

## **A cost-effective analysis of various disease modifying anti-rheumatic drugs for patients with Rheumatoid Arthritis**

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### **ABSTRACT**

**Background:** Rheumatoid Arthritis (RA) is a chronic disabling disorder that lowers quality of life in the affected patients. Early treatment with disease-modifying anti-rheumatic drugs (DMARDs), provides better control of disease and minimize joint destruction. Long term therapy imparts considerable economic burden to the patients. Cost effective analysis was performed among the patients treated with methotrexate (MTX) alone, hydroxychloroquine (HCQ) alone, and both (MTX+HCQ).

**Methods:** A prospective, observational study for six months to analyze the cost-effectiveness in RA patients with DMARDs-MTX, HCQ and MTX+HCQ. A total of 91 patients were included for analysis; 43 patients in MTX and HCQ group; 37 patients in MTX group and 11 patients in HCQ group. To assess the functional disability, "Stanford Health Assessment Questionnaire - Disability Index" (HAQ-DI) was administered. The patients were followed up for four months. The HAQ-DI at the baseline was compared with that of final follow up. The change in HAQ-DI and the total costs were used to find out the average cost-effective ratio (ACER).

**Results:** The least ACER was obtained for Hydroxychloroquine and highest was for Methotrexate. But there was no statistically significant difference in ACER between various treatment groups. There was no significant difference in the disease activity improvement between the three groups.

**Conclusions:** MTX, HCQ and MTX+HCQ showed improvement in disease activity without any significant difference. MTX is superior considering direct cost but there is no difference in the total cost between three groups.

**Keywords:** Average cost-effective ratio, Disease modifying anti-rheumatic drugs, Rheumatoid arthritis

### **INTRODUCTION**

Rheumatoid Arthritis (RA) is a chronic and usually progressive inflammatory joint disease. Patients suffer from pain, stiffness, impaired function in daily life and at work, increased dependence on family and friends, decreased participation in leisure activities. RA is associated with morbidity and worsening of quality of life.<sup>1</sup> Treatment involves non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids and early use of disease-modifying anti-rheumatic drugs (DMARDs) and biologicals.<sup>2</sup> Biologicals are very expensive and cannot be afforded by majority of the patients. The management of

RA has become very expensive due to increased use of out-patient medical services, increased hospitalization and major work disability in the course of the disease. Since a number of treatment options are available for these patients, and as these options not only differ in efficacy but also vary widely in cost, it has become important to determine their cost effectiveness.<sup>3</sup> A number of economic evaluations were performed in western countries, of which the results may not be extrapolated to the situations in developing countries.<sup>4</sup> Economic analysis is to be essentially conducted in developing countries for resource utilization at maximum efficiency.

This study is designed to find out the cost effective therapy among the various treatment alternatives with DMARDs in RA patients.

## METHODS

The present study was conducted as a prospective, observational study extending over a period of six months (from September 2010 to March 2011) to examine the cost-effectiveness of various treatment options with DMARDs, which are considered affordable to the study population - Methotrexate alone, Hydroxychloroquine alone, Methotrexate-Hydroxychloroquine combination in rheumatoid arthritis from a patient perspective. The study was carried out at the Rheumatology clinic of the Medicine Department in a tertiary care teaching hospital in south India and was approved by the Institutional Ethics Committee.

### Inclusion criteria

- Age more than 18 years
- With a history of seropositive rheumatoid arthritis
- Has been prescribed with the protocol medications i.e., Methotrexate alone, Hydroxychloroquine alone, Methotrexate-Hydroxychloroquine.
- Has been prescribed with similar non-protocol medications like corticosteroids, NSAIDs etc.

