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FUNCTIONAL AND INFLAMMATORY OUTCOMES OF METHOTREXATE IN RHEUMATOID ARTHRITIS: A SYSTEMATIC REVIEW

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ABSTRACT
Rheumatoid arthritis is a chronic autoimmune disease characterised by persistent inflammation and functional impairment. Methotrexate remains the cornerstone therapy; however, its effects on physical function have not been consistently evaluated. To evaluate the effectiveness of methotrexate-based therapy on inflammatory control and physical function in patients with rheumatoid arthritis. This systematic review followed PRISMA guidelines. Literature searches were conducted in PubMed, Scopus, the Cochrane Library, SpringerLink, and ScienceDirect for studies published between 2016 and 2025. Eligible studies were randomised controlled trials involving adult patients with rheumatoid arthritis receiving methotrexate as monotherapy or combination therapy. The primary outcome was physical function assessed using the Health Assessment Questionnaire Disability Index (HAQ-DI), while secondary outcomes included disease activity measures. Eight randomised controlled trials were included. Methotrexate-based therapy consistently reduced disease activity across studies, with combination regimens generally demonstrating greater inflammatory suppression than monotherapy. Improvements in physical function were observed in several studies, particularly in combination therapy groups; however, these improvements were not consistently proportional to reductions in inflammatory activity. Functional outcomes were also reported heterogeneously across studies. Methotrexate-based therapy is effective in controlling inflammatory activity in rheumatoid arthritis but does not consistently translate into proportional improvements in physical function. Persistent impairment may also be influenced by structural joint damage, chronic pain, fatigue, and psychosocial factors.

Keywords: functional disability; health assessment questionnaire disability index; methotrexate; outcome; physical function; rheumatoid arthritis

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INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease characterized by persistent synovial inflammation, progressive joint destruction, and irreversible functional impairment, resulting in long-term disability and reduced quality of life . RA extends beyond structural damage, affecting daily functioning, work capacity, and socioeconomic participation. Preservation of physical function is therefore a central therapeutic objective (Black et al., 2023; Smolen et al., 2020). Methotrexate (MTX) remains the cornerstone of RA management, recommended as first-line therapy in major international guidelines, including the European Alliance of Associations for Rheumatology and the American College of Rheumatology (Fraenkel et al., 2021; Smolen et al., 2018). The use of MTX is supported by evidence demonstrating efficacy in reducing disease activity, a well-established safety profile, and cost-effectiveness across diverse healthcare settings (Aletaha et al., 2019; O'Brien et al., 2024). MTX also functions as the anchor drug in combination

regimens with conventional and biologic disease-modifying antirheumatic drugs (DMARDs) (Jalil et al., 2025; Taylor et al., 2022).

A substantial proportion of patients do not achieve remission or low disease activity with MTX monotherapy, particularly in moderate-to-high disease activity (Genovese et al., 2019; Hidayat et al., 2024). Combination strategies have demonstrated superior suppression of inflammatory activity and improved clinical response compared with MTX alone (Fleischmann et al., 2019; Huang et al., 2019; Liu et al., 2025). Treatment response remains heterogeneous and is influenced by disease duration, timing of therapy, and individual patient factors, including genetic variability (Abdallah et al., 2022; Claassen et al., 2026; Curtis et al., 2023). Evaluation of MTX effectiveness has traditionally relied on inflammatory measures, including the Disease Activity Score in 28 joints (DAS28), C-reactive protein, and erythrocyte sedimentation rate (Choi et al., 2024; Coras et al., 2020; Kurniari et al., 2021). These indicators quantify systemic inflammation but do not fully reflect patient-centered outcomes. Physical function remains a key determinant of long-term disability and quality of life (Khader et al., 2022; Pisaniello et al., 2022; Teuwen et al., 2024). Physical function is commonly assessed using the Health Assessment Questionnaire Disability Index (HAQ-DI), a validated instrument that measures limitations in activities of daily living. This index captures the cumulative effects of inflammation, structural joint damage, and pain. A reduction of ≥0.22 is considered clinically meaningful (Norton et al., 2014; Teuwen et al., 2024).

