ingegneria sismica
International Journal of Earthquake Engineering
Anno XLIII - Num. 3 - 2026

Effect of disease-modifying anti-rheumatic drugs in osteoarthritis: A meta-analysis

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SUMMARY: ***[Objective]*** *This study focuses on evaluating the actual efficacy of DMARDs (drugs used for anti-rheumatic therapy) in the treatment of osteoarthritis.* ***[Method]*** *The research team conducted a comprehensive literature search in multiple authoritative databases, including PubMed, Cochrane Library, Embase, Web of Science, China National Knowledge Infrastructure (CNKI), Wanfang Database, and CBM, through computer retrieval. The search scope is limited to randomized controlled trials (RCTs) studying the application of DMARDs in the treatment of osteoarthritis, with a time span from the creation of each database to December 2024. Two researchers independently conducted literature screening and data extraction based on pre-set inclusion and exclusion criteria. The research quality was evaluated using the Cochrane bias risk assessment tool and statistical analysis was conducted using RevMan 5.4 software.* ***[Result]*** *After screening, a total of 15 randomized controlled trials were included in this analysis, which involved 8 different DMARDs drugs, including methotrexate, hydroxychloroquine, Iguatemo, adalimumab, etanercept, tocilizumab, Orthokin, and Anakin. In terms of participants, the experimental group had a total of 771 people, while the control group had 784 people. The meta-analysis results showed that DMARDs exhibited significant efficacy in relieving pain in patients with osteoarthritis, with an overall standardized mean difference of [SMD=-0.44, 95% CI (-0.78, -0.10), P=0.01]. Further analysis revealed that conventional synthesized DMARDs had a more prominent effect [SMD=-0.71, 95% CI (-1.23, -0.20), P=0.007], while biosynthetic DMARDs had a relatively weaker effect [SDM=-0.04, 95% confidence interval (-0.20, 0.12), P=0.62]. In terms of specific drugs, methotrexate showed significant efficacy in relieving pain [SD=-0.71, 95% confidence interval (-1.32, -0.11), P=0.02], while hydroxychloroquine [SD=-0.19, 95% confidence interval (-0.53, -0.15), P=0.28] and TNF - α inhibitors [SD=-0.09, 95% confidence interval (-0.37, 0.18), P=0.50] did not show significant efficacy. Similarly, interleukin receptor antagonists did not show significant effects [SMD=-0.01, 95% CI (-0.22, 0.19), P=0.91]. In terms of pain relief for specific types of osteoarthritis, DMARDs have limited relief for osteoarthritis [SMD=-0.12, 95% CI (-0.26, 0.02), P=0.10], while their relief for knee osteoarthritis is more significant [SMD=-0.88, 95% CI (-1.65, -0.11), P=0.02]. In addition, methotrexate, hydroxychloroquine, and interleukin-1 receptor antagonists showed significant effects in improving joint function [SMD=-0.90, 95% CI (-1.73, -0.08), P=0.03].* ***[Conclusion]*** *There are differences in the effectiveness of DMARDs in relieving pain in osteoarthritis. Methotrexate has been proven to be an effective choice for treating patients with moderate to severe osteoarthritis or severe osteoarthritis accompanied by obvious synovitis, especially in the treatment of knee osteoarthritis. On the contrary, hydroxychloroquine, adalimumab, etanercept, tocilizumab, Orthokin, and Anakinra did not show significant pain relief effects in the treatment of osteoarthritis. Meanwhile, methotrexate, hydroxychloroquine, and IL-1 receptor antagonists did not show significant effects in improving overall joint function.*

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https://doi.org/10.65102/is20261102
Published: 10 June, 2026

KEYWORDS: *Osteoarthritis; DMARDs; Synovitis; Methotrexate; Efficacy; Meta-analysis; Rheumatoid arthritis*

1 Introduction

Osteoarthritis (OA), as a typical degenerative joint disease, focuses on the damage and degeneration of articular chondrocytes as its core pathological changes. This condition is particularly common in the knee, hip, and hand joints. The main clinical manifestations of this disease are joint pain, morning stiffness, and functional limitations, among which joint pain constitutes the primary demand for patients seeking medical treatment. Traditionally, the treatment methods for OA have been relatively limited, mainly covering two categories: one is pain relieving drugs for symptoms, such as nonsteroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids; The second is osteoarthritis regulating drugs (DMOAD) aimed at improving the disease progression, such as bisoprolol and glucosamine. These treatment strategies have shown certain therapeutic effects in patients with mild to moderate OA [1]. However, there is currently a lack of effective treatment alternatives for patient populations with severe conditions or poor response to conventional treatments.

