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EFFECTIVENESS OF MEDICATION USE AND DETERMINANTS OF IRREGULAR ADHERENCE AMONG PATIENTS WITH RHEUMATOID ARTHRITIS

Bekenova Gulchekhra Tulegenovna
Tashkent State Medical University, Tashkent, Uzbekistan

Abstract

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disease requiring long-term pharmacological management to prevent joint destruction and disability. This study evaluates the efficacy of methotrexate (MTX) therapy and examines the prevalence, predictors, and reasons for medication non-adherence among RA patients during the first six months of treatment. Data were analyzed from a prospective multicenter cohort of 606 incident MTX users. Disease activity was assessed using DAS28 scores, and adherence was monitored weekly over 26 weeks. Overall, 26% of patients reported at least one episode of non-adherence, with the majority classified as intentional (71%). The mean number of non-adherent weeks was 2.5. Higher baseline disease activity, increased fatigue, multiple comorbidities, and stronger medication concerns relative to perceived necessity were significant predictors of non-adherence. Patients with greater symptom burden were paradoxically more likely to deviate from prescribed therapy. Non-adherence was associated with suboptimal disease control and increased risk of treatment discontinuation. These findings highlight that while MTX demonstrates substantial clinical efficacy when taken consistently, psychological and clinical factors significantly influence adherence behavior. Targeted, patient-centered interventions addressing medication beliefs and comorbidity burden may improve long-term therapeutic outcomes in RA management.

Keywords: Rheumatoid arthritis; Methotrexate therapy; Medication adherence; Treatment efficacy; Disease activity; Medication beliefs; non-adherence predictors

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Introduction

Rheumatoid arthritis is a chronic, progressive autoimmune disease characterized by persistent synovial inflammation, joint destruction, functional disability, and systemic complications. Early and sustained pharmacological intervention is essential to prevent irreversible structural damage and long-term morbidity [7]. Current international treatment guidelines recommend early initiation of disease-modifying antirheumatic drugs (DMARDs), with methotrexate (MTX) considered the first-line conventional synthetic DMARD due to its established efficacy, safety profile, and cost-effectiveness.

Methotrexate therapy has been shown to significantly reduce disease activity, inhibit radiographic progression, and improve functional outcomes when administered according to recommended dosing strategies [15]. Optimal MTX use involves early initiation, dose escalation to achieve therapeutic response, and continuous maintenance therapy with regular monitoring. However, despite its proven clinical effectiveness, not all patients achieve optimal outcomes. One important factor contributing to suboptimal treatment response is medication non-adherence [2].

Medication non-adherence in RA represents a complex and multifactorial challenge. Reported adherence rates vary widely depending on assessment methods, with both underuse and overuse documented [19]. Non-adherence may be intentional, driven by concerns about adverse effects or doubts about medication necessity, or unintentional, such as forgetfulness or misunderstanding of instructions. Psychological factors, disease severity, comorbid conditions, socioeconomic status, and patient beliefs about medication have all been associated with deviations from prescribed regimens [4].

Importantly, the gap between pharmacological efficacy observed in controlled clinical trials and real-world effectiveness is often explained by adherence behavior. Even highly effective medications such as MTX may fail to achieve desired outcomes when treatment is inconsistent. Patients with higher disease activity and fatigue may paradoxically demonstrate increased non-adherence, further complicating disease management [11].

Understanding both the clinical efficacy of RA medications and the determinants of non-adherence is essential for improving long-term therapeutic success [1]. Therefore, this study aims to evaluate the effectiveness of MTX therapy in routine

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clinical practice and to identify the prevalence, predictors, and underlying reasons for medication non-adherence among patients with rheumatoid arthritis during the early phase of treatment [17].

Literature Review

Rheumatoid arthritis management has evolved substantially over the past decades, with early initiation of disease-modifying antirheumatic drugs (DMARDs) recognized as the cornerstone of therapy. According to American College of Rheumatology recommendations, methotrexate (MTX) remains the first-line conventional synthetic DMARD due to its proven efficacy and long-term safety profile.

