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Original Research Article

A Study of Methotrexate Alone vs HCQ Combination with Methotrexate in DMARD-Naïve Patients with Early Rheumatoid Arthritis

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Abstract: *Early and effective disease control in rheumatoid arthritis (RA) is crucial to prevent joint damage and long-term disability. Methotrexate (MTX) remains the cornerstone DMARD; however, combination therapy with Hydroxychloroquine (HCQ) is often considered to enhance efficacy. Objective: To compare the effectiveness of Methotrexate alone versus a combination of Methotrexate and Hydroxychloroquine in achieving disease control in patients with early RA.* ***Methodology:*** *This quasi-experimental study was conducted at CMH Lahore from October 22 to December 31, 2024. A total of 225 patients with early RA were enrolled and divided into two groups: Group A received Methotrexate monotherapy (15–25 mg/week), and Group B received Methotrexate in combination with Hydroxychloroquine (200–400 mg/day). Disease Activity Score using 28-joint count and ESR (DAS28-ESR) was recorded at baseline and 10 weeks.* ***Results:*** *The mean baseline DAS28-ESR score was comparable between groups (Group A: 5.82 ± 0.91 vs. Group B: 5.87 ± 0.85, p = 0.63). After 10 weeks, a significantly greater reduction in disease activity was observed in the combination group (Group A: 4.12 ± 0.74 vs. Group B: 3.38 ± 0.65, p < 0.001). Remission or low disease activity was achieved in 42.7% of Group A and 64.4% of Group B (p = 0.002). Adverse events were mild and similar between groups.* ***Conclusion:*** *The combination of Methotrexate and Hydroxychloroquine is significantly more effective than Methotrexate alone in reducing disease activity in early RA, with a comparable safety profile. Early combination therapy may provide a more robust and timely response in disease control.*

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

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Introduction

Rheumatoid arthritis is a chronic, systemic autoimmune disease that primarily affects synovial joints, leading to progressive joint destruction, disability, and decreased quality of life. It affects approximately 0.5–1% of the adult population globally, with a higher prevalence among females. It is paramount that the disease be identified early and treatment be initiated to reduce the functional outcomes of the disease (1). The period immediately after the appearance of the symptoms (the so-called window of opportunity), encompassing the first six months, is the most optimal time during which an aggressive intervention may change the overall course of the disease. The mainstay of treatment of rheumatoid arthritis has been methotrexate for decades (2). Being a folate antagonist, it inhibits the action of the immune system by inhibiting purine metabolism and decreasing inflammation. It is usually known as the first-line disease-modifying anti-rheumatic drug since its effectiveness has been established to control disease activity, prevent structural damage, as well as to increase patient-reported outcomes (3). Although it has been very effective, a high percentage of patients do not give optimum control of the disease with methotrexate monotherapy, and combination therapy becomes necessary. The most common first-line DMARD against RA and the drug referenced in terms of the treat-to-target approach is MTX to reach clinical remission. MTX-monotherapy has recently become the therapy of choice in the first-line treatment of RA, with a shift in the international guidelines towards initial combination DMARD therapy based on several recent studies (including a meta-analysis with indirect comparisons) (4). But several publications have favored the combined application of the HCQ and the MTX. As per outdated National Institute for Health and Care Excellence guidelines, a substantial proportion of patients in the UK were initiated on first-line combination therapy, which in our practice mostly consisted of MTX and HCQ until the update of 2018 (5).

