International Journal of Drug Development & Research | July-September 2012 | Vol. 4 | Issue 3 | ISSN 0975-9344 | Available online http://www.ijddr.in
Covered in Official Product of Elsevier, The Netherlands
SJR Impact Value 0.03 & H index 2

Comparison of treatment outcome in Rheumatoid Arthritis patients treated with single and two DMARDs in combination with Corticosteroids

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Abstract

Musculoskeletal disorders impose a considerable burden upon society due to long-term morbidity, disability and treatment costs. Among Musculoskeletal diseases, Rheumatoid Arthritis encumbers patients with a significantly higher individual economic burden. The present study seeks to analyse the Pharmacoeconomics aspects of Rheumatoid Arthritis (RA) and to assess the Quality of Life (QoL) of patients treated with the selected combination of drugs used in the therapy of Rheumatoid Arthritis. The treatment costs vary based on the use of single DMARD, combination DMARDs, biological agents, etc. The design of the study was a prospective and observational study for a period of 12 months in a tertiary care referral hospital in Kerala. All the Rheumatoid Arthritis patients who attended the Rheumatology OPD, with 3 months follow-up and who satisfied the inclusion criteria were included in the study. The Cost effectiveness analysis was done by taking the HAQ - DI score as a measure of effectiveness and the improvement in Quality of Life was measured by using the disease activity parameters like Swollen Joint Count, Tender Joint Count, ESR, duration of morning stiffness, etc.

Three groups of Drugs were selected for this study, namely, Group 1: Methotrexate + Corticosteroids, Group 2: Hydroxychloroquine + Corticosteroids, and Group 3: Methotrexate + Hydroxychloroquine + Corticosteroids. It has been observed that the maximum improvement in Quality of Life and the least Average Cost Effective Ratio were obtained in the case of the combination of Drugs in Group 3. The highest Average Cost Effective Ratio was observed in the case of Group 2 Drugs.

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Key words:
DMARD, Disease Activity Score (DAS 28), Health Assessment Questionnaire –Disability Index (HAQ-DI), Quality of Life (QoL).

How to Cite this Paper:
***M. A. Kuriachan, K.G. Revikumar, Andreena Jolly** "Comparison of treatment outcome in Rheumatoid Arthritis patients treated with single and two DMARDs in combination with Corticosteroids" Int. J. Drug Dev. & Res., July-September 2012, 4(3): 228-235

Article History:----------
Date of Submission: 21-06-2012
Date of Acceptance: 11-07-2012
Conflict of Interest: NIL
Source of Support: NONE

INTRODUCTION

Rheumatoid Arthritis is a systemic autoimmune disease of unknown etiology characterized by chronic synovial joint inflammation, causing pain, stiffness

and impaired function. Formation of Rheumatoid Pannus, an inflammatory and invasive tissue, eventually leads to joint destruction. RA has worldwide distribution, with a prevalence estimated at 0.5% to 1%, as revealed in studies across Europe, North America, Asia and South Africa.[1] In India, an estimated seven million people are affected by Rheumatoid Arthritis[2]. Rheumatoid Arthritis is observed more in females, as compared to males, the ratio being 5:1. The 1987 American College of Rheumatology (ACR) had laid down certain diagnostic criteria for Rheumatoid Arthritis[3]. For the diagnosis of Rheumatoid Arthritis, a patient should have at least four of the seven criteria. Criteria 1 to 4 must have been present for at least 6 weeks.

1. Morning stiffness (1 hour or more)
2. Arthritis in three or more joint areas.
3. Arthritis of the hand joint areas.
4. Symmetric Arthritis.
5. Rheumatoid nodules.
6. Serum Rheumatoid factor
7. Radiographic changes in a hand or wrist joint or both.

The development of joint destruction starts early and is most rapid during the first months of Rheumatoid Arthritis[4]. The foot joints are usually affected earlier and in more numbers than the hand joints. Inflammation may extend beyond synovial structures, causing nodules sicca complex, serositis, and vasculitis[5].

Hence, the aim of RA treatment is not only to relieve symptoms and signs, but also to prevent destruction of joints and induce remissions. Thus far, no gold standard of remission criteria in Rheumatoid Arthritis patients is available. In clinical trials, the American Rheumatism Association (ARA) remission criteria or its modification are acceptable[6]. Another option is the Disease Activity Score with the 28-joint count (DAS 28) and a cut point of <2.6 as a definition of remission in Rheumatoid Arthritis[7].

