EFFICACY OF COMBINATION THERAPY OF METHOTREXATE WITH HYDROXYCHLOROQUINE OR SULFASALAZINE IN RHEUMATOID ARTHRITIS PATIENTS IN KUMAON REGION: A COMPARATIVE STUDY

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ABSTRACT

OBJECTIVE
To Compare the Efficacy of combination therapy of Methotrexate (MTX) and Hydroxychloroquine (HCQ) with MTX and Sulfasalazine (SSZ) in Rheumatoid Arthritis (RA) patients of Kumaon region.

METHODS
RA patients of age group in between 18-60 years, a definite rheumatoid arthritis patients based on 2010 ACR/EULAR CRITERIA, presenting to the medicine OPD with Disease Activity Score 28 (DAS 28) Score >3.2 were included in the study, and patients receiving treatment combinations were divided into study groups. In the OPD, HCQ was given at a dosage of 200 mg twice a day, whereas dosage of MTX was 10 to 20 mg/week. The dosage of SSZ was 500 mg to 1000 mg twice a day. The primary end point of the study was based on EULAR DAS 28 response criteria at the end of study period.

RESULTS
The mean values of DAS 28 score show statistical significant decline within the group in every follow-up and during 2nd and 3rd follow-ups DAS 28 score between 2 groups shows statistical significant difference. At the end of study period (6 months), the difference between 2 study groups was not statistically significant. According to EULAR RESPONSE CRITERIA, good response was seen in 26 patients from group 1st and 27 patients from group 2nd.

CONCLUSION
The efficacy of drug combinations, i.e. MTX plus SSZ and MTX plus HCQ, in treating Rheumatoid Arthritis patients are comparable. Combination of MTX plus SSZ, however, shows rapid decrease in disease activity as compared to combination of MTX plus HCQ.

KEYWORDS
Rheumatoid Arthritis, Methotrexate, Hydroxychloroquine, Sulfasalazine.

INTRODUCTION
Rheumatoid Arthritis (RA) is a chronic inflammatory disease that causes joint pain, progressive joint destruction and functional disability, due to the combined effect of chronic synovitis and progressive joint damage.[1] RA affects the small synovial joints of hands and feet in a typical symmetrical distribution. This synovial inflammation may lead to cartilage damage and periarticular bone erosion and is manifested clinically by pain and deformities. These function limiting deformities and extra-articular manifestations adversely affects the quality of life in RA patients. Various studies have shown the efficacy of combination therapy over monotherapy.

The DAS 28 is a measure of disease activity in Rheumatoid arthritis. DAS stands for 'disease activity score' and the number 28 refers to the 28 joints that are examined in this assessment.

Joint damage in rheumatoid arthritis begins early. Hence, treatment of RA now involves early initiation of Disease Modifying Anti-Rheumatic Drugs (DMARD) to slow the disease progress. Treatment of disease in the first months of synovitis is important to retard radiographic progression.[2] This window of opportunity suggests that disease activity in patients with early RA is less severe, is characterized by a smaller load of inflammatory cells and is more responsive to treatment. So aggressive treatment during this phase is more likely to succeed than is the same treatment applied later in the course of disease when autoantigens from damaged joints possibly fuel the disease.[3] Therefore, it is important that RA should be treated and controlled as soon as possible after diagnosis and that this control should be maintained for as long as possible, consistent with patient safety.[4,5]

Various studies conclude that early start of DMARDs proved to be more efficacious than a delayed introduction of DMARDs in the disease progress of RA.[6,7] More recent therapeutic strategies are based on combinations of DMARDs

to control inflammation in the critical early stages of RA.[8,9,10] Hence, the present study aimed to find out the efficacy of combination of DMARDS in producing early disease remission and arresting progression of disease process in RA patients of Kumaon region.

METHODS

This was a single centre prospective open labelled study, which was undertaken for a study period of 1 year, i.e. from January 2014 to January 2015 duly after taking permission from the Institutional Ethical Committee. This study was conducted in Department of Pharmacology and Outpatient Department (OPD) of Medicine of Government Medical College and Susheela Tiwari Government Hospital, Haldwani, Uttarakhand. This study was conducted on definite Rheumatoid Arthritis patients; based on 2010 ACR/EULAR CRITERIA, coming to medicine OPD.[11] The study population involved in this study was treatment naive or chronic cases of RA patients in Kumaon Region. Due written informed consent was obtained from the patients before the recruitment. The consent was explained in vernacular language to the patients, i.e. Hindi. Patients of age group 18-60 years were included in the study with DAS 28 score >3.2. Patient with uncontrolled diabetes mellitus, severe congestive heart failure, interstitial lung disease, active peptic ulcer, inflammatory bowel disease, malignancies, abnormal renal function, abnormal hepatic function, anaemia, leukopenia, thrombocytopenia, pregnant or lactating female patients; patients on biologic DMARD therapy were excluded from the study.

