

## COMPARATIVE EVALUATION OF EFFICACY OF HYDROXYCHLOROQUINE VERSUS METHOTREXATE IN PATIENTS WITH RHEUMATOID ARTHRITIS

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### ABSTRACT

**Aim:** The aim of the study is to compare the efficacy of Methotrexate(MTX) versus hydroxychloroquine(HCQ) in patients with Rheumatoid arthritis. **Materials and methods:** This prospective study involves 100 patients who were diagnosed with rheumatoid arthritis and those who met the study criteria were enrolled for the study. Relevant data such as demographic details, past medical history, drug name were collected from out- patient profile form and by patient interview. **Statistical Analysis:** All the raw data was collected, entered in Excel sheet 2010 in windows 10 version, the statistical analysis was done in SPSS 16.0 Software by an appropriate statistical method, paired sample T-test for knowing the significant p-value <0.05(confidence interval 95%). **Results:** Among 100 patients, 50% of patients have received the drug, Hydroxychloroquine(HCQ) (400 mg/day p.o), 50% patients have received the drug, Methotrexate(MTX)(15 mg/week in divided doses p.o). The study shows that Hydroxychloroquine group having remission rate of 4%(2 patients out of 50) with the remission value <2.6 and shown to be significant with p value < 0.05. Methotrexate group being assessed having remission rate of 8% (4 patients out of 50) with the remission value of <2.6 which is found to be statistically significant (p<0.05) and there is significance decrease in Erythrocyte sedimentation rate(ESR). **Conclusion:** In our study we have observed that methotrexate was more effective in managing rheumatoid arthritis when compared to hydroxychloroquine by comparing the DAS28 score of both groups. Pain and inflammation also reduced by avoiding further exacerbation of condition.

### INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune disease that characterized by inflammatory arthritis resulting in pain, swelling, and stiffness in the joints, and may cause severe joint damage, loss of function and disability. The disease may last from months to a lifetime, and symptoms may improve and worsen over time.<sup>[1]</sup> It is estimated to have a prevalence of about 1% of the population in India. It affects roughly three times as many women as men. People tend to develop rheumatoid arthritis between 40 and 60 years of age, although it can arise at any age.<sup>[2]</sup>

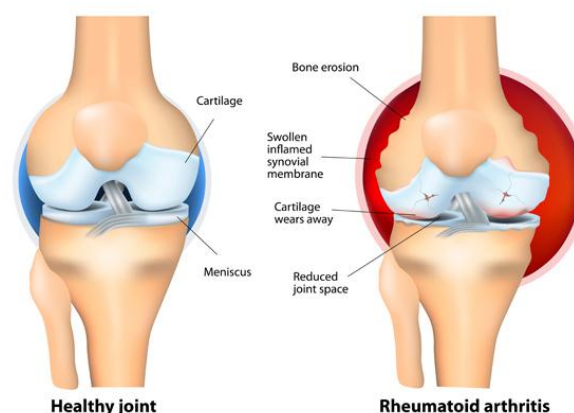


Fig. 1: Healthy joint and Rheumatoid arthritis affected joint.

Rheumatoid arthritis (RA) if left untreated, ultimately causes functional impairment.<sup>[3]</sup> Non-steroidal anti-inflammatory drugs (NSAIDs) help only in symptomatic relief, corticosteroids have problems with chronic use and disease-modifying anti-rheumatic drug (DMARD)

have promised to reduce the disease activity in a better way. Many new drugs were introduced into the market for the treatment of rheumatoid arthritis; however, their efficacy is yet to be established. Studies are necessary in Indian patients to compare the efficacy with methotrexate, an age old DMARD. Present study was aimed to evaluate the efficacy of methotrexate and hydroxychloroquine, an anti-malarial drug orally in the management of rheumatoid arthritis.

## MATERIALS AND METHODS

This is a prospective observational study which doesn't involve any type of invasive techniques and blood samples purely for the study purpose. All the parameters were taken by seeing the data and reports available from the patient which have already been suggested by the physician. The study was carried out for a period of six months i.e. from October, 2019 to March, 2020. This study was performed in outpatient department of an ORTHOPAEDIC HOSPITAL, Guntur, Andhra Pradesh.