The cornerstone of Rheumatoid Arthritis treatment involves DMARDs, either as mono-therapy or in combinations, with or without corticosteroids. The modern approach of Rheumatoid Arthritis treatment includes a very early start of treatment, because even a delay of 4 months can affect the long-term outcome of treatment[8]. During the last decade a strategy of initiating combination treatment with two or more DMARDs has become increasingly popular. The aim of combining DMARDs with different mechanisms of action is to increase efficacy, while maintaining a favourable toxicity profile. At least two differing approaches of combination treatment exist: the step-down and step-up strategies. In the step-down approach, the most aggressive treatment with combinations of DMARDs is at baseline, and once the disease is under control, the drugs with the least favourable toxicity profile are withdrawn. In the step-up approach, the DMARDs are added one at a time until the disease is under control, and therefore administration of multiple DMARDs can be avoided in patients who respond to a single DMARD.

The DMARDs currently used in clinical practice include: Methotrexate, Hydroxychloroquine, Sulfasalazine, Ciclosporin, Pencillamine, Azathioprine, Leflunomide, Oral Gold and Biological modifiers. All DMARDs inhibit the release or reduce the activity of inflammatory Cytokins like TNF α, and Interleukins IL-1, IL-2 and IL-6.

Initially, corticosteroids were used because of their dramatic impact on suppressing inflammation in RA patients. But their use was reduced when their long term side effects emerged. Nowadays, the strategy of corticosteroids treatment includes three possibilities:

1. Step-down with a high initial dose, later tapered off[9], or
2. Bridge- therapy aimed at controlling symptoms in the period of high disease activity before newly started DMARDs start to have an effect[10]. or

3. Long -term low dose strategy of oral corticosteroids together with a single or a combination of DMARDs[11].

Low dose corticosteroids together with DMARDs are able to reduce the rate of erosion progression in RA patients substantially[12]. On the other hand, daily use of corticosteroids has caused the most problems with long term toxicity such as cumulative effects on bone that lead to osteoporosis and other deleterious effects associated with increased mortality[13].

MATERIALS AND METHODS

The main aim of the study is to compare treatment outcomes, both beneficial and adverse and thereby improvement in Quality of Life and economic impact of Rheumatoid Arthritis patients given the three combination therapies of Methotrexate + Corticosteroids (Group 1), Hydroxychloroquine + Corticosteroids (Group 2), and Methotrexate + Hydroxychloroquine + Corticosteroids (Group 3). The study was designed and conducted as a prospective, observational and longitudinal study. The patients who met the inclusion and exclusion criteria were included in the study. The inclusion criteria were (1) Diagnosis of RA as per the American Rheumatism Association 1987 revised criteria[3], (2) Age greater than 20 years, (3) Patients with symptoms for more than 3 months, (4) Patients capable of understanding and giving written, voluntary informed consent.

Patients excluded from study were (1) Patients with psychological problems and other conditions which would interfere with their ability to attend the interview, (2) Patients below the age of 20, (3) Pregnant and lactating women, (4) Patients with other co-morbidities, (5) Patients who undergo Homeopathic or Ayurvedic or other traditional medical treatment along with the Allopathic treatment.

Patients were grouped depending upon the medication they were prescribed, i.e. Group1: Methotrexate + Corticosteroids, Group 2: Hydroxychloroquine + Corticosteroids and Group 3: Methotrexate + Hydroxychloroquine + Corticosteroids. The duration of the study was 12 months. The case sheets of the patients who attended the clinic during this period were analysed and those who met the inclusion and exclusion criteria, gave their informed consent and came under either Group 1 or Group 2 or Group 3 were interviewed. A standard data collection form was prepared and approved by the ethical committee. Demographic data and information regarding the disease were collected by interview technique. The lab data were examined and routine blood count, Tender Joint Count and Swollen Joint Count of the patients under the treatment were noted. The prescriptions of the patients treated with the study drugs were analysed and the co- administered drugs were examined.