### Exclusion criteria

- Patients with co-morbidities like liver failure, interstitial lung diseases
- Hospitalized patients
- Conditions like pregnancy, lactation

All the patients satisfying the inclusion criteria were selected for the study. Three groups of patients were considered for the study:

- Patients taking Methotrexate alone
- Patients taking Hydroxychloroquine alone
- Patients taking Methotrexate and Hydroxychloroquine

Patients taking non-protocol medications like NSAIDs or corticosteroids as adjunctive therapy may also be considered. An informed consent was obtained from all the patients. A questionnaire was then administered to the patients satisfying the inclusion criteria and collected data about patients' demographic details, disease activity, functional disability, medications and those concerning costs. To assess the functional disability, "Stanford Health Assessment Questionnaire - Disability Index" was also administered.<sup>5,6</sup> The patients were followed up every two months for four months

The HAQ-DI at the baseline was compared with that of final follow up. The change in HAQ-DI and the total cost for the follow up period were used to find out the average cost - effective ratio. HAQ-DI consists of 16 questions on

different activities grouped into eight domains. The highest score of each domain was summed and divided by eight to yield a continuous score from 0 (able to perform activities without difficulty) to 3 (unable to perform activities). The effect of DMARD treatment was calculated from the difference between the HAQ score at baseline and end of study ( $\Delta$ HAQ - DI).<sup>7</sup>

Costs are elicited from patient perspective. To evaluate the economic consequences, both direct and indirect costs were included. Direct costs are costs that are directly related to the intervention. It involves both medical and non-medical costs.<sup>8-10</sup>

Direct medical cost involves:<sup>11</sup>

- Cost of medications (both protocol and non-protocol medications)
- Cost required for laboratory investigation
- Cost of toxicity arising due to treatment
- Payment to the healthcare professional

The cost of commonly prescribed brands of each medication was collected from the nearby community pharmacies as well as from CIMS. The drugs were differentiated according to their strengths and the average cost for a single dose was calculated. For obtaining the daily cost, this average cost was multiplied with the dosing frequency. The average cost for laboratory tests was found out to calculate the ADR monitoring cost. To calculate the cost for healthcare professional's time, the salary of health care professionals was collected from the accounts department. Then mean salary per minute was calculated according to the formula:

$$\text{Mean salary /min.} = \frac{\text{Annual salary}}{(\text{Hours/week}) \times (\text{No. of weeks /annum}) \times 60}$$

Direct non-medical cost comprises of:

- Transportation and food costs (average costs of visit per head X no. of persons X no. of visit)
- Out-of-pocket expenses for disease related activities and purchases (cost of knee cap, collar bandage etc.)

Indirect cost includes loss of productivity due to rheumatoid arthritis related disability. This is calculated by human-capital approach.

Monetary value of man days lost = No. of man-days lost X Personal daily income. The result of CEA is expressed as average cost effectiveness ratio (ACER).<sup>12</sup>

$$\text{ACER} = \frac{\text{Health care costs (₹)}}{\text{Clinical outcome (not in ₹)}}$$

### Statistics

The SPSS software was used to analyze the statistics. Chi square test was done to check the baseline significance

between the groups. ANOVA was done to find the significance level between the groups. In this study,  $p < 0.05$  is considered statistically significant.

**RESULTS**

A total of 129 RA patients were enrolled in the study. In one patient, the protocol medication was stopped because her disease was in remission. 37 patients were dropped out from the study during follow up due to financial constraints. Data from these patients were excluded from the analysis. Consequently, a total of 91 patients were included in the analysis; 43 patients in combined treatment group - MTX + HCQ; 37 patients in MTX group and 11 patients in HCQ group.

Mean age of the study population was 50years. Female patients accounted for 81% of the study population. Mean (SD) disease duration was 5.24 (4.62) years. Most of the patients were already on therapy with DMARDs with mean (SD) treatment duration of 2.92 (3.36) years. Commonly seen co-morbidities were diabetes mellitus (10 patients), hypertension (10 patients) and thyroid disorders (4 patients). Majority of the patients had no co-morbidities (68 patients). Majority of the study population (61.5%) were not employed. 36.3% were working as daily wages. There was no statistically significant difference in the demographic characteristics - age, gender, disease duration, treatment duration, and duration of current therapy- between the three treatment groups under study. There was no statistically significant difference in the baseline disease activity - swollen joint count (SJC), tender joint count (TJC), HAQ-DI score, ESR, duration of morning stiffness and pain between the three treatment groups under study (Table 1).