### Inclusion criteria

- I. Patients suffering from Rheumatoid arthritis.
- II. Both males and females
- III. Patients using Methotrexate or Hydroxychloroquine
- IV. Patients of age group 16 – 70 years who are willing to participate in the study

### Exclusive criteria

1. Pregnant women and women who trying to get pregnant
2. Lactating women
3. Patients of age group below 16
4. Patients of age group above 70
5. Patients with active infective diseases
6. Patients with renal dysfunction and hepatic diseases

Patients who are diagnosed with rheumatoid arthritis and who met the study criteria were enrolled for the study. Relevant data such as demographic details, disease history, diagnosis, drug name, dose, laboratory data are collected from medical records of the patient and by patient interview where ever required were collected and documented. A suitable data collection form is designed and used in the study. Monitored the clinical status of the patient for 3 months.

All the necessary data was collected from - Interviewing the out patients and their care takers, Patient's prescriptions, Laboratory findings & Any other relevant sources. Before and after the treatment the patient clinical condition was checked. Advised the patients regarding their medication regimen and importance of medication adherence.

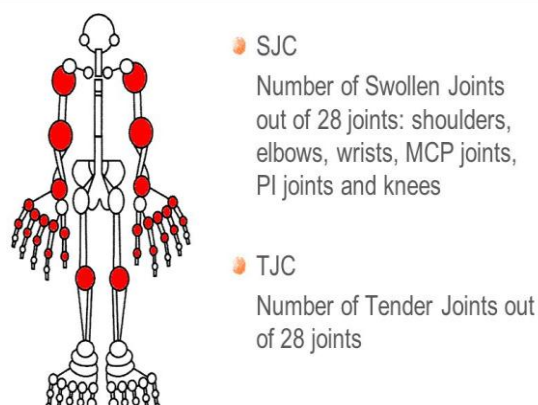
**DAS28 score:** The DAS28 is a measure of disease activity in rheumatoid arthritis (RA). DAS stands for 'disease activity score' and the number 28 refers to the 28 joints that are examined in this assessment. The DAS28 is a composite score derived from 4 of these measures.

This '28' version is a simplification of the original DAS score, which requires 52 joints to be counted. ESR value and global health assessment value ((from 0=best to 100=worst).

DAS28 is a composite formula. Four parameters are used to calculate a disease severity score:

- A) Number of swollen joints out of a total of 28 specified joints
- B) Number of tender joints out of a total of 28 specified joints
- C) Erythrocyte sedimentation rate
- D) Patient's interpretation of well being, with 0 being at their best and 100 their worst
  - a. High disease activity: DAS28 of >5.1
  - b. Moderate disease activity: DAS28 of >3.2 to 5.1
  - c. Low disease activity: DAS28 of 2.6–3.2
  - d. Remission: DAS28 of <2.6

## Components of DAS 28 score JOINTS



**Fig. 2: Components of DAS28 Score.**

- The 28 tender or swollen joint scores target the same joints (shoulders, elbows, wrists, metacarpophalangeal joints, proximal interphalangeal joints and the knees).
- These results are then fed into a complex mathematical formula to produce the overall disease activity score.
- The computation of the score is done through the following equation:<sup>[4]</sup>

$$\text{DAS28} = 0.56 \times \text{TJC28} + 0.28 \times \text{SJC28} + 0.70 \times \ln(\text{ESR}) + 0.014 \times \text{GH}$$

**Morisky medication adherence scale (MMAS)** was used to calculate the medication compliance which contains 8 questionnaires and the information was gathered during patient counselling. This scale is used in our study to know the significance of medication adherence. Scores are summed and range from 0-8.

### MMAS SCORING

- MMAS Score  $\geq 8$  : High Adherence

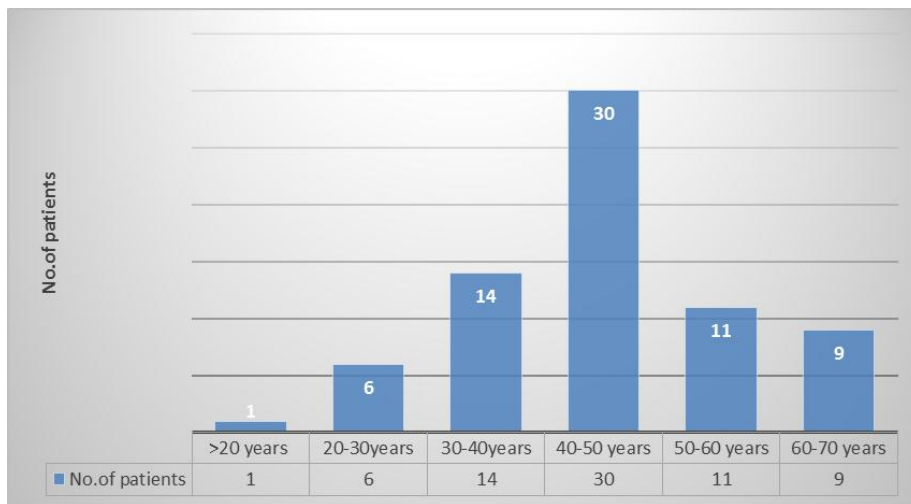
- MMAS Score 6 - < 8 : Medium Adherence
  - MMAS Score < 6 : Low Adherence
- If a patient scores higher on the scale, they are evaluated as more adherent. If they score lower on the scale, they are presumed to be struggling with low adherence.<sup>[8]</sup>