Different tools like Health Assessment Questionnaire (HAQ), ESR value, occurrence of adverse drug reactions, etc. were used to measure the adverse effects, as well as the beneficial treatment outcomes. The HAQ containing questions on eight sections of daily life activities was asked to the patients. The HAQ score was marked from 0 to 4 depending on the level of difficulty experienced in performing each task. The scores of each section were added up and this was adjusted depending on whether the patient used any aids or devices, or needed help from another person. The final score thus obtained was divided by 8 to obtain the HAQ Disability index.

The Direct Costs incurred by the three groups were analysed, taking into account the total cost of medication, the cost of laboratory tests, as also travel costs to and from the hospital for one month. The costs for the drugs were taken from the Rate Contract Lists of Central Purchase Committee, as prepared by the Directorate of Health or CIMS. Laboratory costs include the cost of routine blood tests, Liver Function tests, Ophthalmic tests, ESR etc. during the course of

treatment. The rates for these were taken from the ACR laboratory at Medical College, Calicut, which maintains WHO standards of quality and works under the direct supervision of KHRWS, a society under the Kerala Government.

The Indirect costs arising as a consequence of the treatment, include absence from work or man-days lost due to the disease and the loss of personal as well as family income. The Number of man-days lost was estimated for earning members and the monetary value of man days lost was calculated by multiplying number of days lost with reported daily income. In the case of housewives the minimum wage rate in Kerala was taken as their income. The data obtained was verified at the end of the study. A statistical analysis was performed using two sample two sided T test to test the differences in continuous variables between the three groups. SPSS 13.0 software was used for the statistical analysis.

RESULTS:

The total population of patients treated with Methotrexate + Corticosteroids (Group 1), Hydroxychloroquine + Corticosteroids (Group 2), and Methotrexate + Hydroxychloroquine + Corticosteroids (Group 3) were 170. The average age of the patients was found to be 49.66 $\pm$ 8.33 years, with the male to female ratio being approximately 1:5.

Table 1: Demographics of the Patients

Total No. of Patients	Methotrexate + Corticosteroid		Hydroxychloro-Quine + Corticosteroid		Methotrexate + Hydroxychloro - quine + Corticosteroid		Average Age	Male %	Female %
	No.	%	No.	%	No.	%			
170	85	50	25	14.71	60	35.29	49.66±9.33 years	17.65	82.35

About 89.41%, 84% and 91.67% of the patients treated in Group 1, Group 2 and Group 3 respectively were found to be positive for RF (sero positive) i.e. Out of 170 patients treated, 152 patients were found to be positive for RF (sero positive RA).

Table 2: Distribution of Rheumatoid Factor

S. No.	Drugs	Frequency	RA Factor Positive	%	RA Factor Negative	%
1.	Methotrexate + Corticosteroid	85	76	89.41	9	10.59
2.	Hydroxychloroquine + Corticosteroid	25	21	84.00	4	16.00
3.	Methotrexate + Hydroxychloroquine + Corticosteroid	60	55	91.67	5	8.33
	Total	170	152		18	

Only 160 patients were tested for anti-CCP, out of which 138 (86.25%) patients were found to have positive Anti-Cyclic Citrullinated Peptide (Positive -Anti CCP) and 22 patients (13.75%) were Anti -CCP Negative.

Table 3: Distribution of Anti-Cyclic Citrullinated Peptide

Subject	Frequency	%
Anti CCP positive	138	86.25
Anti CCP positive	22	13.75
Total	160	

In the study population, 35.29 % of the patients had the disease for 0 to 5 years, 39.41 % of the patients had the disease for 6 to 10 years, 20 % of the patients had been suffering for 10 to 15 years and 5.30% were affected by the disease for more than 16 years.

Table 4: Distribution of Disease Duration

Duration of Illness	Frequency	%
0-5 years	60	35.29
>5- 10 years	67	39.41
> 10-15 years	34	20.00
>15 years	09	5.30

The duration of the morning stiffness was 0 to 2 hours for 40% of Group 1 (34 patients), 20% of Group 2 (5 patients) and 70% of Group 3 (42 patients). The duration of the morning stiffness was between 2 to 4 hours in 36.47% of Group 1 (31 patients), 40% of Group 2 (10 patients) and 25% of Group 3 (15 patients). The percentage of patients with morning stiffness for 4 to 6 hours was 23.53% (20 patients) in Group 1, 40% in Group 2 (10 patients) and 5% in Group 3 (3 patients).