After obtaining the results from baseline investigations, patients meeting the criterias of the study were allotted one of the 2 groups. Group I was given tab Methotrexate 0.3 mg/kg/week p.o. with tab Hydroxychloroquine 200 mg p.o. once daily, whereas Group II was given tab Methotrexate 0.3 mg/kg/week p.o. with tab Sulfasalazine 30 mg/kg body weight p.o. in divided doses. All patients were given folate supplementation. Patients were also given concomitant medication like NSAIDs, Calcium supplements, Vitamin D, etc.

To measure the outcomes of the treatment groups, DAS 28 was used to measure the disease activity. DAS 28 provides with a scale indicating current disease activity. If patient's DAS 28 score is less than 2.6, he was considered in remission which means a state of absence of disease activity. The primary end point of the study was based on EULAR DAS 28 response Criteria at the end of study period.[12]

For statistical analysis, SPSS version 21 was used. Differences in the mean values of the clinical outcome variables in the study groups were evaluated by Independent Sample 'T' test and to compare the DAS 28 score within the group on subsequent follow-ups. Paired sample 'T' test was used. For this study, the Confidence Interval percentage was 90% and result was considered significant if the P-value was less than 0.1.

RESULT
Demographic Data

The mean age of patients who participated in the study was 45.98 and 45.72 years in group I and group II respectively (Table 1).

In this study, patients of age between 18 to 60 years were included. Age group 51-60 years had maximum number of patients, i.e. 18 patients in group I and 18 patients in group II (Table 2).

Baseline Characteristics (Table 3)

In both the groups, patients with Rheumatoid factor and C-Reactive protein positive are comparable. Mean age since which patients are on DMARDs are 0.82 and 1.24 in group I and group II respectively.

Disease Activity Score (DAS 28) (Table 4) (Figure 1)

Mean Baseline values of DAS 28 in group I and group II were 5.38±0.68 and 5.31±0.61 respectively. These values showed steady and statistically significant (p<0.05) decline over every follow-ups and at the end of study period group I and group II had DAS 28 of 3.13±0.64 and 3.02±0.57 respectively. During 2nd and 3rd follow-ups, the difference in mean values of DAS 28 of group I and group II were statistically significant (p<0.1).

EULAR Response Criteria in both Groups (Table 5)

According to EULAR response criteria, 26 patients from group I and 27 patients from group II showed good response and the rest showed moderate response to the drugs.

Remission

In the present study, the 10 patients from both group I and group II achieved their remission at the end of 6 months, that is DAS 28 score less than 2.6.

Characteristics of the Study Patients	Group I	Group II
No. of patients (n)	50	50
Age in years (mean±SD)	45.98 (9.54)	45.72 (9.65)
% female	88%	86%
Age of onset (mean±SD)	41.96 (9.15)	40.99 (9.67)
Family history positive n (%)	8 (16%)	9 (18%)

Table 1: Demographic Data of the Study Patients

Age Group (In years)	Group I (n)	Group II (n)
<20	0	1
21-30	2	3
31-40	16	13
41-50	14	15
51-60	18	18

Table 2: Age Distribution

*n – number of patients

Characteristics of the Study Patients		Group I	Group II
Since when on DMARDs (In years)		0.82	1.24
Rheumatoid factor positive, % (Number of patients)	Total	50%, (25)	56%, (28)
	Male	12%, (6)	12%, (6)
	Female	38%, (19)	44%, (22)
C-Reactive Protein, positive, % (Number of patients)	Total	42%, (21)	42%, (21)
	Male	6%, (3)	8%, (4)
	Female	36%, (18)	34%, (17)

Table 3: Baseline Characteristics of the Study Patients

	Group I (MEAN±SD)	Group II (MEAN±SD)	P value
Baseline	5.38(0.68)	5.31(0.61)	0.58
1ST Follow Up	4.36(0.64)	4.29(0.49)	0.58
2ND Follow Up	4.13(0.54)	3.94(0.47)	0.057*
3RD Follow Up	3.81(0.67)	3.58(0.58)	0.072*
4TH Follow Up	3.49(0.65)	3.28(0.60)	0.099
5TH Follow Up	3.13(0.64)	3.02(0.57)	0.36
Table 4: Comparing the Disease Activity Score (DAS 28) of 2 Groups			

(*$p < 0.1$)

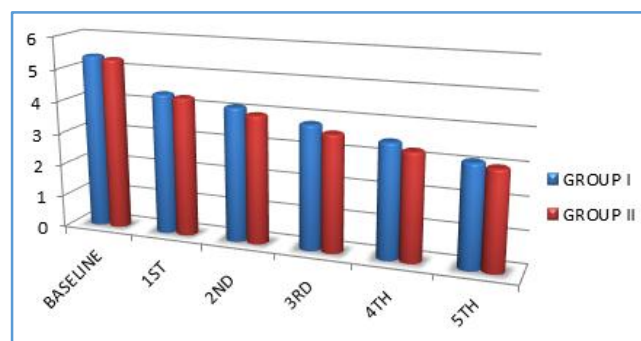|	Group I (No. of Patients)	Group II (No. of Patients)
No Response	0	0
Moderate Response	24	23
Good Response	26	27
Table 5: The EULAR Response Criteria in Both Groups		