**RESULTS**

- Initially 110 patients were included in study, out of which 6 patients were excluded, because of no proper follow up due to lack of response and

patient’s disinterest towards the study; 4 patients were excluded because of infections that were developed for them during the study.

- Finally 100 patients were included in the study. Among 100 patients 50% patients i.e 50 patients were treated with Hydroxychloroquine and another 50% are treated with Methotrexate.
- Before and after patient clinical condition was checked, follow up was done for about 3 months.



**Figure 3: Age distribution of patients.**

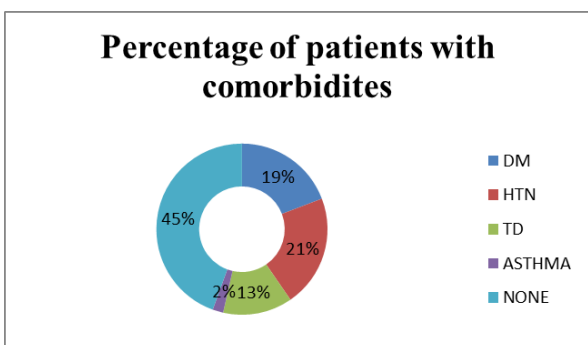
- Age distribution of patients - 39% of patients were between the age of 40-50 years, followed by 28% of patients were between the age of 50-60 years were 17% of patients were between the age of 30-40 years, 9% of patients were between age of 60-70 years
- were 6% of patients between the age of 20-30 years and 1% of patients below the age of 20years.
- According to our study, we have observed that most of the people who were affected with rheumatoid arthritis were from 40-50 age group.

**Table 1: Gender differentiation.**

GENDER	NUMBER OF PATIENTS	PERCENTAGE
Male	10	10%
Female	90	90%
Total	100	100

Table 1 shows the patient characteristics based on gender out of 100 patients 90 patients were females (90%) , 10 patients were males(10%).According to our study, we have observed that females are more prone to rheumatoid arthritis compared to males.

In our study most of the patients (45%) were with no comorbid diseases. And 19% of patients were reported with having DM, 21% of patients were reported with HTN, 13% patients reported with thyroid disease and 2% patients were reported with comorbidity of asthma.



**Fig. 4: Comorbid Diseases.**

**Table 2: Rheumatoid Factor (RF) for patients using Hydroxychloroquine (HCQ) Drug.**

Rheumatoid Factor (RF)	Before Treatment	After Treatment
0-30	39	31
30-60	6	12
60-90	1	5
>90	4	2

- Table 2 shows the pre and post treatment for rheumatoid factor of 50 patients using HCQ drug are included in the study. Out of 50 patients before treatment 39 patients were between RF value (0-30) and after treatment 31 patients were between the RF value (0-30). Before treatment 6 patients were between the RF value (30-60) and after treatment 12 patients were between RF value (30-60). Before treatment 1 patient had a RF value between (60-90)

and after treatment 5 patients were between RF value (60-90). Before treatment 4 patients are with the RF >90 and after treatment 2 patients with RF>90.

- This shows that there was a significant increase in the RF value 30-60 and 60-90 patients when compared with pre treatment. And gradually there is a decrease in RF value 0-30 and >90 patients when compared with pre-treatment.

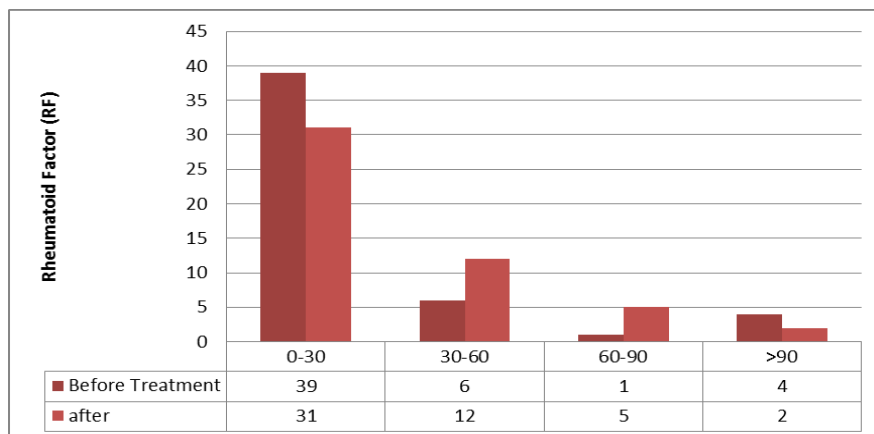


Fig. 5: Rheumatoid factor (RF) for patients using HCQ drug.

