Original Article

Comparison of Clinical Effectiveness and Tolerability of Single versus Split Methotrexate Doses as Initial Therapy in Rheumatoid Arthritis

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ABSTRACT

Background: Methotrexate is a first-line disease-modifying drug for rheumatoid arthritis, and is conventionally administered as a single weekly oral dose. In clinical practice, the weekly dose is sometimes split over 24 hours to reduce gastrointestinal adverse effects, although supporting evidence remains limited. This study aimed to compare the safety and efficacy of a single-dose versus a split-dose of oral methotrexate.

Methods: This open-label interventional study was conducted at the Department of Rheumatology, Sir Ganga Ram Hospital, Lahore, Pakistan, between January and August 2025. A total of 56 patients aged 15-70 years fulfilling the ACR/EULAR-2010 criteria were enrolled. Patients with serious comorbidities, a prior biologic or recent conventional DMARD therapy, or pregnancy and lactation were excluded. Patients were allocated using systematic allocation (odd-even method) to receive either a single weekly oral dose or a split 24-hour oral dose of methotrexate. Methotrexate was initiated at 10 mg/week and increased to 25 mg/week according to response and tolerability. All patients received folic acid supplementation and tapering of low-dose prednisolone. Patients were followed for 24 weeks. Disease activity was measured using the Clinical Disease Activity Index (CDAI). Remission (CDAI ≤ 2.8) was the primary effectiveness endpoint, and methotrexate-related adverse effects were the primary safety outcome. The chi-square test was used to analyze the data, and a p-value ≤0.05 was considered statistically significant.

Results: Out of 56 patients, 47 completed the study (27.7% males and 72.3% females). Baseline disease activity was mild in 4.3%, moderate in 21.3%, and severe in 74.5%. Overall remission rates were 6.4% at week 12 and 34.0% at week 24. At week 24, remission was significantly higher in the split-dose group compared to the single-dose group (48.0% vs. 18.2%, p-value = 0.031). The single-dose group had a higher prevalence of nausea (36.4% vs. 12.0%, p-value = 0.049) and dyspepsia (31.8% vs. 8.0%, p-value = 0.038). The overall incidence of transaminitis was 25.5%, with no significant intergroup difference.

Conclusion: Splitting the oral dose of methotrexate over 24 hours results in higher remission and improved gastrointestinal tolerability compared with a single weekly dose.

Keywords: Rheumatoid Arthritis; Methotrexate; Split Doing; Clinical Efficacy; Adverse Effects

INTRODUCTION

Rheumatoid arthritis is one of the most common autoimmune diseases, with a worldwide prevalence of approximately 0.24%.[1] It is a chronic autoimmune multisystem inflammatory disease, with synovitis as its main clinical manifestation. Over the years, the therapeutic strategies for rheumatoid arthritis have continued to evolve with the addition of targeted synthetic and biologic disease-modifying anti-rheumatic drugs (DMARDs); however, conventional DMARDs continue to play an important role, especially in the management of early disease and in resource-limited settings.[2,3] Current therapeutic guidelines for rheumatoid arthritis suggest methotrexate as an anchoring drug and first-line monotherapy across the entire disease severity spectrum.[2,3]

Because of gastrointestinal intolerance and saturation of oral absorption at higher doses, most clinicians have empirically divided the weekly oral doses of methotrexate into 24-hour doses to optimize peak plasma concentrations and enhance tolerability. The absorption of oral methotrexate is dose-dependent, and the bioavailability of oral methotrexate decreases with an increase in dose, which serves as a pharmacokinetic

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explanation of split dosing. Nevertheless, there is limited evidence supporting superior clinical outcomes with split dosing, and the American College of Rheumatology only conditionally recommends the use of split-dosing of methotrexate since the certainty of its advantage is very low.[2,4] Thus, it remains unclear whether weekly single oral dosing or 24-hour split dosing is more effective in improving tolerability and achieving desirable therapeutic effects.