**Table 1: Baseline parameters of disease activity.**

	MTX-HCQ	MTX	HCQ	Sig.
	Mean (SD)			
SJC	4.14 (6.44)	5.03 (6.96)	1.73 (1.79)	0.315
TJC	4.02 (5.85)	4.84 (6.87)	2.27 (1.68)	0.457
HAQ-DI	1.04 (0.6)	1.09 (0.71)	1.08 (0.70)	0.927
ESR	39.1 (27.8)	51.2 (28.7)	65.8 (53)	0.166
Duration of morning stiffness	24.53 (23.7)	47.5 (73.9)	85 (85.3)	0.201
Pain	47.2	45.9	48.5	0.514

Most of the patients (53.8%) had previously undergone treatment with other DMARDs. Majority of the patients were co-administering NSAIDs and steroids (79.1% and 83.5% respectively). There was no significant difference in the use of NSAIDs, steroids, other analgesics, and other

complementary medications among the three treatment groups.

The most commonly seen ADR was gastritis due to NSAIDs. Alopecia, breathlessness and pruritus due to Methotrexate, facial oedema due to steroids were also seen. One patient had to stop Methotrexate due to pruritus.

**Comparison of disease activity<sup>13-16</sup>**

*Comparison of swollen joint count (SJC)*

There is no statistically significant difference in the reduction of swollen joint count between the three treatment alternatives under study.

**Table 2: Comparison of Swollen Joint Count (SJC).**

	MTX-HCQ	MTX	HCQ	Sig.
	Mean (SD)			
SJC Baseline	4.14 (6.4)	5.03 (7)	1.73 (1.79)	0.318
SJC follow up	2.86 (5.29)	1.21 (2.49)	0.6 (0.89)	0.407

*Comparison of tender joint count (TJC)*

There is no statistically significant difference in the reduction of tender joint count between the three treatment alternatives under study.

**Table 3: Comparison of tender joint count (TJC).**

	MTX-HCQ	MTX	HCQ	Sig.
	Mean (SD)			
TJC Baseline	4.02 (5.85)	4.84 (6.87)	2.27 (1.68)	0.457
TJC Follow up	2.7 (5.14)	1.1 (2.41)	0.6 (0.89)	0.440

*Comparison of erythrocyte sedimentation rate (ESR)<sup>17</sup>*

There is no statistically significant difference in the reduction of ESR between the three treatment alternatives under study.

*Comparison of duration of morning stiffness<sup>18</sup>*

There is no statistically significant difference in the reduction of morning stiffness between the three treatment alternatives under study.

*Comparison of HAQ-DI*

There is an overall significant improvement in HAQ-DI of all the patients (P value 0.000). But there was no significant difference in the HAQ-DI between three groups.

**Table 4: Comparison of HAQ-DI.**

	MTX-HCQ	MTX	HCQ	Sig.
	Mean (SD)			
HAQ-DI Baseline	1.04 (0.60)	1.09 (0.71)	1.08 (0.70)	0.927
HAQ-DI Follow up	0.69 (0.80)	0.49 (0.61)	0.48 (0.62)	0.710
Δ HAQ-DI *	0.42 (0.43)	0.54 (0.57)	0.65 (0.73)	0.379

\*Δ HAQ-DI = HAQ-DI baseline - HAQ-DI follow up, a positive value indicates improvement of function

**Comparison of pain (%)**

There is an overall significant improvement in pain of all the patients (P value 0.000). But there was no significant difference between the three groups.

**Comparison of costs between groups<sup>19</sup>**

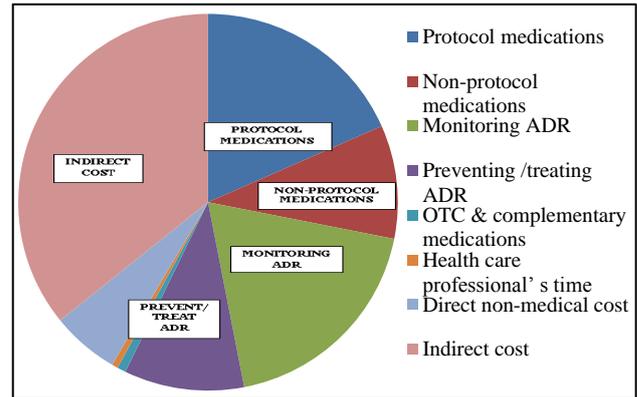
Direct costs accounted for 64.1% of the total costs. Of these, direct medical costs represented 58.4% and direct non-medical costs represented 5.8%. Indirect costs comprised 35.8% of the total costs (Figure 1).