Table 3: ESR for patients using HCQ drug.

ESR (mm/hr)	Before treatment	After treatment
20-40	11	19
40-60	20	22
60-80	11	09
80-100	8	0

Table 5.5 shows the pre and post treatment ESR for 50 patients using HCQ drug. Out of 50 patients 11 patients were between 20-40 ESR and after treatment 19 patients were between 20-40 ESR. Before treatment 20 patients were between ESR 40-60 and after treatment 22 patients

were between ESR 40-60. Before treatment 11 patients were between ESR 60-80 and after treatment 9 patients were between ESR 60- 80. Before treatment 8 patients were between ESR80-100 and after treatment there were no patient between ESR 80-100.

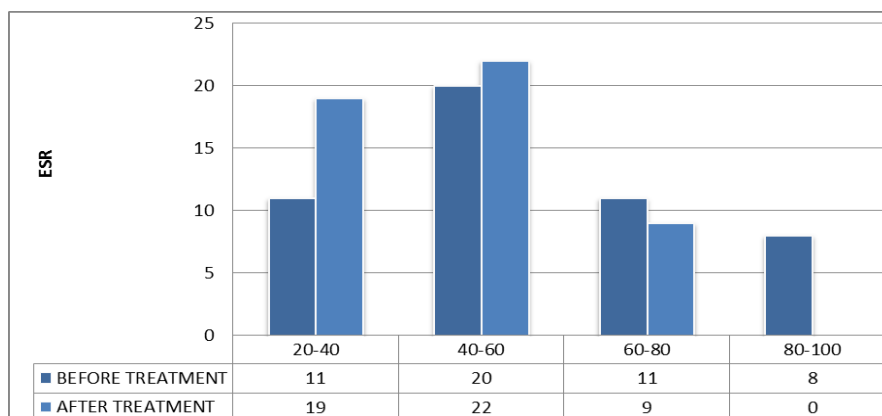


Fig. 6: ESR for patient using HCQ drug.

Table 4: Paired Samples Statistics.

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	Before treatment	58.0000	50	20.99563	2.96923
	After treatment	46.6000	50	16.45774	2.32748

**Table 5: Paired Samples Correlations.**

		N	Correlation	Sig.
Pair 1	Before treatment & After treatment	50	.706	.000

**Table 6: Paired Samples Test.**

		Paired Differences				t	Df	Sig. (2-tailed)	
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
					Lower				Upper
Pair 1	Before treatment – After treatment	11.40000	14.95026	2.11429	7.15118	15.64882	5.392	49	.000

Table 4 shows that pre and post treatment ESR for HCQ drug of 50 patients included in the study, the mean of the pretreatment ESR for HCQ drug was 58.000±20.995 and the mean of ESR for HCQ drug after treatment was 46.600± 16.457. This shows that there was a significant

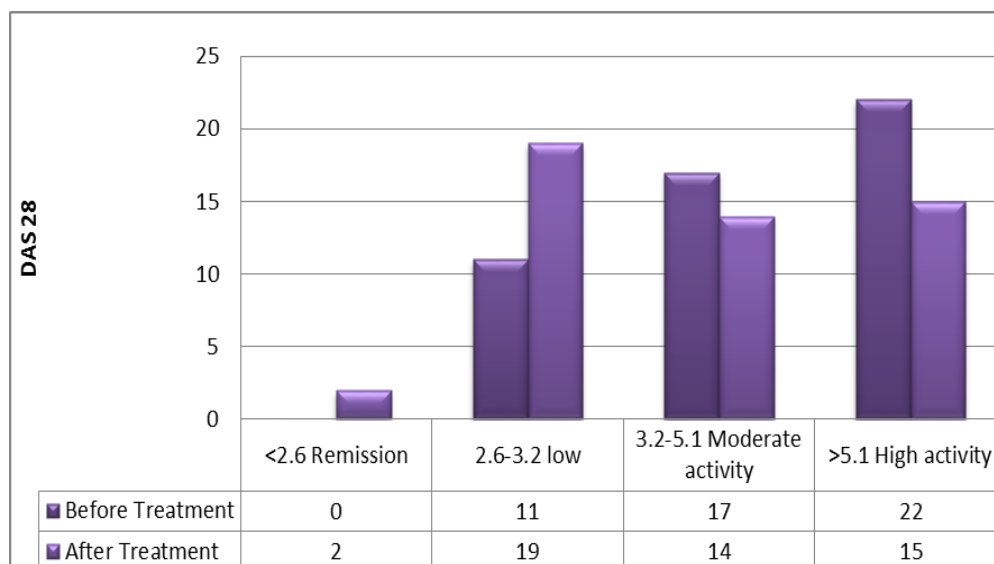
decrease in ESR for HCQ i.e., 11.4 ± 4.538 in treatment of HCQ drug. There was a significant difference in reduction of pain having p-value <0.05(95% confidence interval). By conventional criteria this difference is considered to be statistically significant.

