COMPARISON OF THE THERAPEUTIC EFFICACY BETWEEN METHOTREXATE BASED DUAL & TRIPLE THERAPY IN RHEUMATOID ARTHRITIS

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**Abstract**

**BACKGROUND:** Rheumatoid arthritis (RA) is a systemic chronic inflammatory disease that mainly affects the synovial joints. Historically, RA has been treated using a multitiered pyramid strategy, beginning with symptom-relieving nonsteroidal anti-inflammatory drugs and/or corticosteroids, and subsequently with more potent disease-modifying antirheumatic drugs (DMARDs), such as methotrexate (MTX), sulphasalazine, hydroxychloroquine, leflunomide.

**AIMS:** 1.Comparison of the therapeutic efficacy between methotrexate based dual & triple therapy in Rheumatoid Arthritis. 2.To study the Methotrexate, Sulphasalazine, Hydroxychloroquine, in Rheumatoid Arthritis

**MATERIAL AND METHODS:** The present study was conducted in 60 consecutive RA patients, who attended Out Patient Department or were admitted in the department of Internal Medicine at R.G.Kar Medical College and Hospital, Kolkata, West Bengal, India. Group A consists of 30 patients receiving Methotrexate and sulphasalazine. Group B consists of 30 patients receiving MTX, Sulphasalazine, Hydroxychloroquin.

**RESULTS:** In group-A, 21(70.0%) patients had female and 9(30.0%) patients had male. In group-B, 18(60.0%) patients had female and 12(40.0%) patients had male.

In group-A, the mean age (mean± s.d.) of patients was 48.6000 ± 11.2145 years. In group-B, the mean age (mean± s.d.) of patients was 48.4667 ± 10.3881 years.

We found that, the mean DAS 28 baseline (mean± s.d.) were 5.4667 ±1.3322, 5.6000 ± 1.3287 in group A, B respectively. Difference of mean DAS 28 baseline vs. group was not statistically significant (p=0.6993). The mean DAS 28 6 months follow-up (mean± s.d.) were 3.9333 ± .9072, 3.2667 ± .9444 in group A,B respectively. Difference of mean DAS 28 6 months follow-up vs. group was statistically significant (p=0.0072). The mean DAS 28 12 months follow-up (mean± s.d.) were 2.6667 ± .6065, 2.2000 ± .7144 in group A,B respectively.. Difference of mean DAS 28 12 months follow-up vs. group was statistically significant (p=0.0084).

**CONCLUSIONS:** We found that CRP, RA, DAS-28 score, Anti-CCP and ESR levels were more decreased in triple therapy during follow-up period. In Rheumatoid arthritis patients with Methotrexate based dual therapy vs triple therapy, the latter was found to be significantly more durable.

**KEY WORDS:** RA (Rheumatoid arthritis), MTX (Methotrexate), DMRD (Disease modifying anti rheumatic drug), DAS (Disease activity score), CRP (C reactive protein), Anti CCP (anti-Cyclic Citrullinated Peptide), ESR (erythrocyte sedimentation rate)
Introduction:
Rheumatoid arthritis (RA) is a systemic chronic inflammatory disease that mainly affects the synovial joints. The disease has a worldwide prevalence of 1% and affects women and men disproportionately (2:1, respectively). RA commonly affects people between the ages of 40 and 70 years, with incidence of the disease increasing with age. The signs and symptoms and clinical course of RA can be extremely variable, ranging from mild, self-limiting arthritis to rapidly progressive disease that is associated with significant physical and psychosocial morbidity and premature mortality. Joint destruction from synovitis can occur rapidly and early in the course of the disease. Erosion of the joints can be detected by magnetic resonance imaging as early as 4 months of symptom onset, and as many as 93% of patients will sustain radiographic damage within 2 years if left untreated. Within 5–10 years of being diagnosed, one in two people with RA will be unable to work, and the remainder will have functional disability resulting in reduced earning capacity. Historically, RA has been treated using a multitiered strategy, beginning with symptom-relieving nonsteroidal anti-inflammatory drugs and/or corticosteroids, and subsequently with more potent disease-modifying antirheumatic drugs (DMARDs), such as methotrexate (MTX), sulphasalazine, hydroxychloroquine, lefnulomide. Lard et al. have shown that a delay in initiating DMARD therapy by 4 months resulted in substantially more radiographic damage at 2 years compared with intervention within 15 days of referral. In addition, several combinations, including two or more traditional DMARDs, have been found to be more effective than monotherapy in reducing disease activity and slowing radiographic progression.

