LOW DOSE METHOTREXATE IN SERONEGATIVE SPONDYLOARTROPATHY: RESULT OF A DOUBLE BLIND, PLACEBO CONTROLLED TRIAL

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Abstract:
Objective: To evaluate the efficacy of methotrexate in patients with seronegative spondyloarthropathy (SSA) in a prospective, randomized, double-blind, placebo-controlled trial.

Patients and Methods: 36 patients with SSA who fulfilled the European Spondyloarthropathy Study Group criteria were randomized to receive either weekly oral Methotrexate (MTX) 7.5 mg/week or placebo. Disease activity parameters were measured at baseline 2, 4 and 6 months. Primary outcome variables included, physician’s assessment of disease activity, patient assessment of assessment of disease activity, duration of early morning stiffness, pain on a visual analog scale, and tender and swollen joint counts. Other measures were modified-Schober’s tests, chest expansion, enthesitis site counts, erythrocyte sedimentation rate (ESR) and average daily Indomethacin (NSAID) dose.

Results: 50% of patients in both the groups of 18 patients each showed an over-all improvement. There was a significant reduction in the dose of NSAID required for pain relief in the MTX group (p<0.05).

Conclusion: Methotrexate at 7.5 mg weekly oral dose is ineffective as a slow acting, anti-rheumatic drug (SAARD) in SSA except that it reduced the NSAID requirement. It has an NSAID sparing effect.

Key words: Ankylosing spondylitis, Reactive arthritis, Undifferentiated spondyloarthropathy.
both groups were allowed to take Indomethacin as required, with maximum upto 150mg/day and to report the average daily dose of their previous 2 months intake (based on pill-counts).

Clinical assessment:

Disease activity variables were measured at baseline and then at 2, 4 and 6 months. These variables included: early morning stiffness (EMS) in minutes, assessment of pain on a visual analog scale (VAS from 0 to 10), chest expansion in cms, modified Schober’s test in cms, number of tender joints, number of swollen joints, enthesitis sites, patients assessment of disease activity on a scale of 1-5, physicians assessments of disease on a scale of 1-5 (none=1, mild=2, moderate=3, severe=4, very severe=5), global improvement as assessed by the patient (expressed as percentage improvement in the overall disease status by comparing with the baseline), and average daily dose of Indomethacin as reported by the patient, based on his/her pill count for the previous 2 months.

Laboratory assessment:

Investigations were performed at baseline and then at 2, 4 and 6 months. These were complete blood count urinalysis, ESR (Westergren) and liver and renal function tests.

Radiological assessment:

A prone view of the sacroiliac and the hip joints and a PA radiograph of the chest were done at the time of inclusion in the study. Radiological sacroilitis was considered when there were grade II changes or above.

Statistical methods:

The analysis was based on intent-to-treat principle. We used the 2, 4 and 6 months visit for each randomized patient and compared the data collected at each visit (at 2, 4 & 6 months) with those from baseline visit. All variables from the 2, 4 and 6 months visits were expressed as % change from the baseline (except the enthesitis-indices and the swollen and tender joints scores, which were expressed as numbers). Median test was used for comparing the two groups and p<0.05 was considered significant.

Improvements in the individual, primary outcome measures were defined as follows: (a) patient’s assessment of disease activity on a 1-5 scale (improvement if there was a decrease of atleast one unit, (b) physician’s assessment of disease activity on a 1-5 scale – improvement if there was a decrease of atleast one unit, (c) 30% decrease in the duration of early morning stiffness, (d) 30% decrease in erythrocyte sedimentation rate (e) 30% improvement in the number of swollen joints, (f) 30% improvement in tender joints.

Treatment responders in the AS subgroup were defined as the total numbers of A.S. patients with improvements in either a or b and (in italics) either c or d. Treatment responders in the ReA & UspA subgroups were defined as the total number of patents with ReA or UspA with improvements in either criteria a or b and either e or f.

Results:

Thirty-six patients (35 males and one female) were enrolled in the study. There were 18 patients in each group. The median age of the patients was 30 years and 27 years in the MTX and the placebo group respectively. The median duration of illness in both the groups was 7 years. Radiological sacroilitis was detected in all patients.

The clinical characteristics and disease variables were matched in both the groups, excepting the tender joint score, which was significantly more in the MTX group (Table 1). Four patients from the drug group and
3 patients from the placebo group dropped out of the study due to clinical deterioration. Thus only 14 patients from the drug and 15 patients from the placebo group (total patients-29) completed the study. The median % change at 2, 4 and 6 months evaluation revealed significant differences only in the average daily dose of Indomethacin (Figure). There was no significant difference between the two groups for the following variables: EMS, Pain on the VAS, the physician’s assessment of disease activity (Scale of 1-5), patient’s global assessment & patients assessment of disease on a 1-5 scale and the ESR (Figure). The median number of tender joints decreased from 3 to 0 and the swollen joints reduced from 1 to 0 at the end of 6 months in MTX group. In the placebo group the median value of tender and swollen joints was 0 at entry and there was no change at 6 months. There was no change in the median value of chest expansion in cms, enthesitis site counts and Schober’s test in cms.