Several studies have evaluated the effect of splitting the weekly oral methotrexate dose on clinical outcomes in patients with rheumatoid arthritis, based on the hypothesis that dose fractionation may reduce peak-related adverse effects and improve drug tolerability.[4] The randomized and observational studies comparing single weekly oral dosing with 24-hour split dosing have reported comparable or improved clinical efficacy with split dosing, particularly at higher weekly doses.[5,6] Some trials demonstrated higher remission or response rates and improved gastrointestinal tolerability with split dosing, which was attributed to reduced peak plasma concentrations and improved absorption.[6,7] However, these findings have not been consistent across all studies, and concerns regarding toxicity, particularly elevated liver enzymes, have also been reported with split dosing in some cohorts.[7,8] Other studies have evaluated the safety and efficacy of split dosing using different regimens, reported better tolerability and efficacy, although elevation of liver enzymes was more common in split dosing, particularly in patients with psoriasis.[9,10]

Oral methotrexate is preferred by many patients because of its low cost, ease of administration, and avoidance of injections, especially among patients with impaired functional status and lack of physical and social support. Therefore, an oral dosing strategy that maintains clinical efficacy while minimizing side effects and improving tolerability is desirable. The purpose of this study was to compare a single once-weekly methotrexate regimen with a split 24-hour dosing regimen in terms of clinical efficacy and tolerability.

PATIENTS AND METHODS

This open-label interventional study was conducted at the Department of Rheumatology of Sir Ganga Ram Hospital, Lahore, Pakistan, from January 23 to August 11, 2025, after taking approval from the Ethical Review Committee of Fatima Jinnah Medical University, Lahore. Patients aged 15 to 70 years fulfilling the 2010 European Alliance of Associations for Rheumatology (EULAR)/American College of Rheumatology (ACR) 2010 classification criteria for rheumatoid arthritis with a disease duration of less than 5 years from the onset of symptoms were enrolled in the study.[11] Patients suffering from significant hepatic dysfunction (liver cirrhosis on imaging, baseline alanine transaminase (ALT), aspartate transaminase (AST) two times greater than upper limit of normal, total bilirubin greater than upper limit of normal and untreated chronic hepatitis B and chronic hepatitis C infections), renal dysfunction (serum creatinine >1.5 mg/dL), cytopenias (hemoglobin < 8mg/dl, total leukocyte count <4000 cells/µL or platelets <100000 cells/µL), moderate to severe pulmonary fibrosis, fibromyalgia, extra articular manifestations and overlap autoimmune conditions were excluded. Patients who had ever taken any biological DMARD (including infliximab, etanercept, adalimumab, tocilizumab, and rituximab) and those who had received any conventional DMARD (including methotrexate, leflunomide, hydroxychloroquine, and sulfasalazine) for >1 month at any time or within the preceding 6 months were also excluded. Additionally, patients who did not give consent and female patients who were pregnant, lactating, or planning a pregnancy were also excluded. A total of 56 patients were recruited using non-probability consecutive sampling and allocated into two groups using systematic random allocation (odd-even method). Informed consent was obtained from all enrolled participants. Clinical Disease Activity Index (CDAI) was chosen as a tool for measuring serial disease activity.[12] A self-developed case report form was used to collect all the relevant data.

Patients with odd enrollment numbers were assigned to Group 1 and received a once-weekly dose of methotrexate, while patients with even numbers were enrolled in Group 2 and received a split weekly dose of methotrexate over 24 hours. Methotrexate tablets with a strength of 2.5 mg were used in the study. The starting methotrexate dose was 10 mg for both groups. Dose was increased to 15 mg for both groups after 2 weeks and to 20 mg after 4 to 6 weeks. Patients in Group 1 continued to take an increased dose on the same day without splitting.