The clinical effectiveness of MTX has been widely documented. Kremer (2004) demonstrated that MTX significantly reduces disease activity and slows radiographic progression when administered consistently. Similarly, Smolen et al. (2014) reported that treat-to-target strategies incorporating MTX result in improved remission rates and functional outcomes.

However, real-world outcomes often differ from clinical trial efficacy. A systematic review by van den Bemt et al. (2012) showed that adherence to DMARD therapy in RA varies between 59% and 107%, depending on the measurement method, indicating both underuse and overuse. These findings suggest that medication-taking behavior substantially influences treatment success.

In a large prospective cohort study, Hope et al. (2020) found that 26% of patients initiating MTX were non-adherent within the first six months, with 71% classified as intentional non-adherence. Higher disease activity (DAS28), fatigue, multiple comorbidities, and stronger medication concerns were significant predictors. This study emphasized that patients with greater symptom burden may paradoxically be more likely to deviate from prescribed therapy.

Similarly, Kim et al. (2018), analyzing data from a nationwide Korean cohort, reported a 9.6% prevalence of non-adherence. The most common causes included forgetfulness, absence of symptoms, and medication discomfort. Younger age and higher income were associated with increased non-adherence, while higher functional disability and corticosteroid use were protective factors.

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Psychological determinants of adherence have also been extensively studied. Based on the Necessity–Concerns Framework proposed by Horne and Weinman (1999), medication adherence is influenced by patients perceived need for treatment balanced against concerns about adverse effects. In RA populations, Zwikker et al. (2014) demonstrated that weaker necessity beliefs and an unfavorable necessity–concern differential were significantly associated with non-adherence, even after adjusting for psychological confounders such as anxiety and self-efficacy.

Collectively, existing literature indicates that while MTX and other DMARDs are clinically effective in controlling RA, medication non-adherence remains a major barrier to optimal therapeutic outcomes. Clinical severity, comorbidities, socioeconomic characteristics, and especially medication beliefs all contribute to adherence behavior. Nonetheless, there remains a need for integrated analyses that simultaneously assess treatment efficacy and multifactorial causes of non-adherence during the early treatment phase.

Methods

This study was conducted as a prospective observational cohort analysis designed to evaluate the clinical efficacy of methotrexate (MTX) therapy and to identify the prevalence, predictors, and underlying reasons for medication non-adherence among patients with rheumatoid arthritis (RA) during the first six months of treatment [9]. The study population consisted of adult patients diagnosed with RA who were initiating MTX therapy for the first time. Only incident MTX users were included to ensure accurate assessment of early adherence behavior and treatment response. Patients with prior MTX exposure exceeding two weeks were excluded. Ethical approval was obtained from the relevant institutional review board, and all participants provided written informed consent prior to enrollment.

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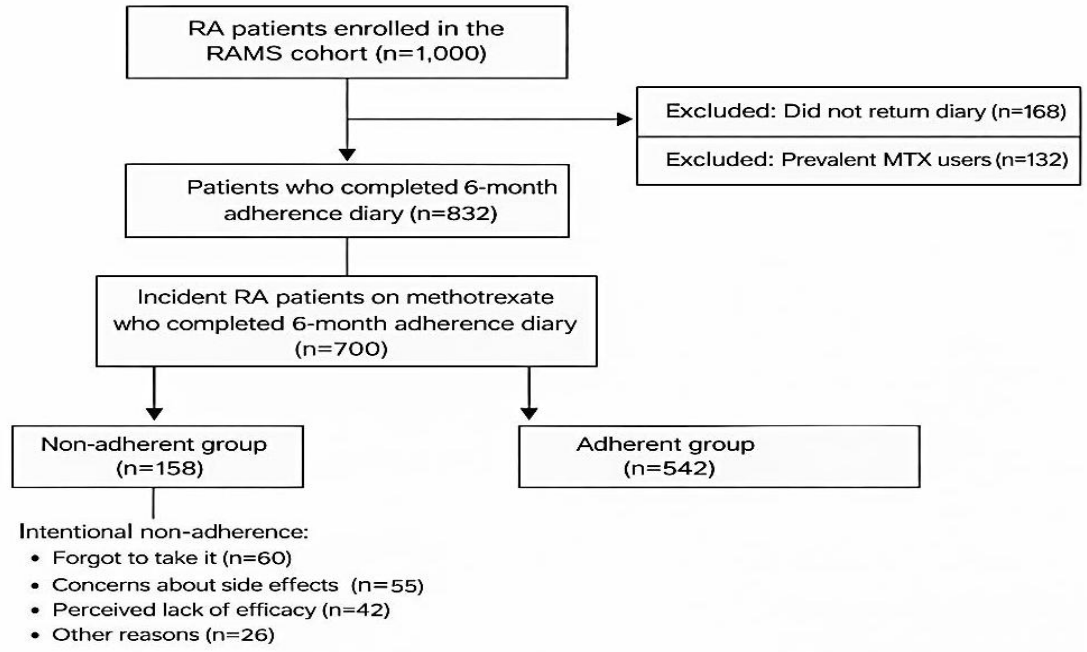