In recent years, with the gradual deepening of research on the pathogenesis of OA, scholars have begun to expand their focus to the comprehensive state of the entire joint structure of OA patients, including but not limited to cartilage, subchondral bone, synovial tissue, ligament structure, joint capsule, and surrounding muscle groups. Specifically, synovitis triggered by cartilage fragments has been shown to be closely related to patients' pain experience [3-6], opening up a new perspective for drug treatment of osteoarthritis. DMARDs, as the main force in the treatment of rheumatoid arthritis (RA), effectively control synovial inflammation by precisely regulating the immune system, thereby alleviating symptoms and delaying disease progression. So, are these drugs also suitable for OA patients with synovitis symptoms? Multiple studies have explored this question, but the results are still controversial. Tracing back to 2010, a randomized, double-blind, placebo-controlled trial conducted by Ferrero et al. showed that after 12 weeks of using methotrexate (MTX) to treat refractory osteoarthritis of the hand (HOA), there was no significant difference in pain relief between the treatment group and the control group [7]. However, the 2014 study by Kingsbury et al. brought a different perspective, as they observed in a multicenter, randomized, double-blind, placebo-controlled trial design that methotrexate significantly improved joint pain, stiffness, and daily mobility in patients with knee osteoarthritis (KOA) [8]. Subsequently, a multicenter randomized controlled trial in Australia also supported the positive role of MTX in the treatment of HOA with synovitis [9]. In addition, a review article published in The Lancet in 2023 further explored the potential value of MTX in the treatment of OA [10]. In addition to MTX, several other commonly used DMARDs, such as hydroxychloroquine (HCQ), adalimumab, and interleukin (IL) receptor antagonists, have also been attempted for the treatment of OA, but have not shown consistent and significant therapeutic effects [11-13]. A meta-analysis in 2018 comprehensively evaluated the application effects of traditional synthetic DMARDs (cDMARDs) and biological DMARDs (bDMARDs) in the treatment of OA, and found that neither of these drugs achieved statistically significant differences in relieving pain in OA patients [14]. However, Sylvain Mathieu et al.'s study [15] reviewed numerous studies on the treatment of OA with DMARDs prior to 2020 (involving multiple drugs such as methotrexate (MTX), hydroxychloroquine (HCQ), adalimumab, tocilizumab, and IL-1 receptor antagonists) and found that MTX has a statistically significant effect in reducing OA pain, while other drugs have not shown similar effects. Since then, new research in this field has continuously emerged.

Based on the above background, this study aims to systematically collect randomized controlled trials (RCTs) on the efficacy of various DMARDs in treating OA at home and abroad, and use meta-analysis method to comprehensively analyze the relevant outcome indicators, in order to comprehensively evaluate the actual effects of common DMARDs in relieving OA pain and improving overall joint function.

2 Data and methods

2.1 Retrieval Strategy

With the help of computer technology, we conducted a comprehensive search of multiple authoritative databases, including PubMed, Cochrane Library Embase, Web of Science, The China National Knowledge Infrastructure (CNKI), Wanfang Data Resource System, and China Biomedical Literature Database (CBM) aim to collect literature on randomized controlled trials (RCTs) using various DMARDs (such as methotrexate, hydroxychloroquine, etc.) for the treatment of osteoarthritis. The time span for retrieval is set from the date of creation of each database to December 2024. In formulating the retrieval strategy, we strictly followed the PICOS principle and carefully constructed a retrieval expression that conforms to the structure of P (research subject) +I (intervention measures)+S (research type). Specifically, the Chinese search terms cover related terms such as anti-rheumatic drugs, methotrexate, hydroxychloroquine, alenzumab, adalimumab, etanercept, rituximab, tocilizumab, osteoarthritis, and randomized controlled trials; At the same time, we also used corresponding English keywords for retrieval to ensure the comprehensiveness and accuracy of the search results.