In Group 2, the amount of oral methotrexate scheduled per week was split into two equal doses with a 24-hour interval. Escalation of doses was the same in both groups and based on the clinical response and tolerability, with a top dose of 25 mg/week. By escalating to 25 mg/week, Group 2 got 12.5 mg on day 1 and 12.5mg on day 2. Methotrexate was taken in the form of 2.5 mg tablets to enable easy division of doses. Folic acid 5 mg daily was administered to all patients in both groups on two consecutive days, after the administration of methotrexate. Furthermore, every patient was given oral prednisolone 5-10 mg/day, and a taper was scheduled to begin in week 8 and aimed at full withdrawal in week 20. The patients were followed up on every two weeks during the initial three months and every four weeks to complete the total follow-up duration of 24 weeks. On each visit,

data regarding disease activity, side effects and tolerability, including subjective complaints and laboratory values of complete blood count, ALT and creatinine, were noted. The main outcome variable of effectiveness was the disease activity, and the measurement level was the Clinical Disease Activity Index (CDAI). CDAI was measured at the baseline and at the follow-up visit (every 2 weeks during the first 12 weeks and every 4 weeks after that up to the 24 weeks). Clinical remission was defined as a CDAI score of <2.8, which was used as the primary safety and tolerability variables[12], both subjective and laboratory-based. Adverse effects (e.g., nausea, dyspepsia, intolerance) were assessed subjectively by interviewing the patients during each follow-up visit on a case report form. Complete blood count, CRP, alanine transaminase (ALT), and serum creatinine were the variables of laboratory safety, which were measured at baseline and at each follow-up. The safety variable that was specifically followed was transaminitis, which was determined as an elevation of ALT greater than the upper limit of normal in the group of patients with normal baseline ALT, or an increase greater than 10 IU/L over baseline in the group of patients with elevated baseline ALT. Data was entered in Statistical Package for Social Sciences (SPSS) software version 26 for grouping and analysis. Qualitative variables like gender and side effect profile were presented as frequencies and percentages. Quantitative variables like age, C-reactive protein (CRP), and CDAI score were presented as mean ± standard deviation. Data were stratified for dosing regimen. Post-stratification Chi-square test was applied to check the significance with a p-value ≤ 0.05 as significant. The primary end point of effectiveness was taken as remission, defined by CDAI score ≤ 2.8 by week 24. Secondary end points include remission as defined by CDAI score ≤2.8 by week 12 and complete discontinuation of steroids by a maximum of week 20 without subsequent increase in disease activity. The primary safety endpoint was taken as the development of any of the side effects of the therapy.

RESULTS

A total of 56 patients fulfilling the inclusion criteria were enrolled in the study. Among them, 5 patients were lost to follow-up, and 4 were excluded for non-adherence to the research protocol. A total of 47 patients completed the study. Of these, 13 patients were male (27.7%), and 34 were female (72.3%). Twenty-two (46.8%) patients were in Group 1 and received a single-dose regimen, while 25 (53.3%) were in Group 2 and received a split-dose regimen. Other patient demographics and characteristics are summarized in Table 1.

At the start of the study, patients with mild, moderate, and severe disease activity were 2 (4.3%), 10 (21.3%), and 35 (74.5%), respectively. By week 12 of methotrexate treatment, only 3 (6.4%) patients achieved remission, which increased to 16 (34%) at week 24, with a mean CDAI reduction of 18.2. At week 12, remission was achieved by 1 (4.5%) patient in Group 1 and 2 (8%) patients in Group 2 (p-value = 0.629). At week 24, remission was achieved by 4 (18.2%) patients in Group 1 and 12 (48%) patients in Group 2 (p-value = 0.031). At week 20, steroids were completely discontinued in 1 (4.5%) patient in Group 1 and 4 (20%) in Group 2 (p-value = 0.121). Nausea developed in 8 (36.4%) patients in Group 1 and 3 (12%) patients in Group 2 (p-value = 0.049). Dyspepsia developed in 7 (31.8%) patients in Group 1 and 2 (8%) patients in Group 2 (p-value = 0.038). A total of 12 patients (25.5%) developed transaminitis as defined by