Figure 1. Study population flowchart and adherence classification

Baseline demographic and clinical data were collected before initiation of MTX therapy. Recorded variables included age, sex, body mass index, smoking status, alcohol consumption, disease duration, previous DMARD use, and socioeconomic indicators [12, 13]. Disease activity was assessed using the Disease Activity Score in 28 joints (DAS28), calculated from tender and swollen joint counts, patient global assessment, and C-reactive protein levels. Comorbid conditions were documented using a predefined checklist, and patients were categorized according to comorbidity burden [6]. Functional status and quality of life were evaluated using validated instruments, including the Health Assessment Questionnaire Disability Index and visual analogue scales for pain and fatigue. Psychological variables were assessed using standardized questionnaires measuring anxiety, depression, illness perception, and medication beliefs, including the Beliefs about Medicines Questionnaire, from which a necessity–concern differential score was derived [16, 20].

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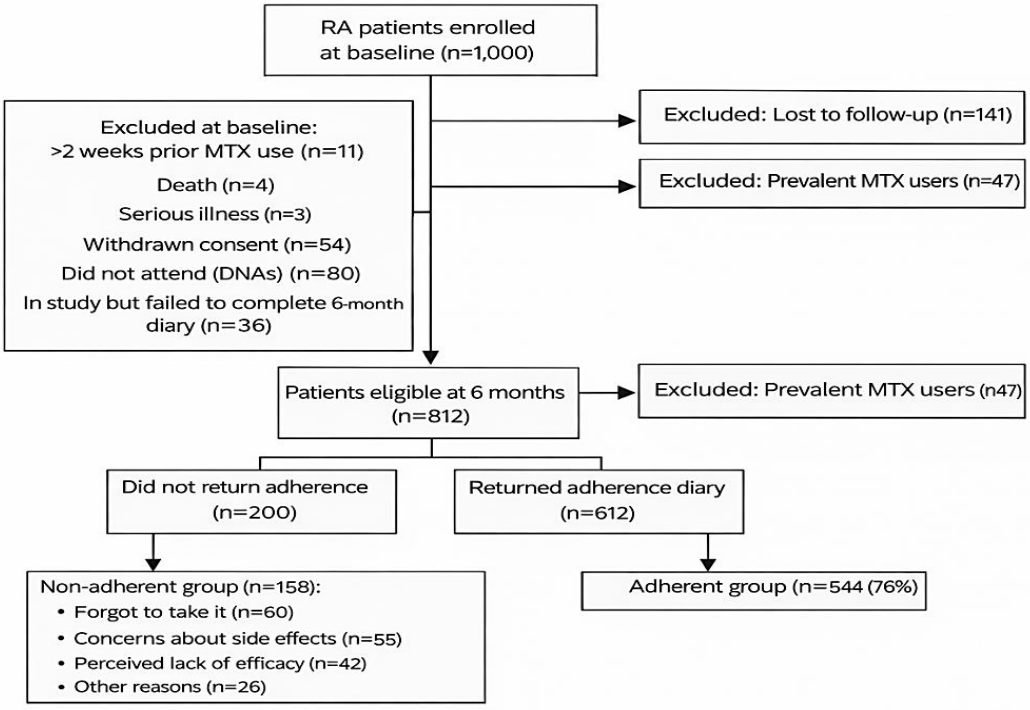