Hydroxychloroquine is also an immunomodulatory compound that has been identified as a useful drug in combined therapy against rheumatoid arthritis. It has quite a good safety profile and extra advantages, such as the possible protection of the cardiovascular system and enhanced lipid metabolism (6). A number of clinical trials and observational studies have also supported the effectiveness of hydroxychloroquine when it is combined with methotrexate, especially in those with an early disease (7). The rationale of the combination therapy is linked to the idea that combined attacks against several inflammatory pathways are used to secure a more prompt and prolonged degradation of disease activity (8). Combination drugs such as methotrexate and hydroxychloroquine have been seen to lead to improved response to treatment, a reduced rate of attainment of remission, and potential slowing/avoidance of using more expensive biologic medications (9). The combination of methotrexate, hydroxychloroquine, and sulfasalazine as part of a triple therapy scheme has been extensively researched and recommended by treatment guidelines (10). Nevertheless, the combination of methotrexate and hydroxychloroquine can be pretty convenient, particularly in the realm of low-resource settings (11). Based on many factors, such as the baseline severity of the disease, prognostic indicators, and comorbidities of the patient, and including the intended goals of the treatment, the choice of going into monotherapy or combination therapy may follow. These strategies have been discussed in studies such as the TEAR and SWEFOT trials. However, the debate exists on which practice is more effective than the other in various clinical situations. Monotherapy with methotrexate is easy and has fewer pills, whereas combination therapy will have a

stronger initial response, especially in patients who have high disease activity or seropositive patients (12).

Thus, the objective of this study was to compare the efficacy of Methotrexate alone versus a combination of Methotrexate and Hydroxychloroquine in achieving disease control in patients with early RA.

Methodology

This comparative quasi-experimental study was conducted at the Department of Rheumatology, CMH Lahore, from 22 October to 31 December 2024. A total of 225 patients diagnosed with early rheumatoid arthritis were enrolled using a non-probability consecutive sampling technique. Participants included adult patients aged between 18 and 65 years who were newly diagnosed with early rheumatoid arthritis, defined as having a symptom duration of six months or less, by the ACR/EULAR 2010 classification criteria. All patients were DMARD-naïve at the time of enrollment.

Patients were excluded if they had a history of prior use of methotrexate, hydroxychloroquine, or any other disease-modifying anti-rheumatic drugs (DMARDs). Additional exclusion criteria included the presence of other autoimmune disorders or mixed connective tissue disease, significant hepatic or renal dysfunction, pregnancy or lactation, and known intolerance or contraindication to methotrexate or hydroxychloroquine.

After obtaining written informed consent and ethical approval, patients were allocated into two groups. Group A received methotrexate monotherapy (starting dose 15 mg/week, titrated up to 25 mg/week as tolerated), while Group B received a combination of methotrexate with hydroxychloroquine (200–400 mg/day). All patients were prescribed folic acid supplementation and monitored monthly for disease activity using DAS28-ESR scoring, functional status, and adverse effects.

Data were analyzed using SPSS version 25.0. Mean and standard deviation were calculated for quantitative variables such as age, disease duration, and DAS28 scores. Frequencies and percentages were determined for categorical variables. The paired t-test was used to compare pre- and post-treatment disease activity scores within groups, while the independent t-test was applied for between-group comparisons. A p-value ≤0.05 was considered statistically significant.

Results

The study enrolled 225 patients with rheumatoid arthritis, split nearly equally into Group A (MTX alone, n = 113) and Group B (MTX + HCQ, n = 112). The mean age was comparable between the groups (43.2 ± 10.6 vs. 42.5 ± 11.1 years; p = 0.58), and females comprised the majority in both groups (77.9% vs. 75.0%; p = 0.61). Symptom duration before treatment initiation was similar (13.4 ± 2.6 vs. 13.1 ± 2.8 weeks; p = 0.29), as were baseline disease activity scores (DAS28-ESR: 5.91 ± 0.72 vs. 5.87 ± 0.69; p = 0.67), indicating well-matched groups at baseline. (Table1)

After 10 weeks, the MTX + HCQ group showed significantly lower post-treatment DAS28-ESR scores (3.65 ± 0.58) compared to the MTX-only group (4.10 ± 0.65), with a highly significant p-value <0.001. The mean change in DAS28-ESR was also greater in the combination group (-2.22 ± 0.41 vs. -1.81 ± 0.46; p <0.001). Remission (DAS28-ESR < 2.6) was achieved in 52 patients (46.4%) in the combination group, markedly higher than 28 patients (24.8%) in the monotherapy group (p = 0.001), suggesting superior efficacy of the combination therapy. (Table2)