Table 1: Demographics and baseline characteristics of patients

Characteristics	Group 1 (Single-dose group)	Group 2 (Split-dose group)	Total
Mean age (years)	47.6 ± 11.9	43.8 ± 9.1	45.5 ± 10.6
Gender			
Males	8 (36.4 %)	5 (20%)	13 (27.7%)
Females	14 (63.6%)	20 (80%)	34 (72.3%)
Mean duration since symptom onset (months)	24.2	16.0	
Rheumatoid factor (RF)			
Positive	18 (81.8%)	21 (84%)	39 (83%)
Negative	4 (18.2%)	4 (16%)	8 (17%)
Anti-citrullinated peptide antibodies (ACPA)			
Positive	8 (36.4%)	13 (52%)	21 (44.7%)
Negative	6 (27.3%)	5 (20%)	11 (23.4%)
Not available	8 (36.4%)	7 (28%)	15 (31.9%)
Mean initial C-reactive protein (CRP) (mg/l)	30.4 (5-83)	24.9 (3.5-90)	27.5 (3.5-90)
Mean CDAI at start	30.3 (8-72)	31.4 (12-61)	30.9 (8-72)
Disease activity at start			
Low	2 (9.1%)	0	2 (4.3%)
Moderate	5 (22.7%)	5 (20%)	10 (21.3%)
High	25 (68.2%)	20 (80%)	35 (74.5%)

Table 2: Comparison of effectiveness and safety parameters among study groups

Outcome	Group 1 (Single dose group, n=22)	Group 2 (Split dose group, n=25)	p-value
Efficacy outcomes			
Remission at 24 weeks	4 (18.2%)	12 (48.0%)	0.031
Remission at 12 weeks	1 (4.5%)	2 (8.0%)	0.629
Steroids discontinued by week 20	21 (95.5%)	20 (80.0%)	0.113
Adverse effects			
Anxiety	0 (0%)	1 (4.0%)	0.343
Dizziness	1 (4.5%)	1 (4.0%)	0.926
Increase in nodules	0 (0%)	0 (0%)	NA
Dyspepsia	7 (31.8%)	2 (8.0%)	0.038
Alopecia	6 (27.3%)	3 (12.0%)	0.184
Rash	0 (0%)	0 (0%)	NA
Glossitis	3 (13.6%)	0 (0%)	0.056
Anorexia	4 (18.2%)	4 (16.0%)	0.843
Gingivitis	0 (0%)	0 (0%)	NA
Oral ulcers	1 (4.5%)	1 (4.0%)	0.926
Diarrhea	0 (0%)	3 (12.0%)	0.093
Nausea	8 (36.4%)	3 (12.0%)	0.049
Vomiting	0 (0%)	0 (0%)	NA
Transaminitis	3 (13.6%)	9 (36.0%)	0.079
Dyspnea	0 (0%)	0 (0%)	NA

elevation of ALT above normal if initial ALT was normal or an absolute increase of ≥10 IU/L from baseline if initial ALT was more than the upper limit of normal. With this criterion, transaminitis developed in 3 (13.6%) patients in Group 1 and 9 (36%) patients in Group 2 (p-value = 0.79). Other side effects are summarized in Table 2.

DISCUSSION

Methotrexate has been in use for rheumatoid arthritis since the 1980s.[13] Since then, several studies have demonstrated superior bioavailability of subcutaneously administered methotrexate compared with oral administration.[4,5,14] However, most of these studies predominantly addressed the pharmacokinetics of the drug rather than looking into clinical response in patients. While subcutaneous methotrexate is widely advocated worldwide, split-dose methotrexate is at least as effective as subcutaneous administration.[8] Therefore, oral split dose of methotrexate seems a reasonable choice of dosing regimen for patients in whom side effects limit single weekly dosing or where subcutaneous mode of administration is not available or acceptable. This study has demonstrated clear effects of splitting the methotrexate dose over 24 hours on its clinical effectiveness in patients with rheumatoid arthritis. These results resonate with the outcomes of pharmacologic studies on methotrexate, in which a single dose above 15 mg was associated with blunted absorption and, theoretically, should lead to a suboptimal clinical response.[5,14] The mean bioavailability of the methotrexate split dose is reported as 28% higher than that of a single dose.[14] Thus, splitting the dose of methotrexate is a better option for improved clinical response.