The objective of this review is to evaluate strategies for combination therapy and of early, aggressive intervention, in terms of efficacy, safety, and cost effectiveness.

Material & Methods
The present study was conducted in 60 consecutive rheumatoid arthritis patients, who attended Out Patient Department or were admitted in the department of Internal Medicine at R.G.Kar Medical College, Kolkata, West Bengal for the period of 1 year from 1st January 2017, to 1st January 2018. The present study is a clinical observational study on the patients of Patients with RA from age 18-60 years not having exclusion criteria

Exclusion Criteria: Pregnancy, Wanting to be Pregnant, All Patients to Contraindication to Methotrexate, Sulfasalazine, Hydroxychloroquine.

The patients meeting the inclusion criteria will be randomised into 2 groups. Group A will be receiving methotrexate a weekly schedule of 7.5-20 given either orally in divided doses or if necessary SC or IM doses to avoid gastrointestinal toxicity for 6 months along with dietary therapy and sulphasalazine 500 mg twice daily for 6 months. Comparing to methotrexate 7.5 to 20 mg weekly, sulphasalazine 500 mg twice daily & Hydroxychloroquine 200 mg twice daily for 6 months.( Group B)

Informed consent form will be filled up and duly signed by patients before enrolling them in this study. Detailed history will be taken from the patients. Complete clinical examination will be done and will be recorded in pre designed pro-forma. Blood examinations will be done in Hematology section of the Pathology Department as per standard procedures of the hospital and relevant biochemical tests will be done from Biochemistry Department. Radiological examinations will be done from Department of Radiology R.G.Kar Medical College, Kolkata.

The following laboratory parameters will be evaluated at 1 months of interval.
RA factor, Anti CCP antibodies, ESR, C reactive protein.
**Ethical Clearance:**
The study required non-invasive investigations to be conducted on the outpatients and indoor patients. Hence, an ethical clearance has been tamed from the institution, R.G. Kar Medical College & Hospital, Kolkata.

**Method of Statistical Analysis:**
The following method of statistical analysis has been used in this Study:
All the relevant data were entered in Microsoft Excel. Continuous variables were presented as mean and standard deviation and categorical variables were presented as absolute numbers and percentages. The comparison of normally distributed continuous variables between the groups was performed using Student’s "t" test. The prevalence rate was expressed in terms of percentage. A "p"-value < 0.05 was considered statistically significant.

**Result**

We studied a total number of 60 cases of rheumatoid arthritis in R.G.Kar Medical College and Hospital, Kolkata.

In group-A, 21(70.0%) patients had female and 9(30.0%) patients had male. In group-B, 18(60.0%) patients had female and 12(40.0%) patients had male. In group-A, the mean age (mean± s.d.) of patients was 48.6000 ± 11.2145 years. In group-B, the mean age (mean± s.d.) of patients was 48.4667 ± 10.3881 years. Difference of mean age vs. group was not statistically significant (p=0.9621).

In group-A, the mean RA factor baseline (mean± s.d.) of patients was 20.5500 ± 9.9629. In group-B, the mean RA factor baseline (mean± s.d.) of patients was 25.1700 ± 6.1366. Difference of mean RA factor baseline vs. group was statistically significant (p=0.0347).

In group-A, the mean RA factor 6 months follow-up (mean± s.d.) of patients was 16.7233 ± 4.2261. In group-B, the mean RA factor 6 months follow-up (mean± s.d.) of patients was 15.1620 ± 4.5890. Difference of mean RA factor 6 months follow-up vs. group was not statistically significant (p=0.1757).

In group-A, the mean RA factor 12 months follow-up (mean± s.d.) of patients was 14.6787 ± 4.6670. In group-B, the mean RA factor 12 months follow-up (mean± s.d.) of patients was 12.4533 ± 2.1289. Difference of mean RA factor 12 months follow-up vs. group was statistically significant (p=0.0208).

