METHOTREXATE IN JUVENILE RHEUMATOID ARTHRITIS: RANDOMIZED, PLACEBO CONTROLLED STUDY

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Abstract:
Objectives: To evaluate, whether short-term treatment with Methotrexate (MTX) at the dose of 10 mg/m² is superior to placebo in patients with Juvenile Rheumatoid arthritis (JRA)

Patients and methods: In this double blind placebo controlled study, 31 patients who fulfilled the ACR criteria for the diagnosis of JRA were randomized to receive either weekly MTX 10mg/m² (n=16) or placebo (n=15) for 6 months. The patients were evaluated at baseline, 3 and 6 months. Measures of disease activity included, visual analog scale for pain, duration of early morning stiffness, number of swollen and tender joints, improvement in systemic features, global improvement by physician and parents, Hb and ESR. Thirty and 50% response were defined using the guideline set aside by WHO/ILAR for drug trial in patients with RA.

Results: The two groups were well matched with respect to patients and disease variables at baseline. Six patients dropped out of the study. In the MTX group, 11(78%) out of 14 achieved 30% or more response as compared to 6/11 (54%) in the placebo group at 6 months. The corresponding figures at 3 months were 10/15 (66%) and 3/11 (27%) respectively in both the groups. The differences were statistically not significant. Furthermore, there was no statistical difference between the individual disease variable values at 3 or 6 months between the two groups.

Conclusion: At the end of 6 months treatment, methotrexate at the dose of 10mg/m² is not significantly superior to placebo in JRA.

Key Word: DMARD, JIA, controlled trial

Methotrexate (MTX) is widely used for the treatment of adult patients with arthritis. Several retrospective and uncontrolled studies have shown a beneficial response to MTX in chronic arthritis of childhood at doses varying from 5-25 mg/m². However, there are only two multicentric, double blind, randomized, placebo-controlled studies showing benefit with MTX. Hence, we conducted a double blind, randomized, placebo controlled trial to assess the efficacy of MTX at the dose of 10mg/m² in patients with juvenile rheumatoid arthritis.

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Patients and methods:

Thirty-one patients with JRA fulfilling ACR criteria and seen between Jan 1997 through June 1998 were included in the study. Patients were enrolled into the study if they had at least four active joints or systemic disease, which did not respond to 6 weeks of non-steroidal anti-inflammatory drugs (NSAID) and/or corticosteroids. Those who had received any disease modifying antirheumatoid drug (DMARD) in the previous three months, or were having infections, renal or hepatic derangement were excluded from the study. After obtaining informed consent from the patient/parent, the patients were randomized in two groups, one received weekly MTX at the dose of 10 mg /m² and
the other received placebo. Both the tablets (placebo and MTX) were identical in appearance and were packed similarly. Both groups received NSAIDs and if required corticosteroids at a dose of 0.5mg/kg/day. The study was approved by the institutional ethics committee.

**Outcome measures:**

The patients were assessed by the same physician (AB), who was blinded to the drug patients the were receiving. They were assessed at baseline, 3 and 6 months. Measurements of disease activity included pain by visual analog scale, duration of early morning stiffness, number of tender and swollen joints, Steinbrocker's functional grade, systemic symptoms (fever, rash, lymphadenopathy, hepatosplenomegaly), global improvement by parent and physician. Laboratory parameters included hemoglobin and erythrocyte sedimentation rate. Additionally, to monitor side effects of drug total leukocyte count, platelet count, serum transaminase levels, urea and creatinine were assayed at each visit. X-rays of the affected joints and chest were done at baseline. The chest X-Ray was repeated at the end of the study period to specifically look for reactivation of pulmonary tuberculosis.

**Definitions of response:**

The modified WHO/ILAR criteria for assessment of response in cases of rheumatoid arthritis were used. The response was graded as: nil (<30%), ≥30% or ≥50% response. The percentage improvement in pain, morning stiffness, number of tender and swollen joints, hemoglobin and erythrocyte sedimentation rate were calculated as:

\[
\text{Value at 3 or 6 months/Value at baseline} \times 100.
\]

**Statistical analysis:**

Chi square test for proportions was used to compare the difference in response rate between the drug and the placebo and the Man Whitney U test was applied for individual disease variables.