Greater suppression of disease activity is associated with improved functional outcomes, as reflected by HAQ-DI scores . The existing literature mainly focuses on inflammatory endpoints, often overlooking the consistent integration of functional measures. This limits the interpretation of treatment effectiveness in clinical practice. Discordance between inflammatory markers and patient-reported function has also been reported (van der Heijde et al., 2022; Verhoeven et al., 2020). This systematic review aims to critically evaluate the effectiveness of methotrexate-based therapy in rheumatoid arthritis by integrating evidence on inflammatory control and physical function, with particular emphasis on the consistency of functional outcome reporting across randomized controlled trials.

METHOD

Eligibility Criteria

This systematic review was conducted in accordance with the PRISMA statement guidelines. Study eligibility was defined using the PICO framework (Population, Intervention, Comparison, Outcome). The population included adult patients diagnosed with rheumatoid arthritis based on established criteria from the American College of Rheumatology or ACR/EULAR classification. The intervention of interest was methotrexate therapy, administered as monotherapy or in combination with other disease-modifying antirheumatic drugs (DMARDs). Comparator groups included placebo, conventional therapy, or alternative DMARD regimens (Table 1).

Table 1.
PICOS of this study

Population	Adult patients diagnosed with rheumatoid arthritis based on established criteria (ACR or ACR/EULAR classification).
Intervention	Methotrexate therapy administered as monotherapy or in combination with other disease-modifying antirheumatic drugs (DMARDs).
Comparison	Placebo, conventional therapy, or alternative DMARD regimens (including non-MTX-based treatments).
Outcome	Primary outcomes: Functional outcomes assessed using validated instruments, particularly the Health Assessment Questionnaire Disability Index (HAQ-DI), including measures of physical function and disability. Secondary outcomes: Disease activity parameters, including Disease Activity Score in 28 joints (DAS28), C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR).
Study Design	Randomized Controlled Trials (RCTs).

Primary outcomes were functional measures, particularly the Health Assessment Questionnaire Disability Index (HAQ-DI) and related indicators of physical function or disability. Secondary outcomes included disease activity measures such as DAS28, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR). Only randomized controlled trials (RCTs) were included. Reviews, meta-analyses, observational studies, case reports, conference abstracts without full text, animal studies, and studies involving pediatric populations were excluded.

Information Sources and Search Strategy

A comprehensive literature search was conducted across PubMed/MEDLINE, Scopus, the Cochrane Library, SpringerLink, and Google Scholar for studies published between 2016 and 2026. The search strategy combined Medical Subject Headings (MeSH) and free-text terms related to methotrexate, rheumatoid arthritis, and functional or musculoskeletal outcomes. Boolean operators (AND/OR) were applied to optimize search performance. Keywords included "methotrexate," "rheumatoid arthritis," "physical function," "musculoskeletal function," "functional disability," and "HAQ-DI" (Table 2). No geographic restrictions were applied. Only studies published in English or Indonesian were included. Reference lists of eligible studies were screened manually to identify additional relevant articles.

Table 2.
Database keywords

Database	Search Terms
PubMed/MEDLINE	("methotrexate") AND ("rheumatoid arthritis") AND ("musculoskeletal function" OR "physical function" OR "functional disability" OR "HAQ-DI")
Science Direct	("methotrexate") AND ("rheumatoid arthritis") AND ("musculoskeletal function" OR "physical function" OR "functional disability" OR "HAQ-DI")
Cochrane Library	("methotrexate") AND ("rheumatoid arthritis") AND ("musculoskeletal function" OR "physical function" OR "functional disability" OR "HAQ-DI")
SpringerLink	("methotrexate") AND ("rheumatoid arthritis") AND ("functional outcome" OR "musculoskeletal function" OR "physical function")
Google Scholar	"methotrexate" AND "rheumatoid arthritis" AND ("physical function" OR "functional disability" OR "HAQ-DI")

Study Selection

All retrieved records were imported into reference management software, and duplicates were removed. Titles and abstracts were screened independently by two reviewers to identify potentially eligible studies. Full-text articles were subsequently assessed based on predefined inclusion and exclusion criteria. Disagreements between reviewers were resolved through discussion until consensus was reached. The study selection process was documented using a PRISMA flow diagram.