Figure 2. Study recruitment and early methotrexate adherence classification

Adherence to MTX therapy was monitored prospectively using a structured weekly patient diary over a 26-week period. Participants recorded MTX dosage, route of administration, occurrence of side effects, and whether any dose was missed. A week was classified as non-adherent if MTX was not taken without medical advice [3, 10]. Non-adherence was further categorized as intentional or unintentional based on patient-reported reasons. Intentional non-adherence included concerns about side effects, perceived lack of efficacy, or voluntary dose omission, whereas unintentional non-adherence included forgetfulness or logistical barriers.

Statistical analyses were performed to determine the rate of non-adherence and to identify baseline predictors of early non-adherence. Logistic regression models were used to assess associations between demographic, clinical, and psychological variables and the likelihood of non-adherence [5, 18]. Variables significant in univariable analyses were entered into multivariable models. Model discrimination was evaluated using the area under the receiver operating characteristic curve, and goodness-of-fit was assessed using standard calibration tests. Missing baseline data were addressed using multiple imputation techniques

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[8, 14]. Sensitivity analyses were conducted to confirm the robustness of findings under alternative adherence definitions.

Results

A total of 606 incident rheumatoid arthritis patients initiating methotrexate therapy were included in the final analysis after validation of six-month adherence diaries. The study population consisted predominantly of women (69%) with a mean age of 60 years. Baseline disease activity was moderate, with a mean DAS28 score of 4.2, and the median symptom duration was 10 months.

Table 1. Baseline Characteristics of Patients According to Methotrexate Adherence Status

Variable	All patients	Adherent	Non-adherent
Women, (%)	419 (69%)	303 (68%)	116 (73%)
Age, years (mean ± SD)	60 ± 13	60 ± 14	59 ± 14
DAS28 (mean ± SD)	4.2 ± 1.2	4.1 ± 1.2	4.4 ± 1.3
Fatigue VAS, cm (mean ± SD)	4.9 ± 2.8	4.7 ± 2.8	5.5 ± 2.9
≥2 Comorbidities, n (%)	84 (14%)	54 (12%)	30 (19%)
CRP, mg/L (median [IQR])	5.5 [2.1–16.9]	5.5 [2.2–17.5]	6.0 [2.0–16.1]
HAQ (mean ± SD)	1.1 ± 0.8	1.1 ± 0.7	1.2 ± 0.8
BMQ Necessity (mean ± SD)	19.7 ± 3.6	19.7 ± 3.6	19.5 ± 3.5
BMQ Concern (mean ± SD)	15.1 ± 3.8	14.9 ± 3.9	15.5 ± 3.6

During the first six months of treatment, 74% of patients demonstrated full adherence to methotrexate therapy, whereas 26% reported at least one episode of non-adherence. The mean duration of non-adherence among affected individuals was 2.5 weeks. Among non-adherent patients, intentional non-adherence accounted for the majority of cases (71%), while 19% were classified as unintentional, and the remainder had unspecified reasons. The most frequently reported causes of intentional non-adherence were perceived side effects, suspected infections not requiring antibiotics, and concerns about general health impact. Unintentional non-adherence was primarily attributed to forgetfulness or running out of medication. Nausea, fatigue, headache, and dizziness were the most commonly reported adverse effects associated with missed doses.