2.2 Inclusion and exclusion criteria

The selection criteria are as follows: (1) The research type should be a randomized controlled trial aimed at comparing the effects of different DMARDs in the treatment of osteoarthritis. This type of experiment should use appropriate random sequence generation methods and scientific grouping methods. There is no limitation on whether blinding or allocation concealment measures should be used; (2) The subjects must meet the classification criteria for osteoarthritis established by the American College of Rheumatology (ACR), or comply with the relevant requirements of the "Guidelines for the Diagnosis and Treatment of Osteoarthritis" issued by the Orthopedic Branch of the Chinese Medical Association in 2018 [16].

The exclusion criteria are set as follows: (1) Literature in languages other than Chinese or English will not be included; (2) Repeatedly published literature works are not considered; (3) If the research type is not a randomized controlled trial, or if there are incomplete data and the study is still ongoing, it will also be excluded.

2.3 Literature screening and data extraction

The literature screening work is carried out independently and rigorously by two professional researchers who strictly follow the predetermined inclusion and exclusion criteria. In the screening process, they uphold an objective and fair attitude, not omitting any literature that may meet the requirements, nor blindly including literature that does not meet the standards. After the two researchers have completed their respective screenings, a detailed comparison and systematic integration of the data obtained by both parties will be carried out.

In the data processing stage, if multiple publications of the same study are found, in order to ensure the timeliness and completeness of the data, only the latest and most complete data

from the study will be selected and included in the final analysis category. When two researchers have different opinions during the screening process and cannot reach a consensus on their own, a third experienced researcher will be invited to participate in the discussion in a timely manner. The third researcher will adopt an objective and neutral stance, comprehensively analyze various viewpoints, and provide professional suggestions until the three parties reach a consensus, thereby ensuring the accuracy and reliability of the screening results.

The information extracted from qualified literature is rich and comprehensive, covering the following key contents: the name of the first author of the literature to accurately trace the source of the research; The publication time of the literature and the timeliness of the research; Number of samples in each group, specifying the scale and representativeness of the study; The specific types of osteoarthritis, such as knee osteoarthritis, hip osteoarthritis, etc; Grading the severity of the condition to provide a stratification basis for subsequent analysis; The specific intervention measures taken, such as the type and dosage of drugs used; The duration of intervention measures and the time span for controlling treatment; Outcome indicators closely related to the research, such as pain score, degree of improvement in joint function, etc; And specific measurement values provide data support for quantitative analysis.

2.4 Estimation of quality

Two independent evaluators used the Cochrane Risk Bias Assessment tool to conduct a comprehensive evaluation of the potential bias risks hidden in the literature from the initial stage of study design to final publication. During the evaluation process, they first carried out their work according to the requirements of the tool, then compared the results obtained, carefully examined any differences, and conducted in-depth discussions on these differences, striving to reach a unified opinion.

This evaluation mainly focuses on the following key areas:

(1) In terms of selection bias, the focus is on examining whether the generation method of random sequences is scientifically reasonable, and whether the allocation of random sequences is effectively hidden to avoid human factors interfering with the grouping of research subjects.

(2) In terms of bias implementation: Pay attention to whether blinding was used during the research process to prevent researchers and participants from being influenced by knowledge of grouping.

(3) In terms of measurement bias: investigate whether researchers have turned a blind eye to the results when measuring and evaluating them, that is, whether they have avoided subjective factors from interfering with the judgment of the results.

(4) Regarding follow-up bias: Evaluate the completeness of the outcome data and check for any missing data due to reasons such as subject loss to follow-up.

(5) In terms of reporting bias: Analyze whether there is a possibility of selective reporting in the literature, that is, whether only data that is beneficial to the research conclusion is reported and unfavorable data is ignored.

(6) Other biases: Consider other factors that may affect the quality of the research, such as whether the sample size is reasonable.

For each evaluation project, judgments are made on three levels: low bias, uncertainty, and high bias. If all items in the literature are evaluated as low bias, the quality of the literature will be rated as A (low bias); If there are no high bias items in the literature, but there are some uncertain biases, it will be rated as B level (moderate bias); As long as any item is rated as high bias, the quality of the literature is rated as level C (high bias).

