

## ORIGINAL ARTICLE

**Predictor Response of Monotherapy with Methotrexate with Triple DMARDS Therapy in Patients of Rheumatoid Arthritis**

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**ABSTRACT**

**Objective:** To compare Monotherapy with Methotrexate with Triple Therapy (Methotrexate, Sulfasalazine, and Hydroxychloroquine) in patients of Rheumatoid Arthritis.

**Study Design:** Quasi-experimental study.

**Place and Duration of Study:** This study was conducted at the Department of Rheumatology, Pak Emirates Military Hospital (PEMH) Rawalpindi, Pakistan from November 2021 to April 2022.

**Methods:** A total of 106 patients were enrolled in this study as per defined inclusion and exclusion criteria. These patients were divided into two groups. Group A was given monotherapy methotrexate, and in Group B triple therapy was given. Patients were followed up till 12 weeks and outcome variables were measured to see disease activity in both treatment groups. Data entry and analysis were done with the help of the statistical package for Social Sciences version 26.

**Results:** Mean DAS score for Groups A and B was  $4.24 \pm 0.22$  and  $4.30 \pm 0.23$ , respectively. For pain assessment, we used a visual analogue scale. The mean visual analogue scale score for Group-A and Group-B patients was  $3.58 \pm 1.16$  and  $3.05 \pm 1.09$ , respectively. The efficacy of treatment was based on the DAS score. As per the DAS score criteria, the efficacy of Group-B treatment was significantly higher than that of Group A. i.e. Good response (Group-A: 49.06% vs. Group-B: 71.70%,  $P$ -value=0.051). The most frequent side effect experienced by patients in both treatment groups was gastrointestinal problems followed by fatigue and headache.

**Conclusion:** The results of this study demonstrate that combination triple therapy is more effective than monotherapy of methotrexate for treating patients with rheumatoid arthritis.

**Keywords:** Arthritis, Drug Therapy, Hydroxychloroquine, Methotrexate, Sulfasalazine.

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**Introduction**

Patients with RA frequently need long-term maintenance, including early treatment, and often retain a mix of nonsteroidal anti-inflammatory medicines (NSAIDs), cortico-

steroids, slow-acting drugs (DADS), immune suppressants, and biologic treatments (biologics).<sup>1</sup> Therapies for RA now aim on disease remission or, at the absolute least, a decrease in activity to lessen or avoid joint deterioration and impairment, reflecting a sea shift in the way RA has been managed in recent decades.<sup>2,3</sup> The development of more effective and safe disease-modifying antirheumatic medicines (DMARDs) and biologic agents (BA) has allowed for this strategy.<sup>1,4</sup>

Joint deformity and loss of function due to rheumatoid arthritis (RA) are inevitable if proper

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treatment is not started right away. Methotrexate (MTX) monotherapy is only effective for 30%-40% of rheumatoid arthritis (RA) sufferers.<sup>5</sup> Outcomes confirmed the role of methotrexate as primary reference csDMARD.<sup>6</sup> Rheumatoid arthritis therapy revolves mostly around the use of methotrexate. Those diagnosed with RA are often advised to start with methotrexate, and other DMARDs, such as biologics or the newly authorized tofacitinib, should be used in conjunction with it.<sup>7,8</sup> Contradictory opinions exist about the practice of combining methotrexate with other typical synthetic DMARDs. Tumor necrosis factor alpha (TNFi) inhibitors and other types of biological disease-modifying antirheumatic medicines (bDMARDs) have significantly increased the efficacy of therapy.<sup>9</sup> Combination treatment with csDMARDs has been shown to be more effective than monotherapy in a growing number of trials.<sup>10</sup> Historically, sulfasalazine (SSZ) and hydroxychloroquine (HCQ) have been used in conjunction with MTX to achieve optimal response and safety.<sup>11,12</sup>

Seventy-seven percent of refractory RA patients showed at least a 50% improvement after nine months of treatment with MTX+HCQ+SSZ triple therapy, without experiencing significant adverse effects from the drugs.<sup>13</sup> However, the best research demonstrated that combination treatment with csDMARDs was not superior to monotherapy with csDMARDs. Previous research found that after discontinuing biological DMARDs, relapse occurred in 58% of RA patients treated with MTX plus cyclosporin.<sup>14</sup> Although it is still debatable whether MTX-based combination treatments are preferable to MTX alone, in everyday clinical practice RA patients are routinely treated with (sometimes temporary) MTX-based combination therapy at an early stage of illness.