Adverse effects were generally mild and comparable between groups. Nausea occurred in 12.4% of MTX-alone patients vs. 9.8% in the MTX + HCQ group (p = 0.52). Elevated liver enzymes were reported in 7.1% and 6.3% of patients, respectively (p = 0.78). Rash was slightly more common in the combination group (5.4% vs. 2.7%; p = 0.31). Notably, visual complaints were reported only in the MTX + HCQ group (4 cases; 3.6%) and none in the MTX-alone group, with this difference reaching statistical significance (p = 0.04). (Table 3)

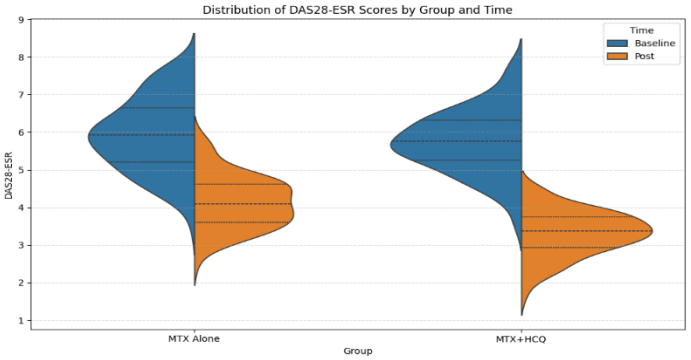

Figure 1: Violin plot showing the distribution of DAS28-ESR scores at baseline and post-treatment for two groups: MTX Alone and MTX+HCQ

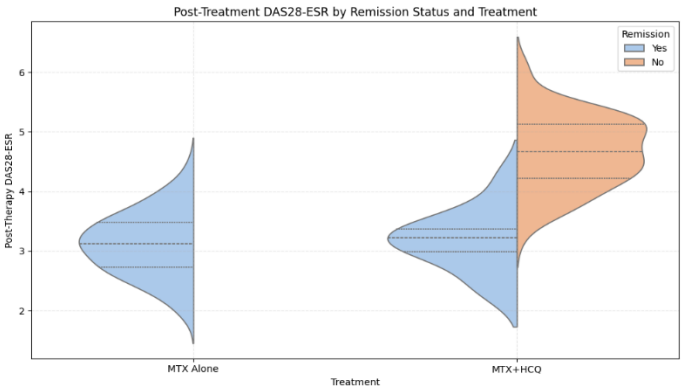

Figure 2: Violin plot illustrating post-treatment DAS28-ESR scores by remission status and treatment group (MTX Alone vs. MTX+HCQ).

Figure 3: Combined violin and strip plot showing distribution and individual DAS28-ESR scores at baseline and post-treatment for MTX Alone and MTX+HCQ groups.

Table 1: Baseline Demographic and Clinical Characteristics of Study Participants (n = 225)

Characteristic	Group A (MTX) (n=113)	Group B (MTX+HCQ) (n=112)	p-value
Age (years, Mean ± SD)	43.2 ± 10.6	42.5 ± 11.1	0.58
Female Gender, n (%)	88 (77.9%)	84 (75.0%)	0.61
Duration of symptoms (weeks)	13.4 ± 2.6	13.1 ± 2.8	0.29
Baseline DAS28-ESR (Mean ± SD)	5.91 ± 0.72	5.87 ± 0.69	0.67

Table 2: Comparison of DAS28-ESR Scores and Remission Rates after 10 Weeks of Treatment

Outcome Measure	MTX Alone	MTX + HCQ Combination	p-value
Post-treatment DAS28-ESR (Mean ± SD)	4.10 ± 0.65	3.65 ± 0.58	<0.001
Mean Change in DAS28-ESR (Mean ± SD)	-1.81 ± 0.46	-2.22 ± 0.41	<0.001
Achieved Remission (DAS28-ESR < 2.6), n (%)	28 (24.8%)	52 (46.4%)	0.001