2.5 Statistical treatment

In this study, we used RevMan 5.4 software as the data analysis tool to conduct heterogeneity

tests and meta-analysis of effect sizes on the collected data. When dealing with various outcome indicators, in order to ensure consistency and comparability of data, different types of outcome indicators such as pain scale scores and joint severity scale scores are standardized using the form of "mean ± standard deviation (± S)". After comprehensive consideration, we ultimately selected the Standardized Mean Difference (SMD) as the core indicator to measure the size of the effect, laying a unified standard foundation for further in-depth analysis.

In the heterogeneity assessment stage, we use Q-tests to determine the heterogeneity status among the included studies. If the test results of Q-test show $P<0.1$ or $I^2>50\%$, it means that there is significant heterogeneity among the included studies. Once this situation occurs, we will use a random effects model (REM) to calculate the merged standardized mean difference (SMD) and its corresponding 95% confidence interval (95% CI). After completing this step, further subgroup analysis and sensitivity analysis will be conducted. Through subgroup analysis, research can be classified and explored from different dimensions, and potential factors that may affect the results can be identified; Sensitivity analysis, on the other hand, helps to evaluate the stability of research results. Through these two analysis methods, we can delve into the specific sources of heterogeneity and interpret research results more accurately.

On the contrary, if the Q-test results do not show significant heterogeneity, it indicates good homogeneity among the included studies. In this case, we will use a fixed effects model (FEM) to merge the effect values of each study, in order to obtain more robust and reliable research conclusions, ensuring the scientific and accurate nature of the research results.

3 Data analysis

3.1 Meta analysis method

In the calculation process, operations are strictly carried out according to specific equation (1) to ensure that the entire analysis process is scientific, standardized, and reproducible, thereby laying a solid foundation for obtaining reliable research conclusions in the future.

$$\ln R = \ln\left(X_t / X_c \right) \tag{1}$$

where, X_t and X_c are indicators related to non-treatment with anti-rheumatic drugs and treatment with anti-rheumatic drugs, respectively.

For each attribute, two key tests need to be conducted, namely heterogeneity test (using Q-test method) and normal distribution test, to ensure the accuracy and reliability of data analysis. In the heterogeneity testing stage of this study, the result obtained through chi square test was $P<0.05$, indicating significant heterogeneity among the included studies. Given this situation, we adopt a random effects model to calculate the effect values of various studies, in order to comprehensively analyze the research results more scientifically.

To ensure the objectivity and comprehensiveness of meta-analysis results and avoid publication bias affecting research conclusions, we conducted publication bias testing on selected literature using the carrier safety factor method. After rigorous testing and analysis, based on the criteria of carrier safety factor method, it can be determined that there is no publication bias in the literature selected in this study, which provides strong support for obtaining reliable research conclusions in the future.

Calculate the overall effect using a weighted resampling method based on a random effects model. If the 95% confidence interval does not coincide with 0, the effect is significantly positive or negative. If the 95% confidence interval overlaps with 0, the effect is not significant. For ease of understanding and presentation, convert to relative rate of change through equation

(2):

$$R_R = \left(e^{\ln R} - 1\right) \times 100\% \tag{2}$$

where, R is the percentage change in the treatment group compared to the control group, i.e. the relative rate of change.

3.2 Treatment efficacy evaluation methods

Regarding the evaluation of the therapeutic efficacy of anti-rheumatic drugs: We strictly follow the established grading criteria for the therapeutic efficacy of anti-rheumatic drugs, and carry out detailed grading and standardized operations for various indicators involved in the treatment process of this type of drug. Specifically, key indicators such as the degree of joint pain relief and improvement of inflammatory indicators are clearly classified according to different levels, and data standards are unified to ensure the accuracy and consistency of the evaluation. On this basis, the improved Nemerol index method is used to comprehensively and systematically evaluate the efficacy of anti-rheumatic drugs from multiple dimensions, providing a scientific and reliable basis for rational clinical drug use.

$$\mathrm{IFI}_i = \begin{cases} \dfrac{x}{x_a}, & x \leqslant x_a \\ 1 + \dfrac{x - x_a}{x_b - x_a}, & x_a < x \leqslant x_b \\ 2 + \dfrac{x - x_b}{x_c - x_b}, & x_b < x \leqslant x_c \\ 3, & x > x_c \end{cases} \tag{3}$$

where, IFI_i is the therapeutic efficacy coefficient of a single treatment indicator for anti-rheumatic drugs; x is the therapeutic efficacy index value of anti-rheumatic drugs; x_a, x_b, and x_c are the first, second, and third level thresholds of the indicators, respectively.