**Table 7: DAS28 for patients Using HCQ drug.**

DAS28 score	Before treatment	After Treatment
2.6	0	2
2.6-3.2	11	19
3.2-5.1	17	14
>5.1	22	15

Table 7- Shows the pre and post treatment DAS28 for patient using HCQ drug. Out of 50 patients after treatment there were 2 Patients at low disease activity score which include 28 joints. Before treatment 11 patients were between the das28 2.6-3.2 and after treatment 19 were between disease activity score

between 2.6-3.2. Before treatment there were 17 patients between DAS 3.2-5.1 and after treatment were 14 patients between DAS 3.2-5.1. Before treatment 22 patients were high disease activity score >5.1 and after treatment there 15 patients were at high disease activity score >5.1.



**Fig. 7: DAS28 for patients Using HCQ drug.**

**Table 8: Paired Samples Statistics.**

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	BEFORE TREATMENT	5.3960	50	1.37766	.19483
	AFTER TREATMENT	4.0860	50	1.26806	.17226

**Table 9: Paired Samples Correlations.**

		N	Correlation	Sig.
Pair 1	Before treatment and After treatment	50	.767	.000

**Table 10: Paired Samples Test.**

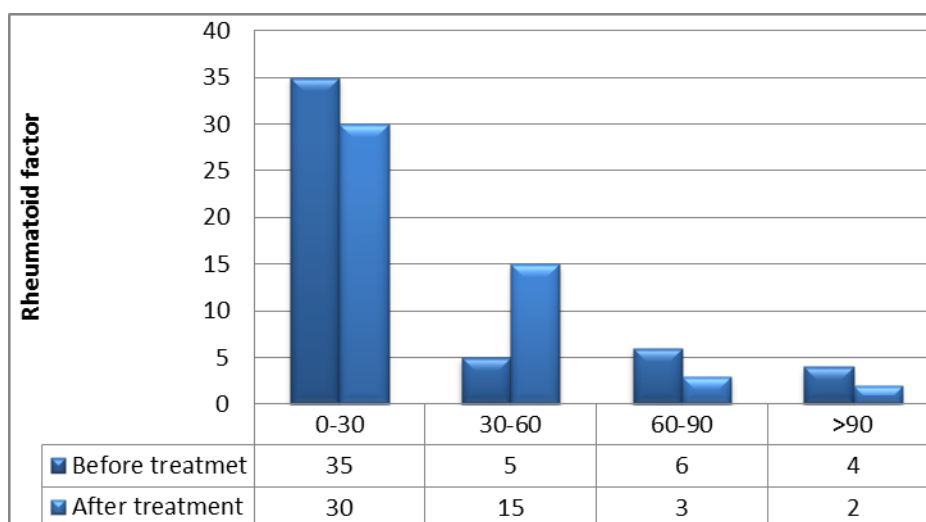
		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
					Lower	Upper			
Pair 1	Before treatment – After treatment	1.3100	.89881	.12711	.85456	1.36544	8.733	49	.000

Table 8: shows that pre and post treatment DAS 28 for HCQ of 50 patients included in the study. The mean of pre-treatment DAS 28 for HCQ drug was  $5.396 \pm 1.377$  and the mean of DAS 28 for HCQ drug after treatment was  $4.086 \pm 1.268$ . This shows that there was a significant decrease in DAS 28 for HCQ drug i.e.,  $1.31 \pm 1.09$ . There was a significant difference in reduction of Pain having p-value  $< 0.05$  (95% confidence interval). By conventional criteria this difference is considered to be statistically significant.