Fig. 1: Disease Activity Score 28 (DAS 28)

DISCUSSION

Rheumatoid arthritis is a debilitating, autoimmune, inflammatory disease that affects the joints of the body that are lined with synovium. The prevalence of Rheumatoid arthritis in the adult Indian population is 0.75%.[13]

Methotrexate is a very frequently used DMARD for Rheumatoid arthritis.[14] In the Indian scenario, Hydroxychloroquine and Methotrexate were the most frequently used combination of DMARDS.[15] Various global studies had concluded that combination DMARD therapy is effective in Rheumatoid arthritis. The evidence is strongest in established Rheumatoid arthritis for combinations of Methotrexate with anti-TNF and/or Sulfasalazine–Hydroxychloroquine given to patients who have partially responded to DMARD monotherapy.[16]

The DAS 28 is a frequent outcome measure used in therapeutic trials. In the present study, the mean values of disease activity score in 28 joints (DAS 28) in Rheumatoid Arthritis patients at baseline in group I and group II were 5.38±0.68 and 5.31±0.61 respectively as seen in an Indian study.[13]

With combination therapy in both treatment groups, the mean values of Disease Activity Score (DAS28) showed steady decline with every monthly followup. On 2nd and 3rd follow-ups statistically significant difference was noted between the two treatment groups, which showed that group II had rapid decline in DAS 28 score when compared with group I. Some of the studies have shown that the improvement with Sulfasalazine was more rapid than Hydroxychloroquine.[17,18] However, at the end of study period, group I and group II had mean disease activity scores (DAS 28) were 3.13±0.64 and 3.02±0.57 respectively with no significant difference statistically. An Indian study which in comparison to present study data had similar DAS 28 value at the baseline and the end of 6 months in treatment group Methotrexate and HCQ reported 7.1±1.04 to 4.4±1.77 respectively.[19] In a study by Schipper L et al, which concurs with the present data states that at the end of 6 months the patients have been given Methotrexate and Sulfasalazine reported Mean±SD values of DAS 28 score, 4.0±1.3.[20] The study suggests that no statistically significant difference in DAS 28 score was seen in both the groups, but the patients who had been given Methotrexate and Sulfasalazine showed early reduction in disease activity as compared to Methotrexate and Hydroxychloroquine group, and as mentioned earlier that it is important that RA should be treated and controlled as soon as possible after diagnosis.[4,5] So here group II shows rapid decrease in disease activity when compared with group I.

The EULAR response criteria classify individual patients as non-, moderate or good responders depending on the extent of change and the level of disease activity reached. For clinical studies, valid tools for interpretation of group results during follow-up have been developed. The EULAR response criteria depending on the DAS/DAS 28 - value achieved at endpoint and the magnitude of change from baseline.[12] In the present study, EULAR response criteria were evaluated and 26 (52%) patients from group I showed good response and rest 24 (48%) gave moderate response. Similar global study conducted in African RA patient treated with Methotrexate and Hydroxychloroquine showed similar results, i.e. 53.9% showed good response using EULAR response criteria, but only 12.7% showed moderate response which do not harmonize with study data.[21] In 24 (48%) patients from group II with respect to EULAR good response was observed, while in 26 (52%) patients, it was a moderate response. While comparing with a study in which Methotrexate and Sulfasalazine, DMARD combination were given, 38% of the patients reported good response and 34% patients reported moderate response.[22]

In general, remission means the state of absence of disease activity in patients with a chronic illness with the possibility of returning disease activity. In RA, remission predicts preserving the functional capacity as well as retarding the radiographic progression.[23] In clinical studies, the definition of remission has to be unambiguous. Numerical limits of disease activity are commonly used; DAS 28 below 2.6 are considered to represent the state of remission.[24]

In the present study, at the end of study period (5th follow-up), 10 (20%) patients from both group I and group II had DAS 28 score less than or equal to 2.6. An international study in which Methotrexate is given along with Hydroxychloroquine or Sulfasalazine or other conventional synthetic DMARDs achieved remission in 7% of the patients.[25] Another Asian multicenter cross-sectional study gave remission rates of RA, which were 8.6% (DAS28 ≤2.6) when treated with Methotrexate and Hydroxychloroquine.[26]

The present study has its limitations, as RA is a chronic disease, so shorter duration of study 6 months might have concealed some findings. Patients were allowed to take concomitant medication, which might have affected the efficacy of the study drugs to some extent. So study needs to be validated with randomised double blind studies.

The study recommends the use of Sulfasalazine and Methotrexate combination as an alternative to Methotrexate and Hydroxychloroquine in RA patients with the advantage that this combination provides early relief in symptoms.

CONCLUSION
The efficacy of drug combinations, i.e. Methotrexate plus Sulfasalazine and Methotrexate plus Hydroxychloroquine in treating Rheumatoid Arthritis patients are comparable. Combination of Methotrexate plus Sulfasalazine, however, shows rapid decrease in disease activity as compared to combination of Methotrexate plus Hydroxychloroquine.

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Page 3306

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