Early Hepatotoxicity of Methotrexate in Rheumatoid Arthritis

M Shakila Parvin¹, Mamun Ur Rashid², A R M Saifuddin Ekram³, H Ara Begum⁴

Abstract

The present study was undertaken to evaluate methotrexate induced early hepatotoxicity in rheumatoid arthritis patients. This study was carried out on ARA criteria fulfilling 35 diagnosed rheumatoid arthritis patients of either gender, aged 20-60 years, presented in Medicine Department of Rajshahi Medical College Hospital, Rajshahi from July 2007 to June 2008. Patients with normal liver function tests and HBsAg and anti-HCV negative cases were given oral Methotrexate (10-25mg/week) for 3 months. Baseline level of SGPT, serum bilirubin and prothrombin time was 10.07 ± 0.32 u/l, 0.59 ± 0.03 mg/dl and 12.97 ± 0.34 seconds respectively. After 3 months of methotrexate therapy, level of SGPT, serum bilirubin and prothrombin time was found to be 12.60 ± 1.16 u/l, 0.70 ± 0.06 mg/dl and 13.87 ± 0.45 seconds respectively. During methotrexate therapy SGPT level changed significantly (p<0.05). Change of serum bilirubin and prothrombin time was not significant.

Introduction

Rheumatoid Arthritis is a chronic multi system disease, seen throughout the world and affects all races¹. The characteristic feature of rheumatoid arthritis is persistent inflammatory synovitis, usually involving the peripheral joints in a symmetric distribution². Rheumatoid Arthritis is a common inflammatory articular disease³. It affects nearly 1% of the adult population worldwide⁴. It can lead to long-term joint damage resulting in pain, loss of function and disability.

Rheumatoid Arthritis is not a fully curable disease. However, many different types of treatment can be used to alleviate symptoms. Pharmacological therapy of rheumatoid arthritis can be divided into DMARDs, analgesics and anti-inflammatory drugs, glucocorticoids, TNF-α blockers and interleukin-1 blocker. DMARDs treatment should be introduced as early as possible in the course of the disease to suppress disease activity and thereby provide the possibility of avoiding joint damage and disability. Among DMARDs methotrexate are most widely used worldwide⁵.

Methotrexate as DMARDs has been found to produce durable remissions and delay or halt disease progression⁶. They have both anti-inflammatory and immunosuppressive action⁷. They interrupt inflammation of joints by the cells of immune system that signal to one another and are thought to set up self-perpetuating chronic inflammation. They also depress cytokine production and cellular immunity. Analgesic and anti-inflammatory drugs improve pain and
stiffness but do not prevent joint damage or slow the disease progression that methotrexate does.

Department of Medicine, Duke University Medical Center, Durham, Carolina did a study from 1979 to 1988. They showed that the prevalence of methotrexate producing hepatotoxicity was low. Joel M Kremer showed from a continuous review of over 375 journals and other resources (2007) that methotrexate causes hepatotoxicity after a cumulative dose for malignant disease but the incidence was low in rheumatoid arthritis and psoriasis. Rau R and Herborn G (2004) reviewed 216 literatures on the efficacy and toxicity of low dose weekly methotrexate treatment in rheumatoid arthritis and stated that methotrexate proved to be very effective, had a relatively rapid onset of action and was well tolerated in most cases.

Among DMARDs physicians in our country commonly use methotrexate. But so far I know, study on methotrexate induced hepatotoxicity has not yet been studied in our country context. So it is thought worthwhile to evaluate methotrexate induced hepatotoxicity in rheumatoid arthritis patients.

Objectives
Objectives of present study were to determine safety, adverse effects and efficacy of methotrexate in treatment of rheumatoid arthritis patients.

Materials and Methods
This prospective study was carried out in the Department of Pharmacology in collaboration with Medicine Department of Rajshahi Medical College Hospital, Rajshahi from July 2007 to June 2008. Rheumatoid arthritis patients fulfilling the criteria of American Rheumatism Association (ARA) were selected from medicine department of Rajshahi Medical College Hospital. A total number of 35 patients of either gender, aged 20-60 years were selected for the study. Icteric or liver damaged patients, severely debilitated and complicated patients were not included in the study. After taking informed consent, complete history, physical examination were done and recorded in a preformed data sheet. 5 ml blood was taken and liver function tests such as SGPT, serum bilirubin and prothrombin time was done. Patients with normal liver function tests and HBsAg and anti-HCV negative cases were given oral methotrexate (dose ~10-25mg/week) for 3 months. After 3 months patients were assessed to observe clinical improvement and blood samples were taken again and same liver function tests were done and compared to control. During this procedure 5 patients were dropped out.