The mean number of days lost per month in Group 1 due to disability of the disease was 7.166 with a standard deviation of 2.82, the mean number of days lost per month in Group 2 was 8.03 with a standard deviation of 3.09 and in Group 3 was 6.036 with a standard deviation of 2.32.

Table 5: Comparison of Man-days Lost

Group	Days lost	STD Deviation
Group 1	7.166	2.82
Group 2	8.03	3.09
Group 3	6.036	2.32

The mean number of co-administered drugs was 3.1 with a Standard Deviation of 1.21 in Group 1, whereas it was 3.01 and 2.9 with Standard Deviation of 1.1 and 1.01 in Group 2 and Group 3 respectively. The mean cost of co-administered drugs for the Group 1, Group 2 and Group 3 were 234.33, 199.56 and 190.35 respectively with Standard Deviation of 129.55, 111.85 and 106.26 respectively.

Table 6: Comparison of Cost of Co-administered Drugs

Group	Mean Cost of Co-administered Drugs	STD Deviation
Group 1	234.33	129.55
Group 2	199.56	111.85
Group 3	190.35	106.26

The mean direct cost incurred by Group I was Rs. 806.35 with a Standard Deviation of 145.55, whereas Group 2 incurred Rs 852.65 with a Standard Deviation of 159.85 and Group 3 Rs. 919.35 with a Standard Deviation of 163.24.

Table 7: Comparison of Direct, Indirect and Total Costs

Group	Direct Cost (Mean SD)	Indirect Cost (Mean SD)	Total Cost (Mean SD)
Group 1	806.35 (145.55)	788.36 (245.03)	1596.71
Group 2	852.65 (159.85)	881.49 (267.56)	1734.14
Group 3	919.35 (163.24)	601.22 (209.35)	1520.77

The Tender Joint Count and Swollen Joint Count at baseline and after follow up period of 3 months and 12 months in all groups were recorded, as given in table No.8.

Table 8: Comparison of Swollen Joint Count and Tender Joint Count

		Group1	Group2	Group3
		Mean(SD)	Mean(SD)	Mean(SD)
Baseline	Swollen Joint Count	5.05 (4.1)	4.97 (3.9)	5.15 (4.28)
After 3 months		3.75 (2.61)	3.85 (2.88)	3.15 (2.65)
After 12 months		2.86 (1.96)	3.0 (2.1)	2.11 (1.31)
Baseline	Tender Joint Count	4.96 (4.23)	4.56 (3.92)	5.01 (4.33)
After 3 months		3.82 (3.59)	3.79 (3.29)	3.13 (2.73)
After 12 months		2.33 (2.03)	2.88 (2.56)	1.98 (1.66)

The mean ESR values were also compared at baseline and after follow-up of 3 months and 12 months. Significant improvement in ESR values was not found in the patients during the follow up period.

Table 9: Comparison of ESR Values.

	Group 1	Group 2	Group 3
	Mean(SD)	Mean(SD)	Mean(SD)
Baseline	58.80 (26.33)	52.36 (24.42)	50.85 (24.20)
After 3 months	50.12 (24.52)	46.44 (20.32)	40.42 (19.12)
After 12 months	42.54 (20.12)	39.88 (18.41)	31.18 (16.46)

The HAQ-DI at the baseline followed by 3 and 12 months for the Group 1, Group 2 and Group 3 are as given below, in Table No. 10.

Table 10: Comparison of HAQ-DI at the baseline followed by 3 and 12 months for Group 1, Group 2 and Group 3

	Group1 Mean (SD)	Group2 Mean (SD)	Group3 Mean (SD)
HAQ-DI Baseline	2.21(1.21)	3.17(2.08)	3.11(2.01)
HAQ-DI After 3 months	1.97(1.11)	2.97(1.99)	2.67(1.88)
HAQ-DI After 12 months	1.38(1.01)	2.61(1.56)	1.88(1.22)
Δ HAQ- DI*	0.24 (0.17)	0.20(0.17)	0.44(0.29)

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

The least average cost effective ratio was obtained for Methotrexate + Hydroxychloroquine + Corticosteroid (Group 3) and the highest average cost effective ratio was obtained for Hydroxychloroquine + Corticosteroid (Group 2).

