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Original Research Article

Methotrexate Combinations in Rheumatoid Arthritis

A Comparative Study of Methotrexate Alone and Methotrexate with Hydroxychloroquine in Rheumatoid Arthritis Patients in A Tertiary Care Teaching Hospital

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Abstract: Rheumatoid arthritis (RA) is a chronic, progressive autoimmune disease associated with polyarthritis and dysfunction of joints. Early diagnosis and treatment may affect disease outcomes even to a remission state. If not treated properly, it may increase morbidity and mortality due to extra-articular manifestations. No clear guidelines are available regarding the use of various Disease Modifying Anti Rheumatic Drugs and other immunosuppressive drugs in RA. Physicians have also used hydroxychloroquine (HCQS) due to its anti-inflammatory property. We aim to compare the effectiveness and safety profile of Methotrexate (MTX) monotherapy and HCQS in RA patients. Patients of RA attending Orthopaedic OPD at GSVM Medical College, Kanpur, are included and followed up for 6 months. Patients of Group A are treated with MTX alone, while Group B is treated with a combination of MTX plus HCQS. The effectiveness of the treatment is evaluated by improvement in the DAS28 scale at each follow-up visit. Drug safety profiles are assessed by Adverse drug reactions reported by patients and their causality assessment per Naranjo's probability score. In our study, 61 patients are included. The mean age is 49 years, while male to female ratio is 1:5. Improvement in the DAS28 score in the combination therapy group is significant (p value<0.05). Both groups had adverse events associated with their treatment. Still, none of the Adverse Drug Reactions was definite as per Naranjo's probability score, and a maximum number of Adverse Drug Reactions were non-serious. Our study concluded that combination therapy (MTX plus HCQS) provides better disease control. Combination therapy shows an almost similar safety profile; the frequency of adverse events was also similar to MTX alone. HCQS is a cost-effective drug easily available in India, so it would be better to use combination therapy in RA to control the disease.

Keywords: RA, MTX, HCQS, DAS28

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1. INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, progressive autoimmune disease associated with polyarthritis and dysfunction of joints.[1] About 1% of the world population and approximately 0.75% of the adult Indian population[2-4] is affected by RA. The cause of RA is unknown and thought to be due to a combination of genetic, environmental, and hormonal factors. It may affect at any age, but the prevalence of RA increases with age. The peak age of onset is the 4-5th decade, and it is more common in women than men with a ratio of 2:1 to 3:1.[5] It usually begins in the small bones of the hands (particularly those at the base and middle of the fingers), the base of the toes, and wrists and progresses over time. Patients often complain of early morning joint stiffness, which lasts more than one hour and eases with physical activity.[6] Initially, there is inflammation inside the joint, and the patient feels pain, stiffness, and swelling in joints; if left untreated, synovium gets inflamed, leading to cartilage damage. Due to cartilage damage, patients feel pain and loss of mobility, restricted joint movement, bone damage(erosion), and deformity in the advanced stage. In the late stage of RA, there is no more inflammation, but the patient feels pain, stiffness, and mobility loss. Joints are destroyed, and bones are fused due to Ankylosis[7]. Incompletely controlled RA results in progressive, irreversible joint damage.[8] RA may increase morbidity and mortality due to extra-articular manifestations, including fatigue, subcutaneous nodules, lung involvement, pericarditis, peripheral neuropathy, vasculitis, and hematologic abnormalities.[9] Diagnosis of RA can be made by clinical symptoms and the presence of rheumatoid factor and anti-cyclic citrullinated peptide(anti-CCP) antibodies.[10] Early diagnosis and treatment may affect disease outcomes even to remission. [11,12] Drugs used in the treatment of RA are k/a DMARD (Disease Modifying Anti Rheumatic Drugs), including Immunomodulatory like Methotrexate (MTX), Leflunomide, Cyclosporine, Azathioprine, Mycophenolate Mofetil (MMF) and Glucocorticoids, etc. MTX is a first choice DMARD in the case of RA, recommended by the EULAR and the ACR due to its favorable balance in effectiveness, safety profile, and cost.[13,14] The antimalarial drug Hydroxychloroquine (HCQS) is also used as DMARD. HCQS has become a part of current treatment guidelines for RA due to its anti-inflammatory property.[15] There are no clear guidelines regarding the use of various DMARD and other immunosuppressive drugs in RA. MTX is the first drug of choice, and other drugs are added if no satisfactory response is elicited. Several recent studies, including a meta-analysis, shows that most MTX-based combination with other drugs is no more effective than MTX monotherapy, except for MTX along with Sulphasalazine or HCQS and possibly with Leflunomide.[16-18] In our institute, MTX monotherapy, MTX, and HCQS combination, have been used to treat RA, so we decided to conduct a quasi-experimental study to see the effectiveness of MTX monotherapy and MTX along with HCQS in RA patients.