In group-A, the mean CRP baseline (mean± s.d.) of patients was 5.2467 ± .5680. In group-B, the mean CRP baseline (mean± s.d.) of patients was 5.2567 ± .6442. Difference of mean CRP baseline vs. group was not statistically significant (p=0.9494).

In group-A, the mean CRP follow-up 6 months (mean± s.d.) of patients was 4.1333 ± .6984. In group-B, the mean CRP follow-up 6 months (mean± s.d.) of patients was 3.1900 ± .7649. Difference of mean CRP follow-up 6 months vs. group was statistically significant (p<0.0001).

In group-A, the mean CRP follow-up 12 months (mean± s.d.) of patients was 3.0967 ± .7486. In group-B, the mean CRP follow-up 12 months (mean± s.d.) of patients was 1.4333 ± .4802. Difference of mean CRP follow-up 12 months vs. group was statistically significant (p<0.0001).

In group-A, the mean DAS 28 baseline (mean± s.d.) of patients was 5.4667 ± 1.3322. In group-B, the mean DAS 28 baseline (mean± s.d.) of patients was 5.6000 ± 1.3287. Difference of mean DAS 28 baseline vs. group was not statistically significant (p=0.6993).

In group-A, the mean DAS 28 6 months follow-up (mean± s.d.) of patients was 3.9333 ± .9072. In group-B, the mean DAS 28 6 months follow-up (mean± s.d.) of patients was 3.2667 ± .9444. Difference of mean DAS 28 6 months follow-up vs. group was statistically significant (p=0.0072).

In group-A, the mean DAS 28 12 months follow-up (mean± s.d.) of patients was 2.6667 ± .6065.
In group-B, the mean DAS 28 12 months follow-up (mean± s.d.) of patients was 2.2000 ± .7144. Difference of mean DAS 28 12 months follow-up vs. group was statistically significant (p=0.0084).

In group-A, 29(96.7%) patients had positive anti CCP baseline. In group-B, all patients had positive anti CCP baseline. Association of anti CCP baseline vs. group was not statistically significant (p=0.3132).

In group-A, 24(80.0%) patients had positive anti CCP 6 months follow up. In group-B, 22(73.3%) patients had positive anti CCP 6 months follow up. Difference of mean anti CCP 6 months follow up vs. group was not statistically significant (p=0.5415).

In group-A, 20(66.7%) patients had positive anti CCP 12 months follow up. In group-B, 16(53.3%) patients had positive anti CCP 12 months follow up. Difference of mean anti CCP 12 months follow up vs. group was not statistically significant (p=0.2918).

### Table1: Distribution of mean CRP Baseline: Group

<table>
<thead>
<tr>
<th>CRP Baseline</th>
<th>Number</th>
<th>Mean</th>
<th>SD</th>
<th>Minimum</th>
<th>Maximum</th>
<th>Median</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group-A</td>
<td>30</td>
<td>5.2467</td>
<td>.5680</td>
<td>3.9000</td>
<td>6.0000</td>
<td>5.1000</td>
<td>0.9494</td>
</tr>
<tr>
<td>Group-B</td>
<td>30</td>
<td>5.2567</td>
<td>.6442</td>
<td>3.9000</td>
<td>6.0000</td>
<td>5.3500</td>
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</tr>
</tbody>
</table>

### Table2: Distribution of mean CRP follow-up 6month : Group

<table>
<thead>
<tr>
<th>CRP follow-up 6month</th>
<th>Number</th>
<th>Mean</th>
<th>SD</th>
<th>Minimum</th>
<th>Maximum</th>
<th>Median</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group-A</td>
<td>30</td>
<td>4.1333</td>
<td>.6984</td>
<td>3.0000</td>
<td>5.1000</td>
<td>4.2500</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

### Table3: Distribution of mean CRP follow-up 12 month: Group

<table>
<thead>
<tr>
<th>CRP follow-up 12month</th>
<th>Number</th>
<th>Mean</th>
<th>SD</th>
<th>Minimum</th>
<th>Maximum</th>
<th>Median</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group-A</td>
<td>30</td>
<td>3.0967</td>
<td>.7486</td>
<td>2.2000</td>
<td>4.8000</td>
<td>2.9500</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Group-B</td>
<td>30</td>
<td>1.4333</td>
<td>.4802</td>
<td>1.0000</td>
<td>2.5000</td>
<td>1.3000</td>
<td></td>
</tr>
</tbody>
</table>
DISCUSSION

Present study was conducted in the department of Medicine in R. G. Kar Medical College and Hospital, 60 patients were selected using above defined criteria divided in two groups.