In this study, 34% of patients achieved remission by 24 weeks, consistent with the methotrexate response rate reported in previous studies of rheumatoid arthritis using different disease activity measures.[15,16] It is lower than the 42.7% reported in an earlier study, where CDAI at 6 months was 42.7%.[17] However, the conventional group in that study also contained patients who were taking a methotrexate-based combination drug treatment. It should be noted that the response rate at 3 months was only 6.4%, despite a higher initial prednisolone dose. It could be due to the initial low starting dose of methotrexate of 10 mg compared with the initial higher dose of up to 15 mg used in other studies.[17,18]

With respect to the safety profile in terms of side effects, nausea and dyspepsia were more common with single-dose methotrexate. Transaminitis was more common with the split dose than with the single dose (36% vs. 13.6%), but did not reach statistical significance (p-value = 0.079). The overall percentage of transaminitis is similar to that previously reported in other studies (7.5% to 26%) using different criteria.[19] No drug discontinuation was needed for any of the patients, and no patient developed an ALT level above twice the normal limit. The clinical significance of such elevated liver enzymes depends on the duration of enzyme elevation; a study in rheumatoid arthritis patients reported a positive correlation with hepatic fibrosis on liver biopsy, whereas another study in psoriatic arthritis failed to demonstrate such an association. [20,21]

This study has several limitations. First, methotrexate serum levels were not assessed, which would have provided a more objective pharmacokinetic account of the discrepancy in efficacy and adverse effects between the different dosing regimens. Second, the sample size was small, which could limit the generalizability of the results. Third, the follow-up time was 24 weeks, which was insufficient to evaluate the long-term performance, safety, and long-term remission.

CONCLUSION

Split dosing of oral methotrexate over 24 hours in patients with rheumatoid arthritis was more likely to be clinically effective, with better remission rates than a dose of 1 mg weekly. The split-dose form of the medication was also better tolerated in the gastrointestinal tract, with fewer cases of nausea and dyspepsia, but close laboratory monitoring is necessary. These results suggest that split dosing can be an effective approach to maximize the effect of methotrexate therapy in carefully selected patients, but further research with extended follow-up is necessary to confirm these findings and evaluate the long-term safety of this treatment.

Author Contributions: NZ conceived and designed the study, analyzed and interpreted the data, drafted the manuscript, and critically revised it for important intellectual content. BAB and SS contributed to the study's conception and design, as well as to data analysis and interpretation. FA contributed to data acquisition, study design, and data analysis. ZH participated in data analysis and interpretation and assisted in drafting the manuscript. All authors critically revised the manuscript, approved the final version, and agree to be accountable for all aspects of the work.