Characteristics of Included Studies

Data extraction was performed using a standardized form. Extracted variables included author, year of publication, study location, sample size, patient characteristics, intervention details, comparator groups, duration of follow-up, and outcome measures. Primary outcomes focused on functional measures, particularly HAQ-DI and related indicators of physical function. Secondary outcomes included disease activity parameters such as DAS28, CRP, and ESR. Information on methotrexate dosage, duration of therapy, and combination regimens was also recorded where available.

Risk of Bias

Methodological quality was assessed independently by three reviewers using the Cochrane Risk of Bias tool (RoB 2). This tool evaluates potential bias across domains, including the randomization process, deviations from intended interventions, missing outcome data, outcome measurement, and

selective reporting. Each study was categorized as having low, some concerns, or high risk of bias. Discrepancies were resolved through discussion until consensus was achieved.

Data Synthesis

Given the variability in intervention strategies and outcome reporting, a quantitative meta-analysis was not performed. Findings were synthesized narratively. The synthesis focused on the relationship between inflammatory control and functional outcomes, particularly changes in HAQ-DI, as well as differences between methotrexate monotherapy and combination therapy approaches.

RESULT

A total of 556 records were identified through database searching. After removal of 177 duplicate records, 379 records were screened based on titles and abstracts, of which 337 were excluded. A total of 42 reports were sought for retrieval, with 4 reports not retrieved. The remaining 38 full-text articles were assessed for eligibility, and 30 were excluded due to inappropriate study design (n = 15), unrelated topic (n = 11), and insufficient data (n = 4). Finally, 8 randomized controlled trials (RCTs) were included in the final analysis. The study selection process followed PRISMA guidelines and is illustrated in the flow diagram (Figure 1).