GROUP-A patients were treated with Methotrexate + Sulphasalazine.

GROUP-B patients were treated with Methotrexate + Sulfasalazine + Hydroxychloroquine.

Salim B et al 107 found that Ninety five patients were enrolled with a mean age (years) ± SD of 51.7±8.9 and a mean duration of disease (years) of 8.6±7.1. We found that in group-A, the mean age (mean± s.d.) of patients was 48.6000 ± 11.2145 years. In group-B, the mean age (mean± s.d.) of patients was 48.4667 ± 10.3881 years. Difference of mean age vs. group was not statistically significant (p=0.9621).

The treatment of RA with the combination of MTX, HCQ, and SSZ has been called triple therapy. This combination was originally shown to be more effective than either MTX alone or the combination of SSZ and HCQ in a study O’Dell JR, Haire CE, Erikson N, Drymalski W, Palmer W, Eckhoff PJ, et al in 1996 14. An obvious question that arose from our initial trial was whether all 3 drugs were necessary in this combination, or whether patients treated with the double combinations of MTX and either SSZ or HCQ would do just as well. The relevance of this question was highlighted by the fact that the double combination of MTX and HCQ is by far the combination most commonly prescribed by clinicians in the US 15. The results of the present trial corroborate the results of initial combination trial, in which they demonstrated the efficacy of the tripleDMARD combination therapy (MTX, HCQ, and SSZ), and provide evidence that all 3 drugs in combination are better than the MTX double combinations. Furthermore, as in previous trial, the present study showed that this combination of medications was well-tolerated, and study withdrawals were similar in all 2 groups. Two other groups of investigators recently reported on the efficacy of the triple combination of MTX, SSZ, and HCQ 16,17. Both studies were open, but randomized, trials in patients with early RA. In the Finnish RA trial 17, patients were randomized to receive either triple therapy plus prednisolone or SSZ plus prednisolone at the discretion of the treating physician. The main end point of that trial was remission at 2 years, and patients randomized to triple therapy were more likely to have achieved remission at 2 years (odds ratio 2.7). Importantly, those authors have also reported that patients treated with all 3 drugs were less likely to develop a C1–C2 subluxation 18. In the second trial, Turkish patients were...
randomized to receive single, double, or triple therapy\textsuperscript{16}. Primary end points included an ACR 50% response, remission according to the ACR criteria, and no radiographic progression. In all cases, double therapy was better than single therapy, and triple therapy was better than double therapy, except for the criterion of no radiographic progression, which favored triple therapy but did not reach statistical significance for the comparison between double and triple therapy. The open nature of these trials is an obvious weakness, but importantly, the radiographic outcomes in both trials were blinded. James R. O’Dell, Robert Leff et al\textsuperscript{19} showed in their trial, a subset of the patients who were enrolled were defined as MTX suboptimum responders, that is, patients who continued to have active disease despite treatment with MTX at a dosage of 17.5 mg/week. These patients responded well in their trial. Those who received all 3 drugs had the best results (71% achieving ACR 20% response). This and other trials continue to demonstrate the superiority of combination therapy in the treatment of RA. Trials in early disease have consistently shown that combination therapy is superior to monotherapy\textsuperscript{16,17,20,21}. The triple combination of MTX, SSZ, and HCQ is well-tolerated and relatively inexpensive. The superior efficacy of this combination over single or double therapy has now been demonstrated in 2 trials of patients with early RA\textsuperscript{16,17} and in 2 trials of patients with more established RA\textsuperscript{14}. Direct comparison of this therapy with other effective, but more expensive, alternatives would seem prudent.

**CONCLUSION**

We found that CRP, RA, DAS-28 score, Anti-CCP and ESR levels were more decreased in triple therapy during follow-up period. In Rheumatoid arthritis patients with Methotrexate based dual therapy vs triple therapy, the latter was found to be significantly more durable. Given cost differences and similar outcomes, the variable durability demonstrated provides additional evidence supporting triple therapy over dual therapy first choice of treatment in Rheumatoid arthritis.

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