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RESEARCH ARTICLE

METHOTREXATE AND HYDROXYCHLOROQUINE COMBINATION THERAPY IN THE TREATMENT OF RHEUMATOID ARTHRITIS BASED ON CLINICAL DISEASE ACTIVITY INDEX SCORE

Anjali Menon[1], Patel Radhika[2], Patel Devanshi[2], Khambata Bhavya[2], Tailor Vivek[2], Anshu Srivastava[3], Bhagawati Saxena[1*]

[1]Department of Pharmacology, Institute of Pharmacy, Nirma University, Sarkhej-Gandhinagar Highway, Ahmedabad – 382481, Gujarat, India

[2]Department of Pharmacology and Pharmacy Practice, SAL Institute of Pharmacy, Opp. Science City, Ahmedabad-380060, Gujarat, India

[3]Department of Pharmaceutics, Institute of Pharmacy, Nirma University, Sarkhej-Gandhinagar Highway, Ahmedabad – 382481, Gujarat, India

bsaxenapharm@gmail.com, bhagawati.saxena@nirmauni.ac.in

ABSTRACT

In the Indian population, the incidence of rheumatoid arthritis (RA) is found to be 0.75%. Methotrexate (MTX) is a folate antagonist which is approved as a first-line drug by the U.S. Food and Drug Administration (FDA) for the treatment of RA. MTX monotherapy has its limitations. Hydroxychloroquine (HCQ) belongs to the category of disease-modifying antirheumatic drugs (DMARDs). Thus, the present work aims to study the effectiveness of MTX and HCQ combination therapy in the management of RA based on the Clinical Disease Activity Index (CDAI) Score. A Bicentric Retrospective Observational Study was conducted on RA patients managed with the combination therapy of MTX and HCQ in the tertiary care hospitals of Ahmedabad city. Demographic information, CDAI score, RA factor, comprehensive therapy plan, and treatment results (remission) were all obtained using devised data input forms. The baseline CDAI score and CDAI score after one year and two years were noted. A total of a 576 RA patients on combination therapy of MTX and HCQ were enrolled to participate in the research study, of which 84% i.e. n=484 were female and

16% (n=92) were male. Data indicated that out of a total 576 patients, 26.2% (n=151) belonged to the age group of 40-49 years and 26.04% (n=150) were identified to be of age between 50-59 years. Interpretation of the results revealed that all groups significantly improved after receiving the combination therapy. However, remission was achieved in 56 patients (9.7%) with combination therapy. Thus, treating active RA with the combination of MTX and HCQ is efficacious.

Keywords: Rheumatoid Arthritis, Methotrexate, Hydroxychloroquine, Combination Therapy, Clinical Disease Activity Index Score

INTRODUCTION

Rheumatoid arthritis (RA) is a type of autoimmune disorder that is characterized by a chronic and often progressive inflammatory illness with polyarticular symmetric joint and systemic symptoms. The incidence of RA worldwide between 1980 and 2019 was reported to be 460 per 100,000 people, with some regional and methodological differences [1]. Amongst the Indian population, the prevalence of RA is 0.75% in adult populations [2]. Studies show that women are more likely than men to acquire RA due to hormonal variations [3,4]. Males have a decreased risk of RA because testosterone and progesterone depress the immune system and estrogen boosts humoral immunity [5-8].

Methotrexate (MTX) (structure is shown in **Fig. 1**) is a folate antagonist and the first-line drug approved by the U.S. Food and Drug Administration (FDA) for the pharmacotherapeutic management of RA [9,10]. Monotherapy with MTX has its own limitations. MTX induces liver toxicity [11, 12], pulmonary toxicity [13, 14], and stomatitis [15]. Even with extensive patient monitoring, improvements in disease parameters are evident quite quickly when using MTX alone, but they tend to plateau after approximately six months without any

