 to December 2008.

JIA patients who fulfilled the criteria according to International League of Association for Rheumatology (ILAR) classification⁹, attending inpatient department and Rheumatology follow up clinic run by department of paediatrics, BSMMU and treated for at least 6
months with 10 mg/m² per week oral MTX, were enrolled in the study. Patients who received steroid (oral or I/V), intra-articular steroid injection and any other disease modifying drugs in recent past were excluded from the study. Patients having renal or hepatic impairment were also not included in the study.

Informed consent was taken from the parents/attendants before enrollment of their child in the study. Prior to that they had been informed about the nature of the study. Among the total 75 juvenile idiopathic arthritis (JIA) patients on oral MTX, 50 improved by The American College of Rheumatology 30 (ACR 30) improvement criteria. Nine patients could not continue oral MTX due to toxicities like persistent nausea and vomiting. Sixteen patients did not improve with oral MTX. These two groups of patients (16+9) were included in the study (Fig – 1). Injection methotrexate was given by subcutaneous route weekly, at a dose of 10 mg/m²/week. Oral MTX and injectable MTX given to the study cases were prepared by the same company (CHOOKNGWAE pharma corporation, Seoul, Korea). Insulin syringe (1 ml = 100 unit) was used for giving S/C MTX in the cases. Site of injection was anterolateral thigh in majority of the patients and in forearm in some patients. First injections in all the patients were given by the authors. Patients or other attendants were trained the technique of S/C injection. Subsequent injections were given by them.

A questionnaire was prepared for collection of data. Data included the following variables: age, sex, disease subtypes, disease duration, response to oral MTX.

Disease activity measures were assessed at the time of enrollment as base line. Follow up of the patients were done at 4 weeks, 12 weeks and 24 weeks of S/C treatment. ACR-30 core set variables were used to assess outcome and clinical improvement. These are

1. Number of joints with active arthritis
2. Number of joints with limited range of motion
3. Physician global assessment of disease activity using visual analog scale (VAS)
4. Parents/patients global assessment of disease activity using VAS
5. Child Health Assessment Questionnaire in Bengali (CHAQ - B)
6. Erythrocyte sedimentation rate (ESR).

Response to S/C MTX was assessed by comparing the variables after 6 months of S/C MTX with the initial results during enrollment. Improvement was considered as defined by ACR 30 criteria. ACR 30 criteria defines the improvement as: at least three of the six core set variables should be improved by minimum 30% from the base line and no more than one of the remaining variables worsening by 30% or more.

**Fig 1:** Flow chart showing the process of inclusion of study population
Results
Twenty five JIA cases were given S/C MTX instead of oral MTX due to inefficacy (16) and toxicities (9). Toxicities included severe and persistent nausea and vomiting. Age group of the cases between 0 to 5 years was 0, between 5 to 10 years was 12 and between 10 to 15 was 13. Sixteen patients were male and 9 were female, male: female ratio being 2:1. Table -I shows subtypes of the JIA cases. Majority cases (52%) were polyarticular JIA.

Table – I
Subtypes of JIA cases (n = 25)

<table>
<thead>
<tr>
<th>Types of arthritis</th>
<th>Number (n)</th>
<th>Percentage(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polyarticular</td>
<td>13</td>
<td>52</td>
</tr>
<tr>
<td>Systemic onset</td>
<td>4</td>
<td>16</td>
</tr>
<tr>
<td>Oligoarticular extended</td>
<td>6</td>
<td>24</td>
</tr>
<tr>
<td>Enthesitis related</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>Total</td>
<td>25</td>
<td>100</td>
</tr>
</tbody>
</table>

It is evident from Table-II that 76% JIA cases who did not improve with oral MTX had improvement according to ACR-30 criteria after 6 months of subcutaneous MTX therapy.

Table – II
Improvement status of the patients after 24 weeks of S/C MTX who failed to oral MTX (n=25)

<table>
<thead>
<tr>
<th>Improvement status</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improved</td>
<td>19</td>
<td>76</td>
</tr>
<tr>
<td>Not Improved</td>
<td>6</td>
<td>24</td>
</tr>
<tr>
<td>Total</td>
<td>25</td>
<td>100</td>
</tr>
</tbody>
</table>

Table – III
Improvement status of different parameters according to ACR-30 criteria at 4 weeks, 12 weeks and 24 weeks from base line (n = 25)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Number (%) 4 weeks</th>
<th>12 weeks</th>
<th>24 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active arthritis</td>
<td>15 (60)</td>
<td>18 (72)</td>
<td>21 (84)</td>
</tr>
<tr>
<td>Limited range of</td>
<td>13 (52)</td>
<td>15 (60)</td>
<td>20 (80)</td>
</tr>
<tr>
<td>movement</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VAS Patients/parents</td>
<td>10 (40)</td>
<td>15 (60)</td>
<td>17 (68)</td>
</tr>
<tr>
<td>VAS Physician</td>
<td>12 (48)</td>
<td>15 (60)</td>
<td>19 (76)</td>
</tr>
<tr>
<td>CHAQ-B</td>
<td>14 (56)</td>
<td>18 (72)</td>
<td>19 (76)</td>
</tr>
<tr>
<td>ESR</td>
<td>12 (48)</td>
<td>14(56)</td>
<td>14(56)</td>
</tr>
</tbody>
</table>

Table-III shows that while improvement of different core set variables according to ACR-30 criteria were analyzed individually, improvement of active arthritis was highest (84%), limited range of motion was improved in 80%, Visual analog scale (VAS) parents/patients was improved in 68%, VAS physician was in 76%, CHAQ-B was also improved in 76% cases. Improvement of ESR was the lowest (56%).

Discussion
This study was carried out with the aim to asses the efficacy of subcutaneous administration of methotrexate in children with juvenile idiopathic arthritis who have failed to response adequately or were intolerant to oral methotrexate. As most of the oligoarticular JIA patients respond to NSAIDs and intraarticular steroid, oligoarticular persistent type were not included in this study.

At final follow up (24 weeks) it was found that 19 out of 25 patients (76%) improved according to ACR-30 improvement criteria among the study cases.

The beneficial effect of switching from oral to subcutaneous MTX in our patients who failed to oral MTX may be best explained by the increased bioavailability of SC MTX. This could also be due to the fact that there was better adherence to MTX therapy when it was given by the parenteral route. As because parenterally treated patients have less side effects12, this also could be a contributing factor for better compliance. Alsufyani et al also found similar type of improvement in their study3. They found 75% improvement in switched group who have failed to improve initially with oral MTX. Bakker et al also found similar result in their study13.

When improvement of different core set variables according to ACR-30 criteria were analyzed individually, improvement of active arthritis was highest (84%). Minimum improvement was found in the laboratory variables ESR (56%). Islam et al found similar findings in their study14. They found that 59% cases which was also lowest (Table–III). MTX toxicity was less marked in patients once switched to SC MTX.
Conclusion
It may be concluded that the efficacy of subcutaneous MTX is better than oral MTX in JIA patients according to ACR-30 improvement criteria. Patients who fail to respond adequately to oral MTX or intolerant to oral MTX due to gastrointestinal toxicities, can be treated with S/C MTX before increasing the dose or adding a second disease modifying anti-rheumatic drugs (DMARDs).

References