Calculate the integrated fertility index (IFI) based on the obtained treatment efficacy coefficient:

$$\mathrm{IFI} = \sqrt{\frac{\mathrm{Ave}\left(\mathrm{IFI}_i\right)^2 + \mathrm{Min}\left(\mathrm{IFI}_i\right)^2}{2}} \times \left(\frac{n-1}{n}\right) \tag{4}$$

where, $\mathrm{Ave}\left(\mathrm{IFI}_i\right)$ and $\mathrm{Min}\left(\mathrm{IFI}_i\right)$ are the average and minimum values of the treatment efficacy coefficients for all treatment efficacy indicators, respectively; n is the number of therapeutic efficacy indicators used in the calculation, with n=5 in this study. After standardization, the value of IFI_i ranges from 0 to 3.

3.3 Statistical analysis

Use Microsoft Excel 2013 for data collection and organization. The mapping and equation fitting were performed using Origin8.0 software.

4 Bearfruit

4.1 Literature screening results

In the initial stage of this study, we obtained a total of 5259 relevant articles through multi-channel retrieval. To avoid data redundancy, duplicate articles are first removed. After this operation, the remaining number of articles is 3042.

Subsequently, we carefully studied the titles and abstracts of these articles, and based on the predetermined screening criteria, excluded 55 articles that did not meet the requirements. These excluded article types include non-randomized controlled trials, review articles, case study reports, meta-analysis results, animal experimental studies, and conference summaries.

Next, full-text reading and in-depth evaluation were conducted on the remaining articles, and 15 articles that fully met the research criteria were ultimately selected. To clearly present the specific process of literature screening, we have drawn a flowchart, which can be seen in Figure 1.