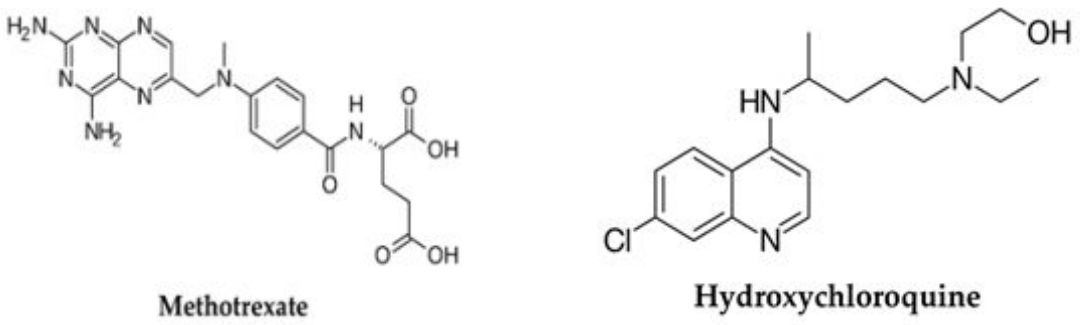

Figure 1: Structure of Methotrexate and Hydroxychloroquine

further improvement [16, 17]. Therefore, a combination of other disease-modifying antirheumatic drugs (DMARDs) with MTX will be the preferred pharmacotherapeutic approach for managing RA. The DMARDs reduce phagocytosis, T-cell activation, and pro-inflammatory cytokines such as tumour necrosis factor. They also have a marginally beneficial impact on those with active RA and systemic rheumatoid diseases, serving as immunomodulators and having marginal anti-inflammatory effects [18-21]. Hydroxychloroquine (HCQ) (structure is shown in **Fig. 1**) belongs to the category of DMARDs and is reported to be a safer drug than methotrexate when it comes to hepatic side effects [22]. Additionally, the potency, safety profile, and dosage of MTX are all reported to be improved by HCQ [23]. The extent of severity in RA is expressed as the Clinical Disease Activity Score (CDAI), which represents a simple summation of joints involved in the disease [24]. The study therefore aims at evaluating the effectiveness of the combination therapy of MTX and HCQ in the treatment of RA on the basis of CDAI.

METHODOLOGY

A bicentric retrospective observational study was carried out on RA patients receiving combination therapy of MTX and HCQ in the tertiary care hospitals of Ahmedabad city. Pediatric patients were excluded from the study. Informed consent from the enrolled patients were taken. Data entry forms were designed, and the data collected were demographic details, CDAI score, RA factor (RF), detailed treatment plan, and outcomes (remission) of the treatment. After approval from the Ethics Committee, subject data was collected over a period of January 2016- July 2021 and scrutinized according to inclusion and exclusion criteria. The data was collected in self-designed data entry forms. The CDAI score was recorded at baseline, after first year and second year of the study. The data was handled confidentially, with no access to any personnel other than the researchers. The data was analyzed statistically using SPSS 20 software with Friedman test (moderate and high severity groups) and Wilcoxon signed-rank test (low severity group).

RESULTS AND DISCUSSION

A total 576 patients RA patients on combination therapy of MTX and HCQ were enrolled to participate, out of which 84% i.e. 484, were female while 16% (n=92) were male. This can be attributed to the fact that the hormonal changes that females go through during menopause increase the risk of developing the disease. Apart from this, estrogen can enhance the humoral immunity in several systems while androgens and progesterone are considered as natural immunosuppressor and thus males are at a lower risk of developing RA [3-8].

It was found that out of total 576 patients, 26.2% (n=151) lie in the age group of 40-

49 years and 26.04% (n=150) lie in the age group of 50-59 years **(Fig. 2)**. The study shows similar results to another study conducted in Gujarat which observed that the age group of 40-59 years is mostly affected with RA [25]. The antibody test results of patients for the diagnosis of RA revealed that, 88.6% (n=514) patients tested seropositive for rheumatoid factor (RF), while 11.4% (n=64) patients tested seronegative **(Fig. 3)**. Seropositive patients have RF while seronegative patients do not have RF. However, significant local and systemic symptoms of RA persisted even in the absence of RF and therefore considered to be RA patient.