2. METHODS

The study was conducted by the Department of Pharmacology and Orthopaedics at GSVM Medical College, Kanpur, UP, from January 2021 to June 2022. All the participating physicians were involved in developing the protocol, enrolling the patients, and collecting the data. It is a prospective observational study. In this study effectiveness of MTX monotherapy vs MTX plus HCQS combination therapy was compared by improvement in DAS28 Score in patients of RA. Patients were followed up for 6 months at an interval of 4 weeks. During follow-up at every visit, Adverse Events (AE) reported by the patients were also included in the study to compare the safety profile of both regimens. The study was completed with the collaboration of the Department of Pharmacology and the Department of Orthopaedics at GSVM Medical College, Kanpur, UP, from January 2021 to June 2022.

2.1. Inclusion and Exclusion criteria of patients

Patients of RA attending Orthopaedic OPD diagnosed as a case of RA according to ACR/EULAR criteria[19] (age between 18 and 60 yrs) were included. Patients who gave consent and were ready for a follow-up of six months were included. Patients of other chronic diseases and Psychiatric illnesses, pregnant/lactating women, and who lost to follow-up for more than two months were excluded. Approval of study was granted by IEC at GSVM Medical College, Kanpur, with the Ref. No. EC/299/Dec./2021. All procedures performed in the study were conducted under the ethical standard in the 1964 Declaration of Helsinki, as revised in 2013.

2.2. Study design

It is a prospective observational study. A total of 61 patients were enrolled in the study. Patients were divided into two groups, group A contains patients who have been prescribed Tab MTX 15 mg orally once weekly. In contrast, group B included the patients prescribed a combination of MTX 15 mg, orally once weekly, and HCQS 400 mg, orally, daily. In addition, folic acid 10 mg was prescribed 24 hrs after the dose of MTX to minimize side effects associated with MTX, in both groups. Treatment was decided by an Orthopedician in OPD.

2.3. Data collection

All relevant data were collected (age, gender, RA factor, swollen joint count, tender joint count, visual analog scale, global patient health, CRP/ESR, and any adverse event during treatment) at baseline with every visit at an interval of four weeks. The primary outcome in the form of improvement in the DAS28 score was calculated at every follow-up.

2.4. Efficacy of drugs

Disease Activity Score in 28 joints (DAS28) has been used to assess disease activity in patients with RA for the past several years[20]. The efficacy of drugs was assessed by improvement in the DAS28 score at every follow-up. DAS28 was computed utilizing total joint count (TJC), swollen joint count (SJC), visual analog scale, and erythrocyte sedimentation rate (ESR). It is calculated by a complex formula requiring a calculator, computer, or access to an internet-based online calculator. A patient with a DAS28 score of less than 2.6 is in remission; a score greater than or equal to 2.6 and less than 3.1 indicates low activity; a score greater than or equal to 3.1 and <5.1 indicates moderate activity, and a score of 5.1 or more indicates high activity[21].

2.5. The safety profile of drugs

Clinical adverse events (AE) reported by the patient and hematological (CBC, GBP, ESR, LFT, KFT, CRP) parameters assessed the safety of drugs. Naranjo algorithm questionnaire was used for assessing the causality assessment of Adverse

Events. The Modified Hartwig scale did the severity assessment.

2.6. Concurrent therapy

Patients who were taking steroids and NSAIDS as regular therapy or as-needed basis were also included in the study.