**Direct medical costs**

There was statistically significant difference in acquiring the protocol medications - MTX, HCQ (p = 0.000), and folic acid (p = 0.000), and monitoring ADR (p = 0.000) between the various treatment groups. There was no

statistically significant difference in acquiring OTC and complementary medications and in total cost required to prevent or treat ADR (p value 0.328 and 0.836 respectively) between the treatment groups. There was no significant difference in total cost required for non-protocol medications (p = 0.222) between the treatment groups.

There was statistically significant difference in total direct medical costs between the three treatment groups (P = 0.000).



**Figure 1: Distribution of total cost.**

There was statistically significant difference in the total direct cost (P =0.000), highest value (₹1637) was for the combination group (MTX-HCQ). But there was no significant difference in the total costs (P= 0.376) between the treatment groups.

**Table 5: Mean (SD) of various components of direct medical costs incurred in RA patients receiving different DMARDs.**

	MTX-HCQ	MTX	HCQ	Sig.
	Mean (SD)			
Protocol medications	593.4	209.2	129.9	0.000
Monitoring ADR	489.3	60.84	425.9	0.000
Steroid	106	120.5	65.4	0.061
Folic acid	74.36	26.8	3.4	0.000
Non-protocol medications	229.4	196.4	175.3	0.222
OTC and complementary medications	10.9	29.5	21.8	0.328
Total cost to prevent/ Treat ADR	203.7	186	224.1	0.836
Total direct (medical)	1528	394	989	0.000

Direct, indirect and total costs

**Table 6: Mean (SD) direct, indirect and total costs (₹) incurred in RA patients receiving different DMARDs.**

Cost category	MTX-HCQ	MTX	HCQ	Sig.
	Mean (SD)			
Direct (medical)	1528	394	989	0.000
Direct (non-medical)	109	73	134	0.512
Total direct cost	1637	396	1106	0.000
Indirect	660	1714	967	0.436
Total (direct + indirect)	2297	1781	2073	0.376

**Average cost effectiveness ratio<sup>20</sup>**

The least ACER (₹ per outcome) was obtained for Hydroxychloroquine (2,544) and highest ACER was obtained for Methotrexate (6,125). But there was no statistically significant difference in ACER between various treatment groups.

**Table 7: Average cost-effective ratio of different DMARDs.**

DMARDs	Total cost (₹)	Mean ΔHAQ DI	Mean ACER (SD)	Sig.
MTX-HCQ	2296.6	0.42	2,757 (11112)	0.331
MTX	2072.9	0.54	6,125 (9888)	
HCQ	1533.6	0.65	2544 (907)	

**DISCUSSION**

Being a chronic disabling disease RA requires long time treatment with drugs. DMARDs are commonly prescribing group. Increase in the healthcare costs and limited healthcare resources, cost effective analysis of drugs are gaining much importance in developing countries like India. Majority of our study population were females. Mean age was 49 years and mean disease duration was around 5 years. The patients should obtain remission or at least a low level of disease activity using the most cost-effective therapy. Most of the patients were already on therapy with DMARDs.<sup>21</sup> The baseline disease activity parameters like swollen joint count, tender joint count, ESR, duration of morning stiffness, pain and HAQ-DI were similar between the groups. Direct costs accounted for 64.2% of the total costs. Of these, direct medical costs represented 58.4% and direct non-medical costs represented 5.8%. Indirect costs comprised 35.8% of the total costs. There was statistically significant difference in the total direct cost; highest value was for the combination group (MTX+HCQ). But there was no significant difference in the total costs between the treatment groups. The least ACER (₹ per outcome) was obtained for Hydroxychloroquine (2,544) and highest ACER was obtained for Methotrexate (6,125).