Results
Out of 30 patients 12 were male and 18 were female with a male: female 2:3 (Fig. 1). Mean age of the study population was 36.70±8.95 years (Table-I). Occupational distribution reveals most of the patients (40%) were housewife followed by farmer (30%), service holder (20%) and businessmen (10%) (Fig. 2).

After getting methotrexate therapy for 3 months, most of the patients (80%) showed marked improvement in symptoms (Fig. 3). Results of liver function tests were analyzed and it revealed significant change was observed in level of SGPT after three months of methotrexate therapy but no significant changes observed in serum bilirubin and prothrombin time (Table-II, Fig. 4).

![Fig. 1: Sex distribution of the patients (n=30).](image)

**Table-I: Age distribution of the patients (n = 30)**

<table>
<thead>
<tr>
<th>Age Range/Interval</th>
<th>Number of Patients</th>
<th>Age (Mean±SD in years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-30</td>
<td>6</td>
<td>36.70±8.95</td>
</tr>
<tr>
<td>31-40</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>41-50</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>51-60</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>
Fig. 2: Occupational distribution of the patients (n=30).

Fig. 3. Percentage of clinical improvement of the patients (n=30).

Table- II: Result of Liver Function Tests

<table>
<thead>
<tr>
<th>Liver function tests (N=30)</th>
<th>Before Methotrexate Therapy Mean ±SEM</th>
<th>After Methotrexate therapy Mean ± SEM</th>
<th>t value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SGPT</td>
<td>10.07±0.32 U/L</td>
<td>12.60±1.16 U/L</td>
<td>2.25</td>
<td>*&lt; 0.05</td>
</tr>
<tr>
<td>Serum Bilirubin</td>
<td>0.59±0.03 mg/dl</td>
<td>0.70±0.06 mg/dl</td>
<td>1.85</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Prothrombin time</td>
<td>12.97±0.34 sec</td>
<td>13.87±0.45 Sec</td>
<td>1.7</td>
<td>&gt; 0.05</td>
</tr>
</tbody>
</table>

* Indicates significant

Fig. 4: Mean level of SGPT before and after 3 months of methotrexate therapy and percentage of increases after therapy.

**Discussion**

Marked (>50% joint symptoms improvements) improvement of joint symptoms occurred in 80% patients. Some researchers observed the beneficial effects of methotrexate. Weinblatt ME et al., (1998) showed marked improvement occurred more than 50% patients. Improvement of 69% patients occurred in another study. Our study is in well agreement with those studies.

Several studies showed female were more affected than male. In this study female are also affected more than male which is also in agreement with the studies mentioned above. The peak incidence of rheumatoid arthritis is in third and fifth decades of life. In the present study mean age of the patients was 36.7 years which was in well agreement with above study. In present study, only occupational distribution of patients was revealed but difference of methotrexate effects was not studied.

Significant change was observed in level of SGPT after three months of methotrexate therapy. Similar observations on SGPT were made by number of researchers. Taqween MA (2005) demonstrated SGPT was elevated during follow up. Among SGPT elevated patients all patients remained stable with methotrexate treatment. Weinblatt ME (1985) showed slight elevations in liver enzyme in 48% of patients. Transient slight elevations in liver enzymes up to 53% patients were found in a more recent study. In present study elevations in liver enzymes up to 50% patients were found which is also in agreement with the studies mentioned above. The slight
differences may be due to differences in patient dosing and concurrent use of other drugs.

Bathon JM et al. (2001) showed methotrexate increases serum aminotransferases up to 32 percent\textsuperscript{16}. Several studies showed these elevated levels returned to normal after dose reduction, a change in the concurrent NSAID therapy, folic acid supplementation or even the unchanged continuation of treatment\textsuperscript{17,11}. In our study methotrexate increases level of SGPT up to 25 percent that is in agreement with Bathon JM et al. study.

No significant changes observed in serum bilirubin in this study. Taqween MA (2005) showed serum bilirubin remained unaltered during methotrexate therapy\textsuperscript{13}. Observations of present study about serum bilirubin are in well agreement with this study.

In present study no significant changes observed in prothrombin time during methotrexate therapy. We did not exclude exposure to coumarin drugs and vitamin k deficiency that may increase prothombin time\textsuperscript{19}. From observations from this study we can assume that methotrexate does not alter the synthetic function of liver.

**Conclusion**

From the results it can be concluded that methotrexate therapy could produce mild hepatocellular damage but not an alarming severe hepatotoxicity. Hence methotrexate can be useful as DMARDs in treatment of rheumatoid arthritis with close monitoring especially periodic determination of SGPT that becomes normal after stoppage of therapy. Further study on large population in this aspect may clarify therapeutic exploration.

**References**


All correspondence to:
M Shakila Parvin
Assistant Professor
Department of Pharmacology
Islami Bank Medical College
Rajshahi.