REFERENCES

1. Cross M, Smith E, Hoy D, Carmona L, Wolfe F, Vos T, et al. The global burden of rheumatoid arthritis: estimates from the global burden of disease 2010 study. Ann Rheum Dis. 2014;73(7):1316–1322.
2. Fraenkel L, Bathon JM, England BR, St Clair EW, Arayssi T, Carandang K, et al. 2021 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. Arthritis Rheumatol. 2021;73(7):1108–1123.
3. Smolen JS, Landewé RBM, Bergstra SA, Kerschbaumer A, Sepriano A, Aletaha D, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2022 update. Ann Rheum Dis. 2023;82(1):3–18. https://doi.org/10.1136/ard-2022-223356
4. Asghar MS, Kumar K, Iqbal S, Sagar, Parkash O, Kumar S, Singh M, Jawed R, Akram M, Yasmin F, Tahir MJ, Yousaf Z. Rheumatoid arthritis in Pakistan: clinical characteristics and management challenges. J Community Hosp Intern Med Perspect. 2022;12(4):34–42. https://doi.org/10.55729/2000-9666.1085
5. Prasad C, Dhir V, Gupta R, Thomas K, Aggarwal A. Methotrexate dosing strategies in rheumatoid arthritis. Arthritis Rheumatol. 2023;75(Suppl 9):1583.
6. Asghar MS, Kumar K, Iqbal S, Khan MA, Abbas A. Clinical profile and treatment outcomes of rheumatoid arthritis patients in Pakistan. J Coll Physicians Surg Pak. 2023;33(5):523–528.
7. Braun J, Kästner P, Flaxenberg P, et al. Comparison of the clinical efficacy and safety of subcutaneous versus oral methotrexate in patients with active rheumatoid arthritis. Ann Rheum Dis. 2008;67(2):253–259. https://doi.org/10.1136/ard.2006.068429
8. Visser K, van der Heijde D. Optimal dosage and route of administration of methotrexate in rheumatoid arthritis: a systematic review of the literature. Ann Rheum Dis. 2009;68(7):1094–1099. https://doi.org/10.1136/ard.2008.092668
9. Prasad CB, Dhir V, Gupta R, Thomas KN, Devarasetti PK, Pai VS, Jain A, Naidu G, Saini P, Leishangthem B, Khullar A, Manthri R, Sharma SK, Sharma A, Aggarwal A, Jain S. Split vs single-dose oral methotrexate in rheumatoid arthritis: a randomized controlled trial (SMART study). Clin Rheumatol. 2025;44(10):3869–3879.
10. Radmanesh M, Rafiei B, Moosavi ZB, Sina N. Methotrexate-induced cutaneous ulceration in patients with rheumatoid arthritis. Int J Dermatol. 2011;50(10):1291–1293.
11. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO, et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum. 2010;62(9):2569–2581.
12. Aletaha D, Nell VPK, Stamm T, Uffmann M, Pflugbeil S, Machold K, et al. Acute phase reactants add little to composite disease activity indices for rheumatoid arthritis. Arthritis Res Ther. 2005;7(4):R796–R806. https://doi.org/10.1186/ar1743
13. Cronstein BN, Aune TM. Methotrexate and its mechanisms of action in inflammatory arthritis. Nat Rev Rheumatol. 2020;16:145–154.
14. Hoekstra M, Haagsma C, Neef C, Proost J, Knuif A, van de Laar M. Bioavailability of higher dose methotrexate comparing oral and subcutaneous administration in patients with rheumatoid arthritis. J Rheumatol. 2006;33(3):481–485.
15. Detert J, Bastian H, Listing J, Weiß A, Wassenberg S, Liebhaber A, et al. Induction therapy with high-dose methotrexate in early rheumatoid arthritis: the CAMERA-II trial. Ann Rheum Dis. 2013;72(6):844–850.
16. Chatzidionysiou K, Sfikakis PP. Low-dose methotrexate in rheumatoid arthritis: mechanisms and clinical applications. RMD Open. 2019;5(2):e000993.
17. Østergaard M, van Vollenhoven RF, Rudin A, Hetland ML, Heiberg MS, Nordström DC, et al. Treat-to-target strategies and methotrexate optimization in rheumatoid arthritis. Ann Rheum Dis. 2023;82(10):1286–1295. https://doi.org/10.1136/ard-2022-223203
18. Molina JT, García FJ, Alén JC, Ruiz MÁ, Abelló JC, Meseguer AL, Muelas JV, Sandoval TP, Carrera JQ, Larraz PT, Mendoza AZ. Recommendations for the use of methotrexate in rheumatoid arthritis: up and down scaling of the dose and administration routes. Reumatol Clin (Engl Ed). 2015;11(1):3–8. https://doi.org/10.1016/j.reumae.2014.02.006
19. Sotoudehmanesh R, Anvari B, Akhlaghi M, Shahraeeni S, Kolahdoozan S. Adverse effects of low-dose methotrexate in rheumatoid arthritis patients. Middle East J Dig Dis. 2010;2(2):104–109.
20. Willkens RF, Leonard PA, Clegg DO, Tolman KG, Ward JR, Marks CR. Liver toxicity in patients receiving methotrexate for rheumatoid arthritis. Ann Rheum Dis. 1990;49(8):591–593.
21. Grismer LE, Gill SA, Harris MD. Methotrexate dosing strategies and toxicity in rheumatoid arthritis. J Clin Rheumatol. 2001;7(4):224–227.