### Methods

This quasi-experimental study was conducted at the Department of Rheumatology, Pak Emirates Military Hospital (PEMH) Rawalpindi, Pakistan from November 2021 to April 2022. Ethical approval was obtained from the Ethical Review Board Committee of the hospital with reference

number: A/28/169 held on dated: 15<sup>th</sup> October 2021. Total 106 patients were enrolled in this study as per predefined inclusion and exclusion criteria. Sample size calculation was done with the help of magnitudes taken from a previous study and with the help of WHO sample size calculator. Sample size of 106 was calculated with 10% level of significance, 80% power of study and by taking expected percentage of improvement in clinical and lab parameters with Monotherapy as 60% and with combination therapy as 79% among male patients.<sup>15</sup>

**Inclusion Criteria:** Patients aged 18 to <70 years fulfill EULAR/ACR diagnostic criteria of RA, with diseases duration <1 years were included in the study.<sup>16</sup>

**Exclusion Criteria:** Patients who were already taking methotrexate or any other disease-modifying anti-rheumatic drug (DMARD) were not included in the study. Patients were not considered if they had other diseases or conditions, such as those affecting the heart, brain, lungs, kidneys, liver, endocrine system, or gastrointestinal tract.

At the beginning and end of the twelve-week period, patients were evaluated. The research proforma collected data on the patients' ages, genders, occupations, length of illness, and drugs used. The patients were asked if they had ever had high blood pressure, diabetes, IHD, chronic HCV, a stroke, or smoked. Each participant's pain was assessed using the Visual Analog Scale for Pain (VAS) at baseline and week twelve. The DAS 28 and VAS were all computed at these intervals. ESR and C-reactive protein (CRP) levels were measured at week 0 and week 12 of treatment (CRP). Tender joints (TJ), swollen joints (SJ), and the VAS for pain (0-10), as well as ESR or C-reactive Protein, were measured clinically using an online calculator to get DAS 28. Tender Joints (TJ), Swollen Joints (SJ), and the Visual Analog Scale (VAS) for Pain were used to develop the Clinical Disease Activity Index (0-10). The hospital's electronic medical record (EMR) identified the presence or absence of the RA factor (RA factor) and anti-CCP positivity or negative in all patients. Data entry and analysis

were done with the help of SPSS version 25. Mean $\pm$ SD was used to present quantitative variables, while frequency and percentage were used to show qualitative variables. *Chi-square* test was applied to see association between qualitative variables. i.e. (Efficacy between treatment groups) *P*-value <0.05 was considered statistically significant.

### Results

In this study we enrolled 106 patients and divided them into 2 groups of equal sample size. Each groups contains 53 patients each. The mean age of patients in Group A and Group B was 46.32 $\pm$ 15.18 and 45.83 $\pm$ 14.86 years. (Table-1). In Group-A 31 (58.5%) patients were female while in Group-B 37 (69.81%) were female. Mean duration of disease in Group-A and in Group-B was 8.71 $\pm$ 1.64 and 8.43 $\pm$ 1.72 months. Mean DAS score for Group-A and B was 4.24 $\pm$ 0.22 and 4.30 $\pm$ 0.23 respectively. For pain assessment we used VAS. Mean VAS score for Group-A and Group-B patients was 3.58 $\pm$ 1.16 and 3.05 $\pm$ 1.09 respectively. The efficacy of treatment was based on the DAS score. As per the DAS score criteria, the efficacy of Group-B treatment was significantly higher than that of Group A. i.e. Good response (Group-A: 49.06% vs. Group-B: 71.70%, *Chi Square* test=5.916, *P*-value=0.051).

(Table-2). Side effects experienced by patients in both groups are given in detail in table-3. The most frequent side effect experienced by patients in both treatment groups was gastrointestinal problems followed by fatigue and headache.