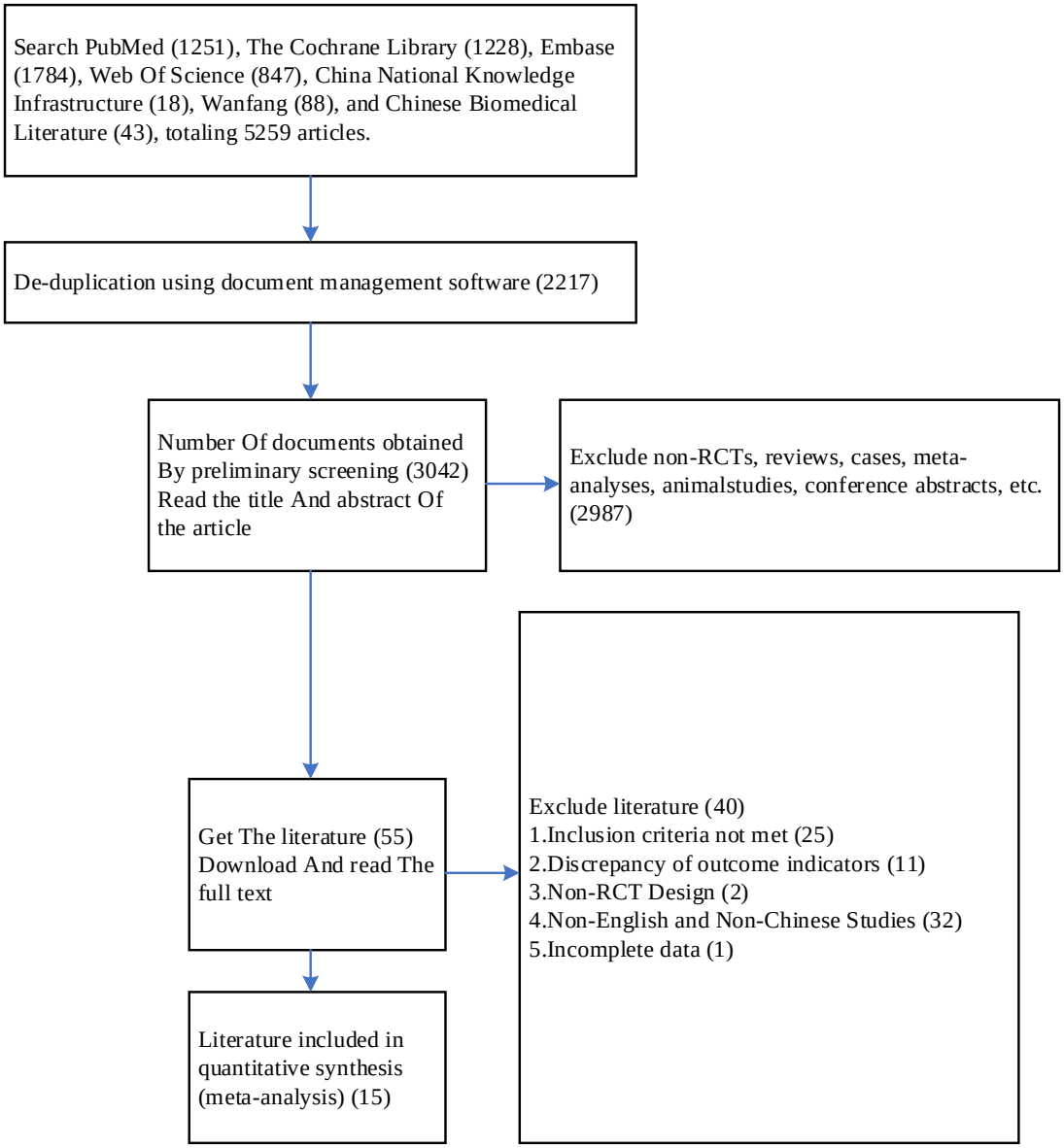

Figure 1: Flow chart of literature screening

After rigorous screening and comprehensive consideration, this study ultimately included 15 high-quality articles as the basis for analysis. Based on the detailed statistics of these included articles, it was found that the patient population involved in the entire study was quite considerable, covering a total of 1555 patients. In order to explore related issues more scientifically, the study set up an experimental group and a control group. Among them, the experimental group included 771 patients, while the control group had 784 patients. This sample allocation ensures that the experimental group has sufficient quantity for intervention research, while also providing reliable reference data for the control group, laying a solid foundation for further in-depth analysis.

4.2 The quality evaluation and basic characteristics of the literature were included

Among the included literature, 13 [7-9, 13, 17-25] were evaluated as grade A, and 2 were evaluated as grade C[26, 27] (2 Chinese studies did not explicitly indicate the use of blind method). The results of bias risk evaluation are shown in Figure 2. The basic characteristics of the included literature are shown in Table 1.