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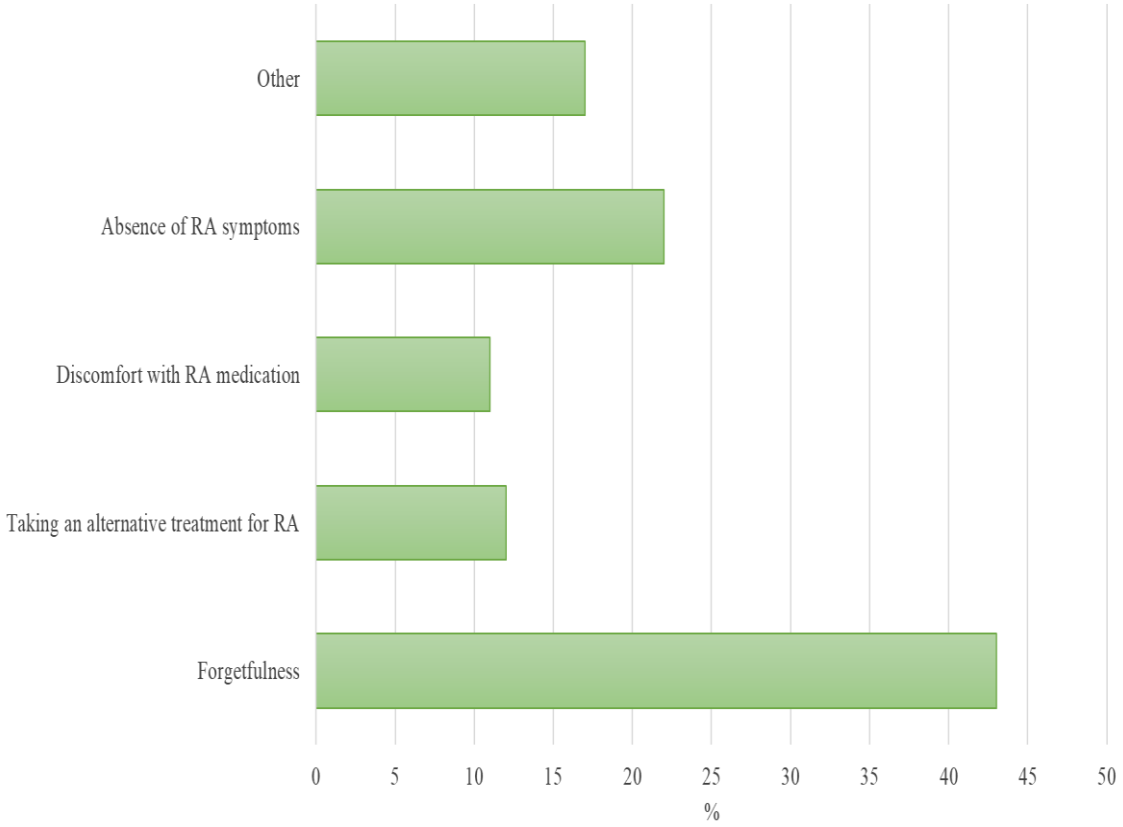

Figure 3. Causes of medication non-adherence in rheumatoid arthritis

In addition, 23% of patients temporarily discontinued methotrexate under medical advice for an average of 6.2 weeks. Treatment discontinuation at six months occurred more frequently among non-adherent patients compared to adherent individuals, indicating a clinically relevant association between early non-adherence and higher risk of therapy interruption.

Univariable regression analyses demonstrated that higher baseline disease activity, increased fatigue scores, and greater tender joint counts were significantly associated with increased odds of non-adherence. Patients with two or more comorbidities were nearly twice as likely to be non-adherent compared to those without comorbid conditions. Psychological factors also played a substantial role; stronger medication concerns and a lower necessity–concern differential were significantly associated with non-adherence.