### Discussion

Conventional DMARDs, including MTX, Lefunamide, Sulfasalazine, and Hydroxychloroquine, have been shown to be quite successful in therapeutic methods. Still, some people don't answer or don't respond enough. Two DMARDs are used as the first line of defense in combination treatment, whereas in non-responders, a combination of a conventional DMARD and a targeted DMARD/bDMARD is used.<sup>17</sup> Many variables, including genetics and the surrounding environment, contribute to the wide range of clinical presentations and treatment responses in rheumatoid arthritis patients. The poor remission rate and high economic consumption of rheumatoid arthritis (RA) remain unsolved despite advancements in therapy, particularly in underdeveloped countries, where roughly 40% of RA patients still do not meet primary clinical outcomes in randomized trials.<sup>18</sup> When compared to double combination treatment or monotherapy, the

**Table-1: Patients characteristics in Study Groups (Frequency, %)**

|                     | Group-A (Monotherapy) | Group-B (Tipple Combination)     |
|---------------------|-----------------------|----------------------------------|
|                     | Methotrexate          | Methotrexate+ Sulfasalazine+ HCQ |
| Variables           | n = 53                | n = 53                           |
| Age                 | 46.32 $\pm$ 15.18     | 45.83 $\pm$ 14.86                |
| Gender (Female)     | 31 (58.5%)            | 37 (69.81%)                      |
| Duration            | 8.71 $\pm$ 1.64       | 8.43 $\pm$ 1.72                  |
| DAS (mean $\pm$ SD) | 4.24 $\pm$ 0.22       | 4.30 $\pm$ 0.23                  |
| VAS (mean $\pm$ SD) | 3.58 $\pm$ 1.16       | 3.05 $\pm$ 1.09                  |

**Table-2: Comparison of Efficacy of Treatment Groups**

| DAS Score          | Group-A     | Group-B     | Total | <i>Chi-Square</i> value | <i>P</i> -value |
|--------------------|-------------|-------------|-------|-------------------------|-----------------|
| Poor (<0.6)        | 13 (24.53%) | 6 (11.32%)  | 19    | 5.916                   | 0.051           |
| Good (>1.2)        | 26 (49.06%) | 38 (71.70%) | 64    |                         |                 |
| Moderate (0.6-1.2) | 14 (26.42%) | 9 (16.98%)  | 23    |                         |                 |
| Total              | 53          | 53          | 106   |                         |                 |

**Table-3: Side Effects in Treatment Groups (Frequency, %)**

|                           | Group-A (n =53) | Group-B (n =53) | Total      |
|---------------------------|-----------------|-----------------|------------|
| Variables                 |                 |                 | 106 (100%) |
| Fatigue                   | 17 (32.08%)     | 21 (39.62%)     | 38 ( %)    |
| Dizziness                 | 8 (15.09%)      | 5 (9.43%)       | 13 ( %)    |
| Headache                  | 9 (16.98%)      | 7 (13.21%)      | 16 ( %)    |
| Muscle Weakness           | 5 (9.43%)       | 3 (5.66%)       | 8 ( %)     |
| Palpitations              | 6 (11.32%)      | 3 (5.66%)       | 9 ( %)     |
| Edema                     | 4 (7.55%)       | 2 (3.77%)       | 6 ( %)     |
| Gastrointestinal problems | 22 (41.51%)     | 34 (64.15%)     | 56 ( %)    |

triple combination therapy of synthetic DMARDs (methotrexate, sulfasalazine, and hydroxychloroquine) demonstrated superior safety, efficacy, and excellent tolerability.<sup>19, 20</sup>

This study's efficacy results showed that triple combination therapy is more effective than monotherapy of methotrexate for treating rheumatoid arthritis patients. i.e., there was a Good response (MTX monotherapy: 49.06% vs. Triple combination Therapy: 71.70%,  $P$ -value=0.051). The REACH trial found no significant differences in disease activity, radiographic progression, or functional ability between three treatment groups: one receiving MTX monotherapy, one receiving MTX in combination with other csDMARDs (sulfasalazine and hydroxychloroquine), and one receiving oral or IM glucocorticoids.<sup>21</sup> This finding is in line with the results of this study, showing higher efficacy of triple combination therapy. Similar findings were reported by a local study from Karachi in which Both combinations of MTX & SSZ and MTX & HCQ were equally effective, but the combination of MTX & HCQ was superior in terms of tolerability than the combination of MTX and SSZ.<sup>19</sup>