Patients had established RA with mild to moderate disease activity and slightly impaired functional status at study entry. However, approximately baseline HAQ score was greater than 1, which indicated clinically significant disability.<sup>5</sup> Since indirect cost considers the loss of productivity, this result indicates the extent of disability caused by the disease. Most of the patients had to quit their job due to the disease. This contributed highly to loss of productivity.<sup>22</sup>

The study revealed that there was an overall significant improvement in the swollen joint count, tender joint count

and HAQ-DI, but the differences were not significant between the three treatment groups. This shows that the effects of therapy were almost similar among the groups.<sup>23,24</sup>

The study shows that there was a significant difference in direct medical costs i.e., the costs for acquiring the protocol medications, folic acid and monitoring ADRs. The combination group (MTX-HCQ) showed higher costs for acquiring the as mentioned category. Moreover, the combination group showed a high value for the total direct cost. But the total cost (direct and indirect costs) showed no significant difference between groups. This may be due to the difference in indirect costs i.e., the combination therapy might have improved the functional status of patients and hence loss of productivity may be minimum for the combination therapy.<sup>25,26</sup>

In this study, MTX+HCQ were the mostly prescribed combined DMARDs. Manathip Osiri et al, determined the cost-effectiveness of various DMARDs compared with HCQ for rheumatoid arthritis (RA) treatment. The study concluded that MTX + HCQ was less costly and more effective than HCQ alone. MTX + SSZ and triple therapy (HCQ + MTX + SSZ) were more effective than HCQ with additional costs.<sup>10</sup> Axel Finckh et al, assessed the potential cost-effectiveness of major therapeutic strategies for very early RA. The study concluded that very early intervention with conventional DMARDs is cost-effective but the cost-effectiveness of very early intervention with biologics remains uncertain.<sup>4</sup> Shini VK et al, conducted a study to determine cost effectiveness of various DMARDs used in the management of RA at a hospital in South India. Only direct costs were included in calculating total cost. The study concluded that the most cost effective combination of DMARDs was MTX + HCQ.<sup>11</sup>

Sukhpreet et al, calculated the treatment and monitoring costs in rheumatoid arthritis at a Government hospital in India. The average cost of drug treatment was found to be ₹999±76 per month. The average monthly direct cost of RA was estimated to be ₹623±31. The average indirect cost was found to be ₹368±62 per month. The average monthly cost of monitoring side effects in patients prescribed with DMARDs was 57±5.24 per patient. Methotrexate had the highest cost of monitoring while drug acquisition cost was least among all the DMARDs. The most expensive drug on the basis of acquisition cost, among DMARDs was found to be Leflunomide.<sup>26</sup>

Ferraz et al, compared the efficacy of Methotrexate (7.5mg/week) plus chloroquine (250mg/week) to that of Methotrexate alone (7.5mg/week) in 82 patients. After 6 months, the combination was more effective in tender joint count (P=0.04) and HAQ (P=0.04). The authors state that combined treatment was slightly more toxic and effective, although only 3 patients were withdrawn due to adverse effects out of 2 had combined treatment.<sup>27</sup> Monika Schoels et al, reviewed the cost effectiveness of rheumatoid arthritis (RA) treatments. The study concluded that despite

diverse methodological approaches, health economic analyses are concordant: at onset of disease, traditional disease-modifying antirheumatic drugs (DMARDs) are cost effective- that is, treatment merits outweigh treatment costs. If DMARDs fail, therapeutic escalation with tumour necrosis factor  $\alpha$  inhibitors (TNFi) is cost effective when standard dosing schemes are employed. If TNFi fail, rituximab or abatacept is cost effective.<sup>19</sup>

James R. O'Dell et al, evaluated the efficacy and safety of Methotrexate, sulphasalazine and Hydroxychloroquine and combination of these three drugs in the management of RA. The investigators looked for improvement in composite symptoms of arthritis and also evidences of adverse effects. Combination therapy with Methotrexate, sulfasalazine and Hydroxychloroquine is more effective than either Methotrexate alone or a combination of sulphasalazine and Hydroxychloroquine.<sup>28</sup>

## CONCLUSION

Three regimens of DMARDs (MTX, HCQ and MTX+HCQ) are found to be having similar efficacy. Cost effective wise all the three regimens are similar. Considering direct cost MTX is found to be superior among the three. Rheumatoid arthritis is a chronic disabling disease affecting joints causing destruction. Our study was planned for four months follow up due to constraints of time which may not pick up the long term improvements in such patients. Since not many studies are conducted in this aspect in South India, our results would provide basic data for future long duration community-based pharmacoeconomic studies.

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*Ethical approval: The study was approved by the Institutional Ethics Committee*

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