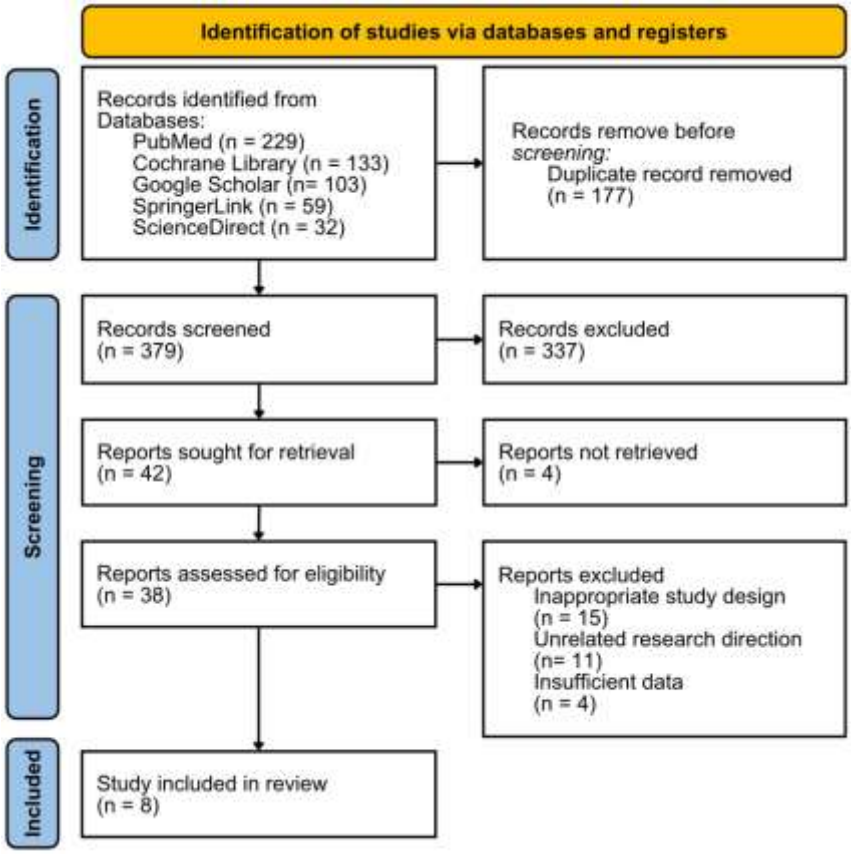

Figure 1. PRISMA Flowchart for Study Selection.

Characteristics of Included Studies

The characteristics of the included studies are presented in Table 3. The review incorporated eight RCTs conducted across diverse settings, including multicenter international trials and single-country studies. Sample sizes varied considerably, ranging from 48 to 2,304 participants. The study populations included both early-stage and established rheumatoid arthritis. Several trials specifically enrolled patients with an inadequate response to methotrexate, reflecting common clinical scenarios. Across studies, methotrexate was consistently used as the backbone of therapy, either as monotherapy or in combination with other agents, including conventional synthetic DMARDs, biologics, and targeted therapies. Comparator groups differed between studies and

included methotrexate monotherapy, placebo in combination with methotrexate, and alternative treatment strategies. The duration of follow-up ranged from short-term assessments at 24 weeks to long-term evaluations extending up to five years.

Table 3.
Study characteristics

Study	Design	Population	RA Stage	MTX Strategy	Comparator	Follow-up
Genovese et al., 2019	Phase 3 RCT (RA-MOBILITY)	Active RA (MTX-IR, n=1197)	Established	Sarilumab + MTX	Placebo + MTX	52 weeks (extension up to 5 years)
Aletaha et al., 2019	Post-hoc analysis of RCT	RA with prior DMARD exposure (n=1024)	Established	Adalimumab + MTX	MTX-based therapy	24 weeks
Bertrand et al., 2024	Pragmatic RCT (CareRA2020)	Early RA (n=379)	Early	MTX + glucocorticoids ± etanercept	csDMARD step-up	2 years
Verhoeven et al., 2020	RCT + follow-up (U-Act-Early)	Early RA (n=317)	Early	Tocilizumab ± MTX	MTX strategy	5 years
Jalil et al., 2025	RCT	Active RA (n=48)	Established	MTX + leflunomide	MTX monotherapy	24 weeks
Fleischmann et al., 2016	Phase 3 RCT (ORAL Start)	MTX-naïve RA (n=956)	Early	MTX vs tofacitinib	Tofacitinib	24 months
Lend et al., 2023	Post-hoc RCT (NORD-STAR)	Early RA (n=812)	Early	MTX + biologics	MTX + active conventional therapy	24 weeks
Feist et al., 2024	Phase 3 RCT (CREDO trials)	Active RA (MTX-IR, n=2304)	Established	Olokizumab + MTX	Placebo / Adalimumab + MTX	24-106 weeks

MTX: methotrexate; RA: rheumatoid arthritis; MTX-IR: methotrexate inadequate response; DMARD: disease-modifying antirheumatic drug; csDMARD: conventional synthetic DMARD; RCT: randomized controlled trial; OLE: open-label extension.