**Results:**

Twenty-five out of the 31 patients completed the study, 14 in the MTX group and 11 in the placebo group. Two and 4 patients dropped out from the MTX and placebo group respectively. Out of these 6, one patient of MTX group inadvertently took 24 tablets. She was treated immediately with supportive management and leucovorin rescue with complete recovery. The patient opted out of study. In the rest, the reasons for drop outs were not known. Both the groups were well matched as respect to patients and disease activity variables (Table I).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Methotrexate</th>
<th>Placebo</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>14</td>
<td>11</td>
<td>25</td>
</tr>
<tr>
<td>Age (Range in yr)</td>
<td>3-18</td>
<td>2-22</td>
<td>2-22</td>
</tr>
<tr>
<td>Female/Male</td>
<td>5/9</td>
<td>5/6</td>
<td>10/15</td>
</tr>
<tr>
<td>Onset: Oligoarthritis</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Polyarthritis</td>
<td>9</td>
<td>7</td>
<td>16</td>
</tr>
<tr>
<td>Systemic</td>
<td>3</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Deformities</td>
<td>2</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Duration of disease (yr)</td>
<td>0.5-7</td>
<td>0.5-9</td>
<td>0.5-9</td>
</tr>
<tr>
<td>Corticosteroid usage (No)</td>
<td>8</td>
<td>3</td>
<td>11</td>
</tr>
<tr>
<td>Previous DMARD usage (No)</td>
<td>3</td>
<td>2</td>
<td>5</td>
</tr>
</tbody>
</table>

At the end of 6 months 11 out of 14 children receiving MTX (78%) showed a response (10>50%, 1>30%) as compared to 6 out of 11 (55%) in the placebo group (4>50%, 2>30%). The corresponding figures at the end of 3 months were 10/15 (66%) and 3/11 (27%) for MTX and placebo group respectively. Although a trend towards better response with MTX was present but it did not reach statistical significance (Fig I).
Furthermore, there were no significant difference in the change in individual parameters studied i.e. pain score, early morning stiffness, global improvement, number of tender and swollen joints, Hb and ESR at 3 months and 6 months between MTX and placebo groups (Fig II).

Side effects included nausea/vomiting in 2, anemia, elevation of transaminases and lymphadenopathy in 1 each. In 3 of these patient’s drug had to be temporarily withdrawn for a period of 1-2 weeks.

Discussions:

This double blind placebo controlled study failed to show that MTX is superior to placebo in the treatment of children with JRA at the dose of 10mg/m²/week. The response rate with MTX of 78% is similar to that seen in previous studies. There are several factors that could have influenced our results; dose of MTX, placebo response rate and small sample size. Previous studies have used a dose ranging from 5⁶ to 25¹¹ mg/m²/wk. We used 10mg/m² dose of MTX in our study as that was shown to be beneficial in a placebo controlled study. The result of our study did not show any beneficial effect of MTX at 10mg/m².

Figure I: Bar showing % of patients who achieved ≥30 % response at 3 and 6 months. None of these differences were statistically significant.

Figure II: Line diagram showing median % change from baseline in different disease activity variables in Mtx group [___] and placebo group [— —] in (a) duration of morning stiffness b) Pain of visual analogue scale c) global improvement (patients) d) number of swollen joints e) number of tender joints f) hemoglobin. As shown in all these parameters there is a trend towards better response in MTX group,
However, closer look at this multicenter study revealed that patients with severe articular disease, who are usually candidates for DMARD, did not show any significant difference between placebo (58%), MTX - 5mg/m²/week (77%) and MTX 10mg/m²/week (68%). Thus it seems that a dose higher than 10 mg/week is needed in severe disease. Indeed, beneficial results with MTX at 15mg/m²/week have been reported in selected patients with extended oligoarticular disease.

High placebo response of 27% (3/11) at 3 months and 55% (6/11) at 6 months also makes it difficult to assess any beneficial effect of MTX, despite the fact that 78% of our patients achieved more than 30% response. Similar observations have been found in placebo controlled studies with hydroxychloroquine, D-penicillamine and Auranofin. This high placebo response is partly related to continued NSIADs use.

Heterogeneity of JRA is itself a confounding variable, with different subsets having different outcome and response to different drugs. In a recent study MTX was found to be beneficial only in patients with extended oligoarticular disease and not in systemic onset disease.

The duration of the study is also critical. The response to MTX starts at 3 months but full response is seen after a variable period of 5-30 months. The initial benefit with MTX is due to its anti-inflammatory effect whereas late benefit is due to its immunomodulatory actions. Thus it is possible that a longer duration of follow-up i.e. one year may show benefit with MTX.

Last, but not the least is the sample size. A larger sample size is needed especially in a disease with high placebo response. JRA is a rare disease, and thus it is difficult to get large number of patients from one center.

Our study also reaffirms that MTX is safe in children. Weekly administration of MTX at low dose has been associated with many reversible but few permanent side effects. Thus regular monitoring is recommended to detect subclinical reversible toxicity.

MTX has become a widely accepted first choice DMARD in JRA. However, this is mainly based on open studies. Even the Cochrane review could find only 2 studies with 165 patients which fulfilled the criteria and they showed only a minor benefit of 3-23% in different patient centered outcomes. Time is ripe for large, multi-centric randomized, double blind placebo controlled studies to get definite answers regarding optimum dose and duration of MTX treatment in different subsets of patients with JRA.

References:


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