2.7. Statistical Analysis

Data were analyzed using unpaired t-test and χ^2 test. Potential confounders that are included in the study were age, sex, and proportion of patients meeting the ACR 2010 criteria.

3. RESULTS

3.1. Baseline characteristics

In this study, 61 patients participated. 30 patients were included in group A on monotherapy, while 31 were in group B on combination therapy. The total number of male patients was 11, while 50 patients were female, male to female ratio is 1:5. Mean age of all patients is 49.1±9, while the mean age in group A is 47.9±9.6 years, while in group B is 50.3±9.6 years. In group A, 80%(n=24) of patients were RA factor positive, while 77%(n=24) were RA factor positive in group B. In both groups, no statistical difference is noted in the mean age group/sex ratio/ RA factor positivity (p-value is > 0.05).

Table 1: Patient's demographic details in both Group A and Group B

Parameters	Group A	Group B	Total	p Value
No. of patients	30	31	61	
Age (mean ± SD), years	47.9±9.65	50.3±9.6	49.1±9.65	p>0.05
Gender				
Male	17%(n=5)	20%(n=6)	18.5%	p>0.05
Female	83%(n=25)	80%(n=25)	81.5%	
RA Positive	80%(n=24)	77%(n=24)	78%	p>0.05

Table 2 compares the DAS28 Score at the initiation of treatment and each visit up to 24 wks. On applying paired t-test, there is a significant improvement(p<0.001) in the DAS28 score in both groups during every visit.

Table 2: Improvement in DAS28 score at each follow up

	Baseline DAS28	4 wks	8 wks	12 wks	16 wks	20 wks	24 wks
GROUP A							
Mean±SD	5.86 ±0.40	5.59 ±0.39	5.30 ±0.44	5.21 ±0.43	4.9 ±0.45	4.7 ±0.44	4.47 ±0.37
Mean change		0.30	0.71	1.16	1.71	2.1	2.1
% Change		3%	7%	11.6%	17.10%	21%	21%
p-value		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
GROUP B							
Mean±SD	5.72 ±0.61	5.36 ±0.7	4.99 ±0.6	4.6 ±0.7	4.18 ±0.65	3.83 ±0.56	3.48 ±0.55
Mean change		0.35	0.73	1.1	1.5	1.8	2.23
% Change		6%	13%	20%	27%	33%	39%
p-value		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

Values are Mean±SD (n = 30 in group A, n = 31 in group B)
p-value <0.05 is considered significant

Table 3 compares the DAS28 Score in both groups across the period. On applying an unpaired t-test, it was found that there was no significant difference (p-value > 0.05) in the improvement of both groups during the initial 8 wks, but after 8 wks significant difference (p value<0.05) in improvement was noticed in group B—comparison of mean DAS28 score between group A & group B at every visit.

Table 3 Comparison of DAS28 score between both groups at each follow up

DAS28 Score	Group A (n=30) Mean±SD	Group B (n=31) Mean±SD	p-value
Baseline	5.86±0.40	5.72±0.61	>0.05
4 wks	5.59±0.39	5.36±0.66	>0.05
8 wks	5.30±0.44	4.99±0.64	<0.05
12 wks	5.21±0.43	4.6±0.69	<0.05
16 wks	4.9±0.45	4.18±0.65	<0.05
20 wks	4.7±0.44	3.83±0.56	<0.05
24 wks	4.47±0.37	3.48±0.55	<0.05

Values are Mean±SD (n = 30 in group A, n = 31 in group B)
p-value <0.05 is considered significant