Inflammatory Control Outcomes

Findings related to inflammatory control are summarized in Table 4. Across all included studies, methotrexate-based treatment strategies were associated with reductions in disease activity, as measured by DAS28 or CDAI. In several trials, combination therapy resulted in greater reductions in disease activity compared with methotrexate alone. Study by Jalil et al. (2025) shown the reduction in DAS28 was more pronounced in the methotrexate plus leflunomide group than in the monotherapy group. Similarly, trials involving biologic agents in combination with methotrexate demonstrated sustained suppression of inflammatory activity over time. In early rheumatoid arthritis, treat-to-target approaches led to substantial improvements across treatment arms. However, differences between strategies tended to diminish over longer follow-up periods, suggesting convergence of outcomes despite differences in initial therapy. The included studies consistently demonstrated that methotrexate, whether used alone or in combination, contributes to effective control of inflammatory activity. Nevertheless, the extent of improvement varied across studies and appeared to be influenced by treatment strategy and baseline patient characteristics.

Table 4.
Inflammatory control outcomes

Study	Outcome Measure	Key Findings on Disease Activity	Comparative Effect	Clinical Interpretation
Genovese et al., 2019	DAS28	Significant reduction in DAS28 compared with placebo + MTX, with sustained response over time	Superior to MTX alone	MTX combined with biologic therapy achieved durable and sustained inflammatory control

Study	Outcome Measure	Key Findings on Disease Activity	Comparative Effect	Clinical Interpretation
Aletaha et al., 2019	DAS28	Reduction in disease activity observed across treatment groups	Variable depending on prior DMARD exposure	Treatment response was influenced by baseline characteristics and prior therapy
Bertrand et al., 2024	DAS28	Decrease in DAS28 across all treatment strategies during follow-up	No consistent superiority	Different MTX-based strategies resulted in comparable long-term inflammatory outcomes
Verhoeven et al., 2020	DAS28	High rates of remission achieved and maintained during follow-up	Comparable between strategies	Long-term treat-to-target approaches resulted in similar inflammatory control regardless of initial strategy
Jalil et al., 2025	DAS28	Greater reduction in DAS28 in MTX + leflunomide group compared with MTX monotherapy (−1.72 vs −1.18)	Combination superior to monotherapy	Addition of leflunomide to MTX improved inflammatory outcomes compared with MTX alone
Fleischmann et al., 2016	DAS28	Significant improvement in disease activity in both MTX and tofacitinib groups	Faster response with tofacitinib	Both treatments reduced disease activity, although earlier improvement was observed with targeted therapy
Lend et al., 2023	CDAI	Reduction in CDAI across all treatment arms	Strategy-dependent differences	Inflammatory outcomes varied depending on treatment strategy and intensity
Feist et al., 2024	DAS28	Sustained reduction in DAS28 observed throughout study period	Superior to placebo; comparable to active comparator	MTX-based combination therapy demonstrated consistent and sustained efficacy in controlling inflammation

DAS28: Disease Activity Score in 28 joints; CDAI: Clinical Disease Activity Index; MTX: methotrexate; DMARD: disease-modifying antirheumatic drug.

Physical Function Outcomes

Physical function outcomes are summarized in Table 5. Most studies that reported functional measures used the Health Assessment Questionnaire Disability Index (HAQ-DI), although the extent of reporting varied. Improvements in physical function were observed in several studies, particularly those evaluating combination therapies. The study shown a greater improvement in HAQ scores was reported in the combination group compared with methotrexate monotherapy. Similar trends were observed in studies involving biologic agents, where improvements in HAQ-DI were reported alongside reductions in disease activity.

However, functional outcomes were not consistently evaluated across all included trials. Some studies did not include standardized functional measures as primary outcomes, while others reported functional status without a detailed quantitative assessment. In long-term follow-up studies, physical function was generally maintained, suggesting that sustained disease control may contribute to preservation of functional status. Taken together, these findings indicate that although methotrexate-based therapies are associated with improvements in physical function, the reporting of functional outcomes remains variable and less consistent than inflammatory measures.