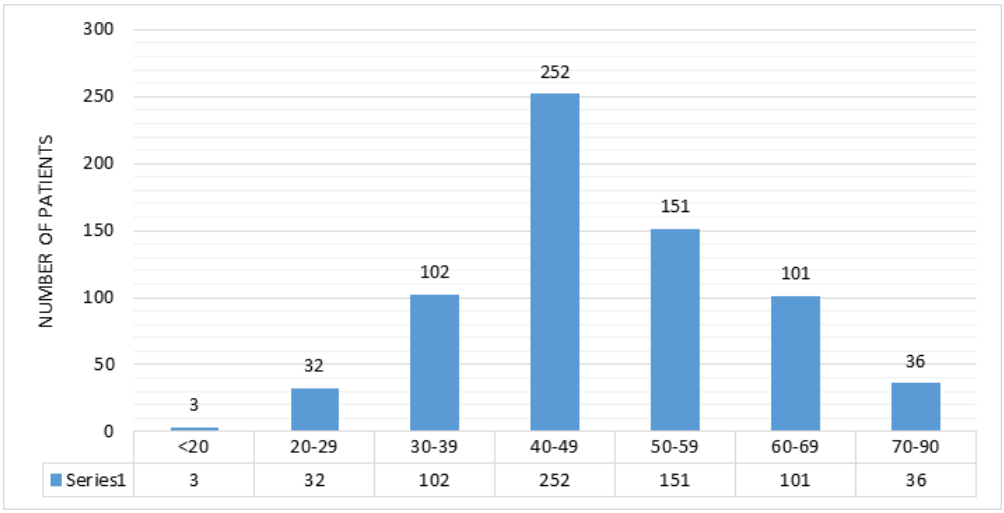

Figure 2: Age Distribution Among the Enrolled Patients (Age is Expressed in Years)

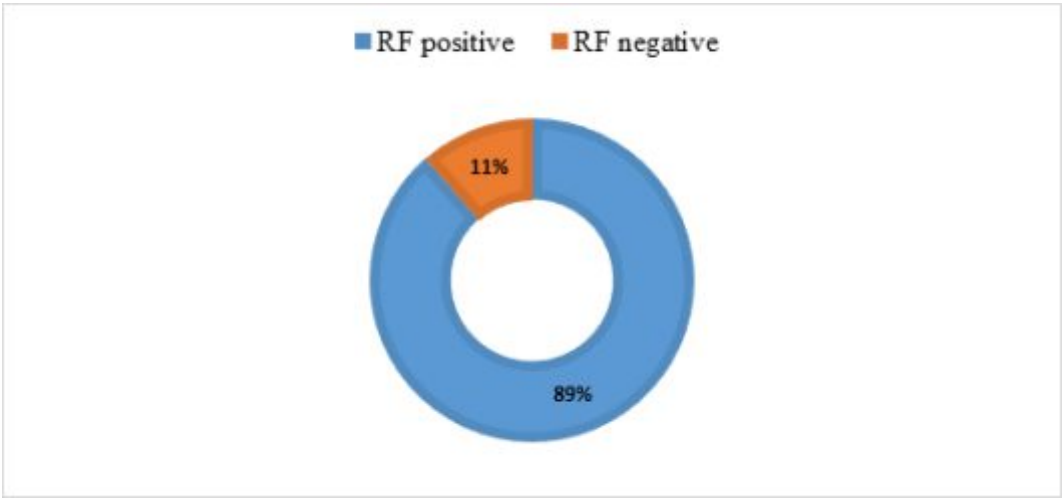

Figure 3: Distribution of Patients Based on Rheumatoid Factor (RF).

Based on CDAI score, 9.7% (n=56) of the total patients had low disease severity, 49.13% (n=283) had moderate disease severity, and 40.7% (n=235) had high disease severity. Significant improvement with the given combination therapy of MTX and HCQ in all group with low, moderate and high disease severity were observed **(Table 1)**. Remission was considered when CDAI score is less than and equal to 2.8. Remission was achieved in 56 patients (9.7%) based on a reduction in CDAI score. The patients with baseline low CDAI score often discontinue treatment and therefore remission was not mostly achieved in that case. High and moderate severity patients were followed up till two years and there was significant decrease in the CDAI score from the baseline indicating high recovery from the initial state. The mean score was 8.01 ± 3.78 and 13.69 ± 6.43 in moderate and high CDAI score category, respectively after treatment for 2 years (Table 2,3). These results are in conformity with the earlier published studies that show the effectiveness of MTX and HCQ combination in RA patients [26, 27].

Table 1: Effectiveness of MTX+HCQ in Enrolled RA Patients Based on CDAI Score

Disease Severity	CDAI Score		
	Baseline	**After 1 year**	**After 2 years**
Low (n=56)	7.77 ± 1.79	4.91 ± 1.91*	DT
Moderate (n=283)	18.03 ± 2.85	12.68 ± 3.25*	8.01 ± 3.78*
High (n=235)	28.31 ± 6.44	20.42 ± 5.46*	13.69 ± 6.43*

CONCLUSION

Results of the present study conclude that treating active RA in all the range of disease severity with combination of MTX and HCQ is efficacious as remission is significantly increased based on CDAI score.

Values are expressed as mean±SD.

*P value <0.001 compared to baseline CDAI is considered to be statistically significant.

DT: Discontinued treatment

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