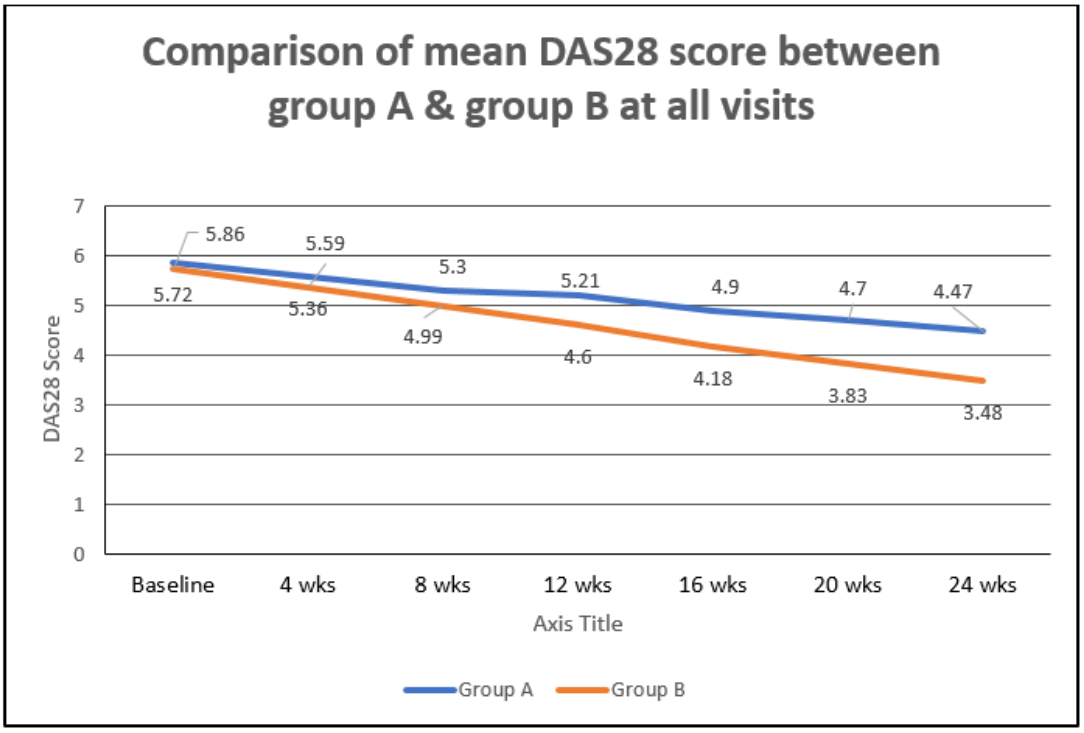

Fig 1: Comparison of the mean DAS28 score between group A & group B at every visit

Fig 1 compares the mean DAS28 score between group A & group B at every visit.

Table 4: Distribution of patients based on adverse effects reported

Adverse effects	Group A(n=30)	Group B(n=31)	p-value
Present	26(87%)	29(94%)	>0.05
Absent	4(13%)	2(6%)	>0.05

Table 4 represents the number and percentage of patients with ADR analyzed by the Chi-square test. In group A, 87 % of patients and 94% of patients in group B experienced adverse effects. However, in both groups, patients experienced adverse events; on the comparison, it was found to be statistically non-significant (p>0.05).

Table 5: Safety profile comparison between two groups

Adverse events	Group A (n=30)	%	Group B (n=31)	%
Pain abdomen	12	40%	12	39%
↓Appetite	8	27%	5	16%
Oral ulcer	5	17%	6	19%
Weakness	4	13%	4	13%
Nausea	4	13%	9	29%
Fever	3	10%	5	16%
Skin rash	3	10%	3	10%
Bodyache	3	10%	3	10%
Jaundice	1	3%	2	6%

Table 5 shows the safety profile of both groups, both groups had adverse effects associated with their treatment, but the maximum number of adverse events were non-serious, and drug withdrawal was not recommended. None of the ADRs was definite in both group, as per Naranjo's probability score. In group A, the percentage of Probable, Possible & Doubtful ADR was 21%, 77%, & 2%, respectively, while in group B it was 31%, 65% & 0%, respectively, and none of them were serious.