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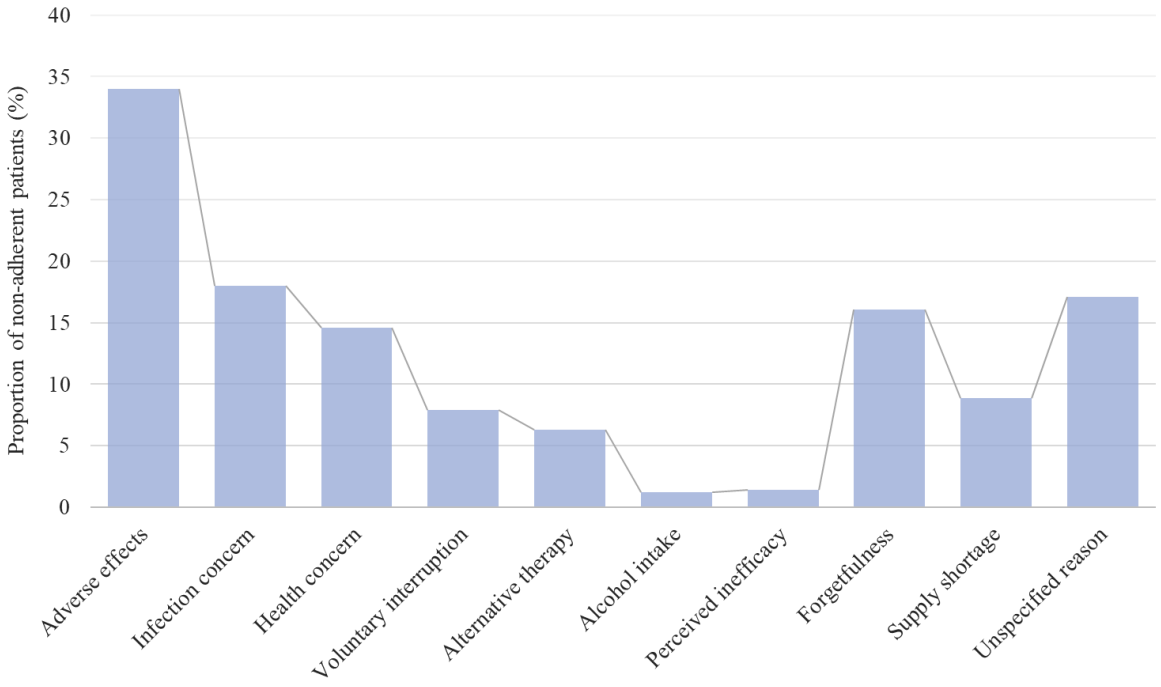

Figure 4. Proportion of reported reasons for early methotrexate non-adherence among patients with rheumatoid arthritis

Multivariable analysis confirmed that higher DAS28 scores, elevated fatigue levels, multiple comorbidities, and greater medication concerns independently predicted early non-adherence. Model discrimination was moderate, suggesting that both clinical severity and medication-related beliefs contribute meaningfully to adherence behavior. Sensitivity analyses using alternative adherence definitions yielded consistent results, supporting the robustness of these findings.

Conclusion

Rheumatoid arthritis patients initiating methotrexate therapy demonstrated substantial clinical benefit when treatment was taken consistently; however, early non-adherence remained a significant and clinically relevant challenge. Approximately one quarter of patients experienced at least one episode of non-adherence within the first six months, with the majority of cases classified as intentional. Higher baseline disease activity, greater fatigue, multiple comorbidities, and stronger medication concerns were independently associated with increased likelihood of non-adherence. Importantly, patients with higher symptom burden were paradoxically more prone to deviating from prescribed therapy, and early non-adherence was associated with an increased risk of

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treatment discontinuation. These findings confirm that real-world treatment effectiveness is closely dependent on adherence behavior.

In conclusion, the study highlights that methotrexate is clinically effective in routine practice, yet its therapeutic potential is partially limited by modifiable psychological and clinical factors. Medication beliefs, particularly elevated concerns relative to perceived necessity, play a central role in early adherence behavior. Therefore, optimizing treatment outcomes in rheumatoid arthritis requires not only pharmacological management but also patient-centered strategies addressing symptom burden, comorbidity management, and medication-related perceptions. Early identification of patients at high risk for non-adherence may improve long-term disease control and reduce the likelihood of premature therapy discontinuation.

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