Table 11 shows the pre and post treatment rheumatoid factor for patients using methotrexate MTX drug of 50 patients included in the study. out of 50 patients before treatment 35 patients were between RF value 0-30 and after treatment 30 patients were between RF value 0-30. Before treatment 5 patients were between the RF value 30-60 and after treatment 15 patients were between the RF value 30-60. Before treatment 6 patients were between the RF value 60-90 and after treatment 2 patients were between RF value 60-90. Before treatment 3 patients were between RF value 60-90. Before treatment 4 patients were RF value  $> 90$  and after treatment 2 patients were RF value  $> 90$ .

**Table 11: Rheumatoid factor (RF) for patients using MTX drug.**

Rheumatoid factor (RF)	Before treatment	After treatment
0-30	35	30
30-60	5	15
60-90	6	3
$> 90$	4	2



**Fig. 8: Rheumatoid factor (RF) for patients using MTX drug.**

**Table 12: ESR for patients using MTX drug.**

ESR (mm/hr)	Before treatment	After treatment
20-40	12	22
40-60	13	22
60-80	17	5
80-100	8	1

Table 12 shows the pre and post treatment ESR for patients using MTX drug. Out of 50 patients 12 patients were between ESR 20-40 and after treatment 22 patients were between ESR 20-40. Before treatment 13 patients were between ESR 40-60 and after treatment 22 patients

were between ESR 40-60. Before treatment 17 patients were between ESR 60-80 and after treatment 5 patients were between ESR 60-80. Before treatment 8 patients were between ESR 80-100 and after treatment 1 were ESR 80-100.

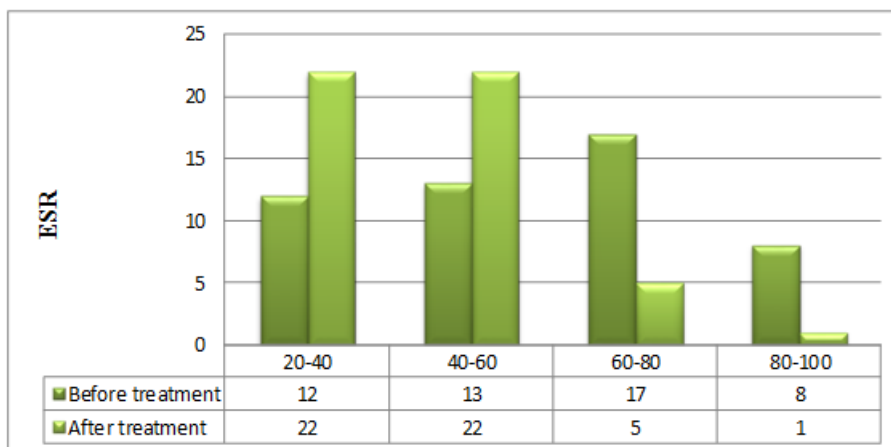


Fig. 9: ESR for patients using MTX drug.

Table 13: Paired Samples Statistics.

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	Before treatment	60.6000	50	19.93971	2.81990
	After treatment	41.3000	50	17.31491	2.44870

Table 14: Paired Samples Correlations.

		N	Correlation	Sig.
Pair 1	Before treatment & After treatment	50	.745	.000

Table 15: Paired Samples Test.

		Paired Differences				t	df	Sig. (2-tailed)	
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
					Lower				Upper
Pair 1	Before treatment – After treatment	19.30000	13.51530	1.91135	15.45899	23.14101	10.098	49	.000

Table 15 shows that pre and post treatment ESR for MTX drug of 50 patients included in the study. The mean of pretreatment ESR for MTX was 60.600±19.93971 and the mean of ESR for MTX drug after treatment was 41.300±17.31491. This shows that there was a significant decrease in ESR for MTX drug i.e., 19.300±26248. There was a significant difference in reduction of ESR having p-value <0.05(95% confidence interval). By conventional criteria this difference is considered to be statistically significant.

Table 16: DAS28 for patients using MTX drug.

DAS28	Before treatment	After treatment
<2.6	0	4
2.6-3.2	12	17
3.2-5.1	17	20
>5.1	21	9

Table 16 shows the pre and post treatment DAS 28 for patients using MTX drug. Out of 50 patients after treatment 4 patients were between the DAS less than 2.6. Before treatment 12 patients were between the DAS 2.6-3.2 and after treatment 17 patients were between the DAS 2.6-3.2. Before treatment 17 patients were between DAS 3.2-5.1 and after treatment 20 patients were between DAS 3.2-5.1. Before treatment 21 patients were DAS >5.1 and after treatment 9 patients were DAS >5.1.