Table 11: Comparison of cost effective ratio for Group 1, Group 2 and Group 3.

DMARDs	Total Cost in Rupees	Mean ΔHAQ-DI	Mean ACER
Group1	1596.71	0.24	6652.96
Group2	1734.14	0.20	8670.70
Group3	1520.77	0.44	3456.30

Corticosteroids commonly prescribed were Deflazacort, Prednisolone, Methyl Prednisolone and Inj. Methyl Prednisolone and nearly 61.76% (105 patients) received Deflazacort. Non-steroidal anti-inflammatory drugs most commonly prescribed were Aceclofenac. To avoid gastric upset, some patients were given gastro protective medicines. The most commonly prescribed one was Famotidine followed by Pantoprazole. Most patients were also advised to apply topical anti-inflammatory gel over the tender and swollen joints after hot fomentation. About 74.71% (127 patients) received calcium supplementation and 21.76% (37 patients) were prescribed Glucosamine Sulphate.

DISCUSSION:

The mean age of the study group was 49.66 ± 9.33 years. In an international study involving numerous countries, Sokka et al found the mean age of Rheumatoid Arthritis patients to be 56.2[14]. According to this data, a majority of the Rheumatoid Arthritis patients are above the age of 40, the male to female ratio being 1:5.

84 to 92 percentage of the patients treated were found to be sero positive. Determination of serum rheumatoid factor (RF) is very important, since patients with sero positive Rheumatoid Arthritis require early and aggressive treatment with DMARDs to prevent or minimize destructive joint damages and to achieve long term outcomes[15]. Estimation of serum Anti CCP is an important tool in the diagnosis of Rheumatoid Arthritis, since Anti CCP has got a greater degree of specificity for RA than RA Factor[16].

The disease duration varied in the study population. Those who had the disease for 5 to 10 years were the most in number (39.41%).

A significant difference is found in morning stiffness duration. The group treated with Methotrexate + Hydroxychloroquine + Corticosteroid (Group 3) had better result as far as this parameter is concerned, followed by Methotrexate + Corticosteroid (Group 1).

The mean number of days that the patients could not work due to the disability caused by the disease was also different for the treatment groups. The group treated with Methotrexate + Hydroxychloroquine + Corticosteroid (Group 3) had lesser number of working days lost and hence Indirect Cost was also less for this group, when compared with the other groups.

There was no significant difference in the mean cost of co-administered drugs and mean Direct Cost between the three different treatment groups.

However total mean cost was the least for the third group, due to the lesser number of man-days lost.

It was observed that there is an overall significant reduction in Swollen Joint Count of all the patients in the first and second follow-up in the case of all the treatment groups. Similarly, an overall significant reduction in Tender Joint Count of all the patients was also observed in the first and second follow-up. The best results were obtained for the patients belonging to the Group 3.

There was no significant difference in the ESR values between the three treatment groups.

HAQ-DI parameter indicates overall improvement of function in the case of all the Groups; however, the maximum improvement was observed in the case of Group 3.

Average Cost Effective Ratio (ACER) is a valuable tool in determining the lowest cost option for the outcome gained. In this parameter also, the best outcome and the least cost was observed for Group 3.

The most commonly found Adverse Drug Reactions were Gastritis, Alopecia and facial Oedema.

CONCLUSION

Combination therapy of DMARDs, with varying mechanisms of action is now becoming more popular. Together with the DMARDs, administration of low doses of corticosteroids has been observed to produce better outcomes in the treatment of Rheumatoid Arthritis.

In the present study, combination therapy of Methotrexate, Hydroxychloroquine and Corticosteroid was found to be more cost effective due to the lesser number of man days lost.

A comparison of the parameters like Swollen Joint Count, Tender Joint Count, ESR values, Duration of Morning Stiffness etc. reveals that improvement in the quality of life was the highest in the case of combination therapy of Methotrexate, Hydroxychloroquine and Corticosteroid.

ACKNOWLEDGEMENT

The authors thank Dr. Binoy J. Paul, former Professor of Department of Medicine, Medical College, Kozhikode for his help, guidance and support during the study.

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