Table 5.
Physical function outcomes

Study	Functional Measure	Key Findings on Physical Function	Between-Group Comparison	Clinical Interpretation
Genovese et al., 2019	HAQ-DI	Significant improvement in HAQ-DI scores compared with placebo + MTX	Combination superior to MTX alone	MTX combined with biologic therapy improved physical function over long-term follow-up

Study	Functional Measure	Key Findings on Physical Function	Between-Group Comparison	Clinical Interpretation
Aletaha et al., 2019	HAQ-DI	Improvement in HAQ-DI observed across treatment groups	Differences observed based on prior DMARD exposure	Functional outcomes were influenced by baseline treatment history
Bertrand et al., 2024	N/A	Functional outcomes were not consistently assessed using standardized measures	N/A	Functional benefit could not be clearly determined
Verhoeven et al., 2020	Functional status	Functional status remained stable during long-term follow-up	Comparable across strategies	Treat-to-target strategies maintained physical function over time
Jalil et al., 2025	HAQ	Greater reduction in HAQ scores in MTX + leflunomide group compared with MTX monotherapy	Combination superior to monotherapy	Addition of leflunomide to MTX improved physical function outcomes
Fleischmann et al., 2016	HAQ-DI	Improvements in HAQ-DI observed in both treatment groups over time	Faster improvement with tofacitinib	Both treatments improved physical function, with earlier response in targeted therapy
Lend et al., 2023	N/A	Functional outcomes were not evaluated as a primary endpoint	N/A	Limited evidence on functional outcomes in this study
Feist et al., 2024	HAQ-DI	Sustained improvement in HAQ-DI reported throughout the study period	Superior to placebo; comparable to active comparator	MTX-based combination therapy provided durable functional improvement

HAQ-DI: Health Assessment Questionnaire Disability Index; MTX: methotrexate; DMARD: disease-modifying antirheumatic drug; N/A; Not applicable.

Risk of Bias Assessment

The risk of bias assessment is presented in Table 6. Most of the included trials were judged to have a low risk of bias, particularly large randomized controlled trials with double-blind designs. These studies demonstrated adequate randomization procedures, low rates of missing data, and consistent outcome measurement. Several studies were assessed as having some concerns, primarily due to limitations related to blinding or deviations from intended interventions. These issues were more commonly observed in open-label designs or secondary analyses of randomized trials. Overall, the methodological quality of the included studies was considered acceptable, although certain limitations should be acknowledged when interpreting the findings.

Table 6.
Risk of Bias Assessment (Cochrane RoB 2 Tool)

Study	Randomization Process	Deviations from Intended Interventions	Missing Outcome Data	Measurement of the Outcome	Selection of the Reported Result	Overall Risk of Bias
Genovese et al., 2019	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Aletaha et al., 2019	Some concerns	Some concerns	Low risk	Low risk	Low risk	Some concerns
Bertrand et al., 2024	Low risk	Some concerns	Low risk	Some concerns	Low risk	Some concerns
Verhoeven et al., 2020	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Jalil et al., 2025	Some concerns	Some concerns	Low risk	Some concerns	Low risk	Some concerns
Fleischmann et al., 2016	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Lend et al., 2023	Low risk	Some concerns	Low risk	Some concerns	Some concerns	Some concerns
Feist et al., 2024	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

DISCUSSION

This systematic review demonstrates that methotrexate (MTX)-based therapy consistently achieves effective inflammatory control in patients with rheumatoid arthritis, as reflected by reductions in disease activity indices such as DAS28 and CDAI. Across the included randomized controlled trials, improvements in inflammatory outcomes were observed regardless of treatment strategy, although combination regimens generally produced greater and more rapid reductions. These findings reinforce the established role of MTX as the anchor drug in RA management, both as monotherapy and as the foundation of combination therapy approaches (Bessette et al., 2024).