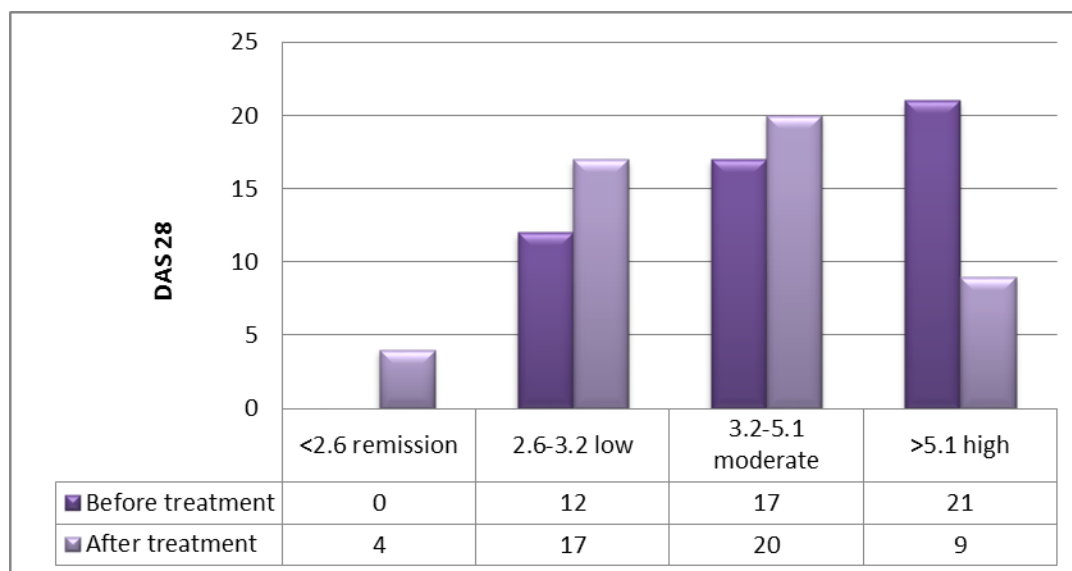


Fig. 10: DAS28 for patients using MTX drug.

Table 17: Paired Samples Statistics.

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	Before treatment	5.0260	50	1.27922	.18657
	After treatment	3.9320	50	1.10186	.16148

Table 18: Paired Samples Correlations.

		N	Correlation	Sig.
Pair 1	Before treatment & After treatment	50	.922	.000

Table 19: Paired sample test.

		Paired Differences				t	df	Sig. (2-tailed)	
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
					Lower				Upper
Pair 1	Before treatment – After treatment	1.0940	.51564	.07292	.94746	1.24054	15.002	49	.000

Table 17 shows that pre and post treatment DAS28 for MTX drug of 50 patients included in the study. The mean of pre-treatment DAS 28 for MTX drug was  $5.0260 \pm 1.27922$  and the mean of DAS 28 for MTX after treatment was  $3.9320 \pm 1.10186$ . This shows that there was a significant decrease in DAS 28 for MTX drug i.e.,  $1.0940 \pm 0.1350$ . There was a significant difference in reduction of DAS 28 for MTX drug having p-value  $< 0.05$  (95% confidence interval). By conventional criteria this difference is considered to be statistically significant.

#### CO-Efficient of Variation (CV %)

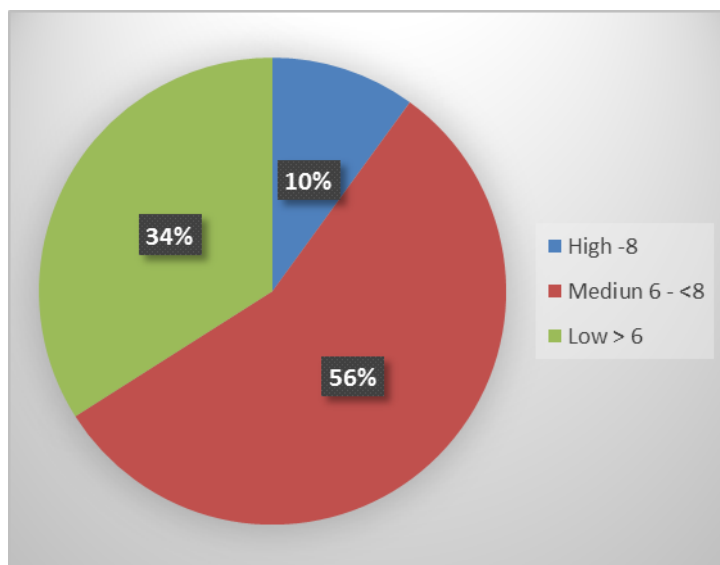
It is a statistical measure of the dispersion of data points in a data series around the mean. Lower the CV value more consistent the results.

$$\text{CO-EFFICIENT OF VARIATION (CV)} = \frac{\text{SD} \times 100}{\text{MEAN}}$$

Table 20: Co-efficient of variation for DAS28 of Hydroxychloroquine and Methotrexate.