The Swefot trial conducted by Van Vollenhoven R et al., examined the efficacy of sulfasalazine and hydroxychloroquine as adjunct therapy in patients with early rheumatoid arthritis (RA) who did not respond to methotrexate (MTX) alone. The results indicated that 25% of the patients obtained a favorable response based on the European League Against Rheumatism (EULAR) criteria after 12 months of treatment.<sup>22</sup>

In a randomized controlled experiment conducted by Johan A Karlsson, it was shown that the addition of infliximab (IFX) or sulfasalazine plus hydroxychloroquine (SSZ+HCQ) to methotrexate (MTX) in patients with active early rheumatoid arthritis (RA) did not provide statistically significant differences in terms of utility or quality-adjusted life year (QALY) gain over a period of 21 months.<sup>23</sup>

Contrary to the results of this study showing the higher efficacy with triple combination fewer studies have reported no significant difference in efficacy of triple therapy and methotrexate monotherapy. The findings of the CareRA study indicate that the addition of additional conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) to methotrexate (MTX) did not demonstrate superiority over MTX alone in patients with early rheumatoid arthritis (RA) who had predictors of aggressive illness. It is worth noting that both treatment arms in the experiment were accompanied by glucocorticoids. The user did not provide any text to rewrite. Furthermore, current randomized controlled trials (RCTs), as assessed by Chatzidionysiou et al. align with these findings, indicating that the combination of conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) does not exhibit superior efficacy compared to methotrexate (MTX) alone.<sup>24</sup>

The 2016 revision of the European League Against Rheumatism (EULAR) guidelines for the treatment of rheumatoid arthritis (RA) indicated that the inclusion of glucocorticoids (GCs) in



combination with conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) may provide potential advantages. However, it is crucial to carefully consider the potential risks associated with GC therapy in order to maintain a balanced approach to treatment. In the circumstances characterized by stringent control measures, it has been seen that monotherapy with MTX is not inferior in terms of efficacy when compared to the use of combination csDMARDs. To be sure, MTX on its own is linked to better tolerability, which is worth noting.<sup>25</sup> Based on the current guidelines, it is advised that methotrexate (MTX) and/or other conventional synthetic disease-modifying antirheumatic medications (csDMARDs) be utilized as the initial treatment strategy for patients diagnosed with rheumatoid arthritis (RA). Combining csDMARDs with either biologic DMARDs (bDMARDs) or targeted synthetic DMARDs (tsDMARDs) should be explored in the case of an unsatisfactory response to first-line therapy.<sup>10</sup>

However, it is generally accepted that a sizable percentage of patients in the rheumatic clinical environment utilize bDMARDs as monotherapy. This finding, which might be due to several reasons, points to the necessity for a monotherapy strategy in the treatment of rheumatoid arthritis (RA). Given the difficulties in tolerability and the adverse effects associated with methotrexate (MTX), the possibility of intolerance to this medicine should be evaluated. In addition, research shows that many patients do not consistently take their methotrexate (MTX) as prescribed. Rheumatoid arthritis (RA) is a chronic condition that requires long-term treatment interventions. Thus, it's crucial that patients take their medication exactly as directed. Poor adherence to medication schedules has been linked to potentially disastrous clinical results, and this link has been well established.<sup>10</sup> Intensive medication therapy initiated with the hope of achieving complete remission or a substantial decrease in symptoms and clinical indicators is

the ultimate objective of RA care.<sup>26,27</sup> But many people with RA still don't get relief from the drugs now available. More research and development of new medications and an increased emphasis on individualized therapy are required to bring the condition under complete control.<sup>26,27</sup>

### Conclusion

Results of this study demonstrate that combination triple therapy is more effective compared to monotherapy of methotrexate for treating patients of rheumatoid arthritis.

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**Conflict of Interest:** The authors declare no conflict of interest

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#### Authors Contribution

**BI:** Idea conception, data collection, manuscript writing and proofreading

**AF:** Study designing, data analysis, results and interpretation

**AM:** Idea conception, study designing, data analysis, results and interpretation, manuscript writing and proofreading

**WA:** Study designing, data analysis, results and interpretation, manuscript writing and proofreading

**ZH:** Data collection, data analysis, results and interpretation

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