Several studies have shown that combination strategies for treatment perform better than monotherapy. This aligns with earlier evidence indicating that combining methotrexate (MTX) with biologic or targeted agents improves the suppression of important inflammatory pathways. These pathways include cytokine-mediated signaling, specifically interleukin-6 and tumor necrosis factor (Bertrand et al., 2024; Genovese et al., 2019; Lend et al., 2024). This finding is particularly significant for patients who have not responded adequately to MTX alone, highlighting the necessity of escalation strategies in clinical practice (Alsharif, 2026). Despite consistent improvements in inflammatory markers, the application of these effects to functional outcomes was not uniform. Although several studies reported improvements in HAQ-DI, functional outcomes were not consistently assessed, and their magnitude varied across trials(Perrotta et al., 2024). This observation aligns with previous findings demonstrating that clinical measures and patient-reported outcomes do not always correspond. Patients may achieve low disease activity based on clinical indices while continuing to experience functional limitations, highlighting a persistent gap between inflammatory control and patient-perceived benefit (Fleischmann et al., 2019).

The relationship between inflammation and physical function is complex and multifactorial. While reductions in disease activity are associated with improvements in HAQ-DI, functional outcomes are also influenced by structural joint damage, muscle strength, and physical performance. Longitudinal evidence indicates that worsening disease activity is associated with deterioration in physical function over time, supporting the importance of sustained disease control, yet also emphasizing that functional impairment may persist even when inflammation is adequately managed (Bertrand et al., 2024; do Espírito Santo et al., 2023; Hernández-Hernández & Díaz-González, 2017). These findings have important clinical implications. Current treat-to-target strategies predominantly rely on inflammatory indices. However, exclusive reliance on these measures may not fully capture treatment benefit. Increasing recognition of this limitation has led to recommendations for integrating patient-reported outcomes into both clinical trials and routine care, ensuring a more comprehensive and patient-centered evaluation of treatment effectiveness (Githumbi et al., 2025). Another important consideration is the variability in treatment response. A substantial proportion of patients do not achieve remission with MTX monotherapy, with estimates suggesting that up to 30- 40% of patients exhibit inadequate response. This variability reflects differences in disease characteristics, treatment timing, and pharmacologic factors, underscoring the need for individualized treatment strategies and timely escalation when necessary (Alsharif, 2026; Feist et al., 2024; Lend et al., 2024).

From a methodological perspective, this review offers several strengths. The inclusion of randomized controlled trials enhances the internal validity of the findings. Furthermore, the integration of both inflammatory and functional outcomes allows for a more comprehensive evaluation of treatment effectiveness. Additionally, the use of a structured risk of bias assessment (RoB 2) provides a systematic appraisal of study quality. Importantly, the inclusion of diverse treatment strategies reflects real-world clinical practice, increasing the applicability of the findings. Nevertheless, several limitations should be acknowledged. Substantial heterogeneity across studies in terms of interventions, patient populations, and outcome reporting limited direct comparability and precluded quantitative synthesis. Functional outcomes, particularly HAQ-DI, were not

consistently reported, restricting the ability to draw definitive conclusions regarding the impact of MTX on physical function. In addition, variability in follow-up duration may influence the interpretation of both short- and long-term outcomes. Some studies also involved open-label designs or secondary analyses, which may introduce potential bias related to deviations from intended interventions and outcome assessment. This review reinforces the central role of methotrexate in achieving inflammatory control in rheumatoid arthritis while highlighting a critical gap in the consistent assessment of physical function. Future research should focus on a standardized evaluation of patient-reported outcomes in addition to conventional inflammatory measures.

CONCLUSION

Methotrexate (MTX)-based therapy effectively controls inflammatory activity in rheumatoid arthritis, both as monotherapy and in combination regimens. Combination therapy, particularly with biologic or targeted agents, generally provides greater reductions in disease activity than MTX alone. However, improvement in inflammatory markers does not always correspond to proportional improvement in physical function. Functional outcomes, especially HAQ-DI, were inconsistently reported across studies, highlighting the gap between disease activity and patient-centered outcomes. MTX remains the cornerstone therapy for rheumatoid arthritis, but treatment evaluation should also incorporate functional assessment and patient-reported outcomes.

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