Nine (50%) patients from both the groups responded to the medications, as determined by the num-

**Table 1: Baseline characteristics of patients of Spondyloarthropathy**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Methotrexate (18)</th>
<th>Placebo (18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modified Schober’s test (cms)</td>
<td>Median (Range) 5.2 (2-6.5)</td>
<td>Median (Range) 4.5 (0.6-5.5)</td>
</tr>
<tr>
<td>Chest expansion (cms)</td>
<td>5 (2-6.5)</td>
<td>5 (5-6.8)</td>
</tr>
<tr>
<td>Early morning stiffness</td>
<td>100 (30-200)</td>
<td>120 (60-240)</td>
</tr>
<tr>
<td>Pain on VAS (1-10)</td>
<td>6 (2-10)</td>
<td>6 (6-10)</td>
</tr>
<tr>
<td>No of tender joints</td>
<td>3 (0-8)</td>
<td>0 (0-12)</td>
</tr>
<tr>
<td>No of swollen joints</td>
<td>1 (0-2)</td>
<td>0 (0-10)</td>
</tr>
<tr>
<td>No of enthesitis sites</td>
<td>1 (0-5)</td>
<td>0 (0-10)</td>
</tr>
<tr>
<td>Assessment of disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(on a scale of 1-5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Score by patient</td>
<td>4 (2-5)</td>
<td>4 (3-5)</td>
</tr>
<tr>
<td>Score by physician</td>
<td>3 (2-4)</td>
<td>3 (1-4)</td>
</tr>
<tr>
<td>ESR (mm/hr)</td>
<td>51 (37-110)</td>
<td>54 (39-80)</td>
</tr>
</tbody>
</table>

* P=0.007; in all other variables, p=not significant

Figure: Line diagram showing median % change from baseline in different disease activity variables (a) early morning stiffness (b) pain on visual analogues scale (c) physician’s assessment of disease on a scale of 1-5 (d) patients’ global assessment (e) ESR (f) Average daily dose of NSAID. There was a significant (p=0.05) reduction in the average dose of NSAIDs in the Methotrexate group.
ber of patients responding in each of the primary outcome variables (Table-2).

Table 2: The number of patients responding in the individual primary outcome variables (end point analysis)

<table>
<thead>
<tr>
<th>Primary outcome variables</th>
<th>Methotrexate (18)</th>
<th>Placebo (18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient’s assessment of disease</td>
<td>Number</td>
<td>Number</td>
</tr>
<tr>
<td>Physician’s assessment of disease</td>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>Pain on visual analog scale</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Early morning stiffness</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>Tender joints</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Swollen joints</td>
<td>5</td>
<td>3</td>
</tr>
</tbody>
</table>

The number of treatment responders by a composite score of primary outcome measures is 9 (50%) patients in both the groups. There is no statistically significant difference in any of the primary outcome variables between the two groups.

Discussion:

This is the only randomized placebo-controlled double blind drug trial evaluating the role of MTX in SSA. We report absence of clinical benefit in most of the disease activity measures except a reduction in the average daily dose of Indomethacin (NSAID). Overall, MTX was not superior to placebo as 50% of patients from both groups were deemed responders.

Two open trials6-7, one comprising 11 and the other 10 patients also reported that MTX reduces NSAID requirement. In the former trial6, 4/9 available patients at the end of 24 months were either able to reduce or stop NSAIDs. Since our’s is a placebo-controlled study, it can be stated more convincingly that MTX reduces NSAID requirement in this subset of patients.

The other reason for the lack of difference in placebo and MTX group is the presence of a high placebo response of (50%). Previous placebo controlled studies in SSA have reported NSAID response between 44%-48%9-10. Thus for detection of a significant difference, larger numbers of patients are required, highlighting need for multi center trials.

Another variable is the dose of MTX used. In the 2 open trials mentioned above6-7 a higher/escalating dose of MTX in a dose range from 7.5 to 12.5 mg/week has been used. Furthermore, the intramuscular route, which is associated with a higher bioavailability, was used in one study. As in rheumatoid arthritis, dose escalation of MTX in partial/non-responders results in a better response; the same may hold true for its use in SSA.

However, in AS the measures of disease activity are perhaps inadequate or less sensitive to detect improvements in a short term study like ours. The longer duration of disease may have further negated any beneficial effects of MTX.

To conclude, MTX at 7.5 mg/week reduced the need for NSAIDs in SSA but did not have any other benefit over placebo. Its disease modifying potential needs to be assessed in a large multi-centric trial, with use of escalating dose of MTX, use of sensitive and previously validated parameters of disease activity and longer follow up.

References:

5. Low dose Methotrexate in seronegative Spondyloarthropathy: result of a double blind, placebo controlled trial.


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<tr>
<td>IAP Rheumatology Chapter members</td>
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<tr>
<td>Others</td>
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