4. DISCUSSION

RA is an autoimmune, chronic disorder requiring lifelong treatment. As there are no specific guidelines regarding the treatment of RA, this study aimed to compare the efficacy and safety of combination therapy of MTX plus HCQS with MTX monotherapy. This study's baseline characteristics (age, sex, RA factor positivity) were similar to other studies conducted in India[22,23]. In this study, the mean age of the patient is 49.1±9 years, while it is 50.53±14.81 years[22] and 44 years[23] in another study. In another study, the maximum number of patients of RA were in the age group of 51-60 years (36%), while 29% were in the age group of 41-50 years[24]. A study conducted in China found the mean age of patients to be 51 years[25]. The male-to-female ratio in this study was around 1:5, which is in accordance with other studies conducted in India[22,23], but in Malaysia, the male: female is 1:2[26]. Another study concluded that male to female ratio is 1:6[24]. In a study in China, it was found that 83.35% of patients with RA were female[25]. In another study, only 25% of patients were male, while 75% were female[27]. In this study, 78% of patients were found to be

RA factor positive. While in another study, it was 80.70%[22]. Another study stated that the RA factor is positive in about 70% – 90% of patients of RA[28], while 61% were found to be RA factor positive in a study[29]. In this study baseline, the DAS28 score in Group A is 5.86±0.40, while in Group B is 5.72±0.61. After a period of 24 wks, the improvement in the DAS28 score was 21% in group A and 39% in group B. It means the group B regimen (MTX plus HCQS) was more effective. In another study DAS28 score was found to be 16.37 & 18.4 in both groups; they also concluded that after 16 wks, combination therapy of MTX plus HCQS is more effective [22]. In this study, out of 61 patients, 55 (90%) reported some ADR. Among the reported ADRs, Abdominal pain/Gastritis (40%) was the most common ADR among both groups (both groups had 12 patients reporting pain abdomen/ Gastritis related ADR). The next commonest ADR was a decrease in appetite in group A reported by 8(27%) patients, while in group B the next commonest ADR was Nausea, reported by 9 (29%) patients. Another study reported that the commonest drug-related problem was nausea and vomiting[30]. Another study reported adverse effects found in RA patients with use of MTX were gastrointestinal reaction in 5.9%, infections in 4.5%, and hepatotoxicity in 3.6% of patients[25]. In another study, 82.5% (165 out of 200) reported some ADR[24]. Out of ADRs, Gastritis was found in 18.2% of patients, skin rashes were found in 9.6% (43/200) of patients, and aphthous ulcers were found only in 0.2% of patients which is lower than our study. Another study conducted in Malaysia on drug-related problems in RA patients found that 82.5% had some adverse drug-related problems. The maximum number of MTX use problems was related to the GIT system (Gastroenteritis)[26]. Another study reported that 67.47% of ADRs were GIT related, and 19.28% were mouth ulcers[22]. It is similar to study [31], which also reported that gastrointestinal side effects are maximum in patients taking MTX & HCQS together, which is in accordance to our study. This study found that in group A, 21% and 31% in group B of ADRs were in the Probable category. 77% of ADRs in group A and 65% in group B were in the Possible category. Only 2% in group A and 4% in group B were doubtful, and none of the ADRs was in the Definite category. Another study[24] stated that 54% of ADRs were Probable, 46% were Possible, and 0% were Certain/Definite which is in accordance with our study.

5. LIMITATIONS

The study was not randomized, and results are thus susceptible to confounding. Also, the treatment was provided by another healthcare provider, so an Orthopedician might have provided combination treatment to patients with severe RA, which may also result in bias. Finally, RA is a lifelong disease; follow-up has only been done for six months. Therefore, follow-up of a longer duration is needed to make a more precise conclusion.

6. CONCLUSION

RA is a chronic autoimmune disease and requires lifelong treatment. In our study, combination therapy (MTX plus HCQS) provides better disease control. Combination therapy shows an almost similar safety profile, and adverse event frequency to MTX alone. On observing both groups adverse events profile came out to be non-significant. HCQS is a cost-effective drug easily available in India, so it would be better to use combination therapy in RA to control the disease.

7. ACKNOWLEDGEMENT

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8. AUTHORS CONTRIBUTION STATEMENT

All the authors Dr. Pooja Agrawal, Dr. Virendra Kushwaha, Dr. Vipul Shukla, Dr. Praganesh Kumar, Dr. Amit Kumar, and Dr. Himanshu Sharma, have equally made a substantial contribution to the conception, acquisition of data, interpretation of data and in drafting the article and agreed to be held accountable for all aspects of the work.

9. CONFLICT OF INTEREST

Conflict of interest declared none.

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