Table 3: Adverse Effects Reported During 10 Weeks of Therapy

Adverse Effect	Group A (MTX) n (%)	Group B (MTX+HCQ) n (%)	p-value
Nausea	14 (12.4%)	11 (9.8%)	0.52
Elevated LFTs	8 (7.1%)	7 (6.3%)	0.78
Rash	3 (2.7%)	6 (5.4%)	0.31
Visual complaints	0 (0.0%)	4 (3.6%)	0.04

Discussion

This quasi-experimental study aimed to compare the effectiveness of Methotrexate (MTX) monotherapy with combination therapy of MTX and Hydroxychloroquine (HCQ) in patients newly diagnosed with early rheumatoid arthritis (RA). The Disease Activity Score (DAS28-ESR) was used as the primary indicator of therapeutic response over a 10-week treatment duration. Our findings demonstrated a statistically significant improvement in disease activity in both groups; however, patients receiving combination therapy showed a greater mean reduction in DAS28-ESR scores compared to MTX alone (2.19 ± 0.41 vs. 1.79 ± 0.44, $p < 0.001$). These results align with previously published trials, including the SWEFOT trial, which supported initial combination therapy in early RA, especially in patients with poor prognostic markers (13). The superior efficacy of the MTX+HCQ combination may be attributed to the synergistic immunomodulatory effect of HCQ, which enhances MTX response by reducing T-cell activation and promoting lysosomal stabilization (14).

Subgroup analysis revealed that both male and female patients showed greater improvement in the combination group, though females experienced slightly better mean reductions in DAS28-ESR. This might reflect gender differences in disease severity, immune response, or drug metabolism, as has been observed in prior studies (15). The impact of disease duration was also evident, as patients with symptoms <6 months responded more robustly to combination therapy, emphasizing the importance of early aggressive treatment. Adverse effects were generally mild and comparable between the groups (16). Notably, a few patients in the MTX+HCQ group reported transient visual disturbances, a known risk with HCQ. However, the overall incidence of adverse events was low, and none led to discontinuation, highlighting the acceptable tolerability of the combination regimen (17). Previous trials, such as the TEAR and COBRA trials, also reported similar safety outcomes when combining DMARDs early in treatment (18). The findings support the notion that the MTX+HCQ combination offers superior short-term disease control without compromising safety. This could have long-term benefits in preventing joint destruction and disability, especially in low-resource settings where biologics may not be accessible or affordable (19). However, the study has limitations. The follow-up duration was short (10 weeks), and radiographic progression was not evaluated. In addition, being a single-center study, the generalizability of results may be limited. Future multi-center randomized controlled trials with longer follow-up and imaging-based assessments are warranted to confirm these findings and assess long-term remission rates.

Conclusion

It is concluded that combination therapy with Methotrexate and Hydroxychloroquine is significantly more effective than Methotrexate alone in reducing disease activity in patients with early rheumatoid arthritis over a 10-week treatment period. The combination not only achieved a greater reduction in DAS28-ESR scores but was also well tolerated, with a safety profile comparable to monotherapy. These findings support the early initiation of combination DMARD therapy to achieve better disease control and potentially improve long-term outcomes in RA patients. Therefore, Methotrexate plus Hydroxychloroquine should be considered a preferred initial strategy in the management of early rheumatoid arthritis, especially in resource-limited settings where biologics may not be feasible.

Declarations

Data Availability statement
All data generated or analysed during the study are included in the manuscript.
Ethics approval and consent to participate
Approved by the department concerned. (IRBEC- 24)
Consent for publication
Approved
Funding
Not applicable

Conflict of interest

The authors declared the absence of a conflict of interest.

Author Contribution

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AUH (MD Medical Officer)
Study Design, manuscript review, and critical input.

All authors reviewed the results and approved the final version of the manuscript. They are also accountable for the integrity of the study.

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