Efficacy & Tolerance of Low Dose Methotrexate in Rheumatoid Arthritis

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Introduction

• COPCORD study observed prevalence of rheumatological disorders in Bangladesh

• Prevalence of RA is 0.397%

• So an estimated 5,16,100 people are affected with RA in Bangladesh
Hypothesis

• Low dose MTX (7.5mg/wk) is an effective & safe DMARD for Bangladeshi RA patient population
Why Methotrexate?

• Low cost
• Easy to administer
• Compliance is better
• Early clinical response
• Retards progression of radiographic erosions
• Gold standard in treatment of RA
## Comparison of price of different DMARDs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Unit price (Taka)</th>
<th>Monthly cost of drug (Taka)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methotrexate 2.5mg</td>
<td>7.5 - 15 mg wkly</td>
<td>4</td>
<td>48 (7.5mg/ wk)</td>
</tr>
<tr>
<td>Leflunomide</td>
<td>20 mg daily</td>
<td>5</td>
<td>150</td>
</tr>
<tr>
<td>Sulphasalazine 500mg</td>
<td>1 g BID</td>
<td>5</td>
<td>600</td>
</tr>
<tr>
<td>Azathioprin 50mg</td>
<td>50 mg BID</td>
<td>8</td>
<td>480</td>
</tr>
<tr>
<td>Hydroxychloroquine 200mg</td>
<td>400 mg daily</td>
<td>25</td>
<td>1500</td>
</tr>
<tr>
<td>Oral gold</td>
<td>3 mg BID</td>
<td></td>
<td>Not readily available in market</td>
</tr>
<tr>
<td>Gold (inj)</td>
<td>50 mg IM wly</td>
<td></td>
<td>Not readily available in market</td>
</tr>
<tr>
<td>Penicillamine 250mg</td>
<td>250 mg daily</td>
<td>11</td>
<td>330</td>
</tr>
</tbody>
</table>
Objectives

- Quantify **efficacy** of MTX in low dose
- Observe **intolerance** to MTX in low dose
Materials & Methods

The place & Time

– Rheumatology Clinic, Shaheed Suhrawardy Hospital, Dhaka

– From October 2001 to April 2003
Patients included

– Suffering from active RA

– Age 16-65 yrs

– Consented to take part
Randomization

- Computer generated randomization chart in blocks of 4
- Envelopes containing drug or placebo arranged in sequence
- Serial number of the envelope corresponded to the order of enrollment
- Allocation took place immediately after confirmation of enrollment
Methods

– Double blind randomized placebo controlled study

– IG received
  • MTX, 7.5 mg/ wk

– CG received
  • Placebo

– Both groups also received
  • Indomethacin 75 mg/ day
  • Omeprazole 20 mg/ pantoprazole 40 mg daily
  • Folic acid 5 mg/ wk

– Each pt was evaluated monthly for six months
Outcome Measures

Efficacy

- TJC (tender joint count)
- SJC (swollen joint count)
- MS (morning stiffness in minutes)
- VAS (visual analogue scale of pain)
- PGA (physicians global assessment)
- HAQ DI (disability index of health assessment questionnaire)
- ESR (erythrocyte sedimentation rate)
- ACR 20 (American College of Rheumatology Response Criteria)
Tolerance

*Clinical*:

- Nausea
- Vomiting
- Diarrhea
- Cough
- Sore throat
- Lymphadenopathy

*Laboratory*:

- Total counts of WBC & platelet
- Hemoglobin
- Alanine aminotransferase
- Serum creatinine
Results

• 132 subjects enrolled
• 99 pts visited at least twice
• 7 visits completed by 43 pts – 22 in IG & 21 in CG
• Baseline characteristics of 2 groups were similar
• Disease activity significantly ↓ at 6 mo in both groups
• Reduction of activity more prominent in IG
• Significant number of pts in IG achieved ACR20 criteria
Randomized: 132 pts

IG: 66

Lost to follow-up ≤2 visits: 28

Lost to follow-up ≥3 visits: 09

Lost to follow-up ≤2 visits: 33

Lost to follow-up ≥3 visits: 08

Excluded: 04

Excluded: 07

Final analysis: 22

CG: 66

Final analysis: 21
Withdrawal & Why

• 7 pts were withdrawn from the IG
  – 5 pts - intolerance to MTX (GI complaints)
  – 1 pt - viral hepatitis
  – 1 pt - TB lymphadenopathy

• 4 pts withdrawn from CG
  – 3 due to increased disease activity & put on steroid & MTX
  – 1 due to change of diagnosis
MTX Intolerance 17%
TBL 3%
VH 3%
Included 77%
Included 84%
Put on MTX & Steroid 12%
Diagnosis Changed 4%
Included 84%
Mean TJC in 7 visits

IG

CG
Mean SJC in 7 visits

IG

Mean

no of swollen joints

NSJ 1
NSJ 2
NSJ 3
NSJ 4
NSJ 5
NSJ 6

CG

Mean

no of swollen joints

NSJ 1
NSJ 2
NSJ 3
NSJ 4
NSJ 5
NSJ 6
Mean MS in 7 visits
Mean ESR in 7 visits

IG

CG
Mean VAS of Pain of 7 Visits

IG

CG
Mean PGA in 7 Visits

![Graph showing the mean PGA in 7 visits for IG and CG groups.](image)
How much Effective?

• Efficacy was quantified by measuring ACR20 achievement

• ACR 20 indicate 20% decrease in:
  – TJC
  – SJC
  – 3 of 5: PGA, Disability, VAS, ESR, PtsGA
### ACR20 Criteria Fulfillment in Both Groups

<table>
<thead>
<tr>
<th>ACR Criteria</th>
<th>No ACR</th>
<th>Count</th>
<th>Expected Count</th>
<th>% of Total</th>
<th>placebo</th>
<th>methotrexate</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACR20</td>
<td>Count</td>
<td>18</td>
<td>13.7</td>
<td>41.9%</td>
<td>10</td>
<td>14.3</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>28.0</td>
</tr>
<tr>
<td>Total</td>
<td>Count</td>
<td>21</td>
<td>21.0</td>
<td>48.8%</td>
<td>22</td>
<td>22.0</td>
<td>43</td>
</tr>
</tbody>
</table>

Pearson Chi-Square: 7.66  df=1  $P=0.006$
## Comparison of Intolerance to MTX

<table>
<thead>
<tr>
<th></th>
<th>placebo</th>
<th>methotrexate</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Count</td>
<td>Expected Count</td>
<td>% of Total</td>
</tr>
<tr>
<td>Intolerant</td>
<td>0</td>
<td>2.2</td>
<td>.0%</td>
</tr>
<tr>
<td>Tolerant</td>
<td>21</td>
<td>18.8</td>
<td>43.8%</td>
</tr>
<tr>
<td>Total</td>
<td>21</td>
<td>21.0</td>
<td>43.8%</td>
</tr>
</tbody>
</table>

Pearson Chi-Square: 4.3  df=1  \( P=0.037 \)
Limitations

• Small sample size
• Drop out rate was high
• Pts global assessment was not done
• No provision for increasing dose of MTX
• Quantification of radiological changes not done
Conclusion

• MTX is effective in RA even at low dose

• Some pts may need to stop the drug due to adverse effect

• No serious biological adverse events

• It is reasonably well tolerated at a dose of 7.5 mg weekly
Thank You