Drugs	Standard deviation	Mean	Co-efficient of variation
HYDROXYCHLOROQUINE	1.26806	4.0860	31
MERHOTREXATE	1.10186	3.932	28



**Medication adherence****Fig. 11: Medication adherence.**

- Out of 100 patients 50 patients are using MTX drug and 50 patients are using HCQ drug are included in study.
- In HCQ drug using patients out of 50 patients 17 patients are low adherent to medication and 28 patients are medium adherent to medication and 5 patients are high adherent to medication.
- In MTX drug using patients out of 50 patients 18 patients are low adherent to medication and 23 patients are medium adherent to medication and 13 patients are high adherent to medication.
- According to our study, we have observed that Patient medication adherence was moderately adherent.

**DISCUSSION**

With the disease modifying therapy currently available, complete remission of rheumatoid arthritis are almost rare. A variety of disease modifying anti rheumatic drugs (DMARDs) are available to control the clinical activity of rheumatoid arthritis, methotrexate an analogue of folic acid and hydroxychloroquine are the most commonly used drugs in monotherapy of rheumatoid arthritis.

Very little research was done before regarding the monotherapy of MTX and HCQ in RA patients making the comparison very difficult. We sought to design and conduct a study that would reflect clinical practice and yield results applicable to patients with RA and their physicians, therefore we allowed patients to continue taking NSAID's and other drugs prescribed to them.

Early Placebo controlled trails demonstrated that weekly low dosage methotrexate produced early symptomatic improvement in most RA patients.<sup>[5]</sup>

A double blind placebo controlled, crossover study of weekly pulse methotrexate dose (15mg), after 13 weeks of therapy patients receiving methotrexate showed greater improvement, judged by degree of joint swelling and tenderness, duration of morning stiffness and subjective assessment of clinical condition compared to those receiving placebo ( $p \leq 0.002$ ).<sup>[6]</sup>

A 36 week randomised double-blind placebo controlled study done by HERA group regarding the usage of hydroxychloroquine of dose 400 mg in RA patients and it has been assessed by students "t" test. Over the course of study there was satisfactory significant improvement in the joint index ( $p=0.004, p=0.034$ ), the pain index ( $p=0.007, p=0.001$ ) and the physical index ( $p=0.020, p=0.011$ ) with the group receiving hydroxychloroquine compared to placebo.<sup>[7]</sup>

We have done a prospective observational study with 100 patients in a time period of 6 months. Among 100 patients 50% patients i.e 50 patients were treated with Hydroxychloroquine and another 50% are treated with Methotrexate. All the patients are being diagnosed and assessed their condition by the various diagnosing tools like ESR, DAS 28, RF, and their adherence is being checked using Morisky's adherence scale. Both the group has been assessed by DAS28 score to check the remission rate after a 3 months period. Hydroxychloroquine group having remission rate of 4% (2 patients out of 50) with the value  $< 2.6$ , and having standard mean deviation of 0.89881 and are shown to be significant with  $p$  value  $< 0.05$ . Another 50%, Methotrexate group being assessed having remission rate of 8% (4 patients out of 50) with the remission value of  $< 2.6$  and having standard mean deviation of 0.07292 and are shown to be significant with  $p$  value  $< 0.05$ .

Morisky medication adherence scale was used to calculate the medication adherence. In our study the

patients having moderate compliance at an initial stage due to lack of knowledge about the comorbidities and usage of medications later, the compliance overcome by patients counselling about the medication use and their disease condition. And finally future studies are needed to provide information on the potential benefits of mono therapy of DMARD's like MTX and HCQ and others with respect to therapy.

## CONCLUSION

Hydroxychloroquine and Methotrexate are the most commonly used primary drug of choice in the treatment of rheumatoid arthritis patients. In our 6 months study, it was Observed that Methotrexate is comparatively more efficacious than Hydroxychloroquine. Remission rate by methotrexate is slightly edge more over with hydroxychloroquine. However further work is required to determine the use of oral methotrexate and hydroxychloroquine in the therapeutic management of rheumatoid arthritis. Medication adherence among the patients was mostly moderate. Measures are to be taken to improve the medication adherence. Clinical pharmacist have major role in improving medication adherence through proper patient counseling.

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