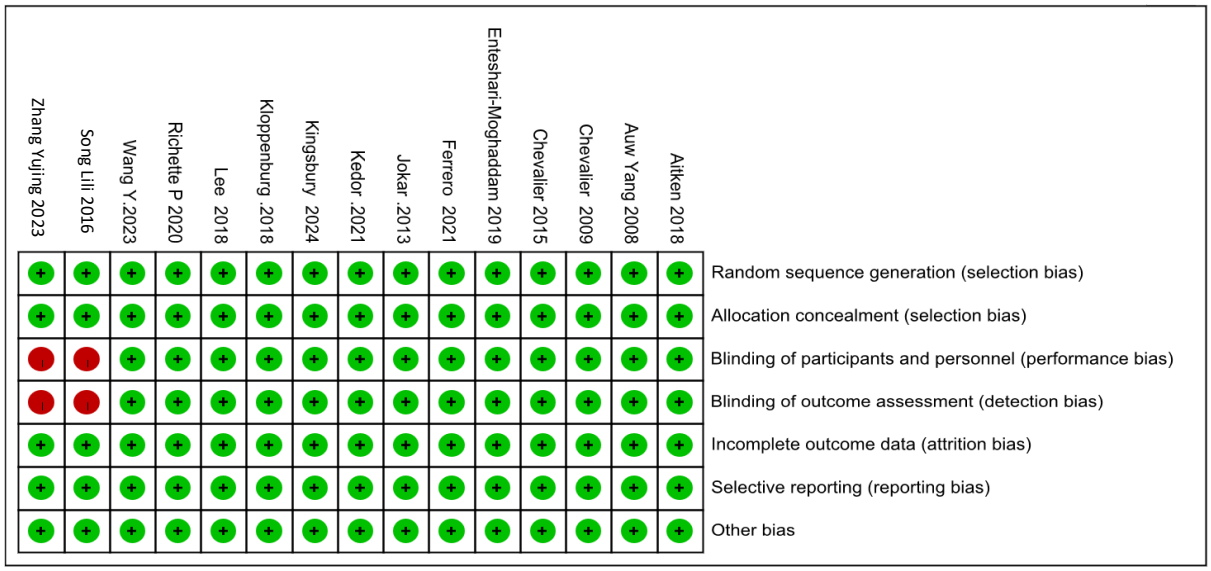

Figure 2: Risk map of inclusion bias

Table 1: Basic characteristics of the included literature

First author	Year	Country	Type of OA	Number of people	Sample size	Sample size	Week
Chevalier	2015	France	Hand OA	76	39	37	6w
Aitken	2018	Australia	Hand OA	41	18	23	12w
Ferrero	2021	France	Hand OA	64	32	32	12W
Jokar	2013	Iran	Knee OA	44	21	23	24w
Auw Yang	2008	France	Hand OA	153	80	73	48W
Kingsbury	2024	France	Knee OA	134	66	68	24w
Kloppenburg	2018	Austria	Hand OA	90	45	45	24w
Lee	2018	Netherlands	Hand OA	196	98	98	24w
Enteshari-Moghadam	2019	Tran	Knee OA	91	41	50	24w
Richette	2020	France	Hand OA	83	42	41	6w
Wang Y	2023	Australia	Hand OA	97	50	47	24w
Chevalier	2009	France	Knee OA	136	67	69	4w
Song Li	2016	China	OA	72	36	36	5w
Zhang Yujing	2023	China	Knee OA	167	85	82	8w

Note: A adalimumab 40mg, subcutaneous injection every two weeks; B methotrexate 10mg, oral, once a week; C hydroxychloroquine 200mg, twice daily; D Orthokin, intra-articular injection; E methotrexate 25mg, oral, once a week; F etanercept 50mg, subcutaneous injection, once a week; G methotrexate 15mg, oral, once a week; H tozilumab 6mg/kg, twice, four weeks apart; I methotrexate 20mg, oral, once a week; J anakinra 150mg, intra-articular injection once; K methotrexate 5mg + sodium hyaluronate 2.5ml, intra-articular injection once a week; L elamodar 25mg, oral, twice daily + glucosamine 250mg, oral, three times daily; M placebo; N sodium hyaluronate 2.5ml, intra-articular injection once a week; O glucosamine 250mg, oral, three times daily. (1) VAS pain score, (2) WOMAC composite score, (3) AUSCAN pain score, (4) AUSCAN pain score molecular table. OA: osteoarthritis; HOA: hand osteoarthritis; KOA: knee osteoarthritis.

4.3 Meta analytic result

4.3.1 DMARDs relieve OA pain

In all 15 studies included in this study, pain rating scales were used to collect relevant data. Among them, the experimental group had a total of 771 participants, while the control group had 784 participants.

After rigorous heterogeneity testing, the results obtained showed that the P-value was less than 0.00001 and the I^2 index reached 90%. This data clearly and unequivocally reveals the highly heterogeneous characteristics among various studies. Given this situation, we have decided to use a random effects model to conduct in-depth analysis of the relevant data. The analysis results indicate that there is a significant difference between the experimental group and the control group. The detailed data results can be found in Table 2, and these differences are statistically significant. Among them, the standardized mean deviation (SMD) is -0.44, the 95% confidence interval (95% CI) is within the range of (-0.78, -0.10), and the P value is 0.01.

Given the significant heterogeneity in the study, to further investigate its source, we conducted sensitivity analysis using literature exclusion method. However, even with this method, the study still showed high heterogeneity, with I^2 values ranging from 80% to 91%. Subsequently, to further analyze the causes of heterogeneity, we conducted subgroup analysis.

4.3.2 Different DMARDs relieve OA pain

In this rigorous study, the experimental group had 225 participants, while the control group had 233 participants. Within the scope of this study, there are 5 articles that explore MTX. After analyzing the collected data, the results showed significant differences among various studies, specifically with a P-value less than 0.00001 and an I^2 value as high as 89%. Based on this situation, we conducted an in-depth analysis using a random effects model, and the results showed a statistically significant difference between the experimental group and the control group. The detailed data is as follows: the standardized mean deviation (SMD) is -0.71, the 95% confidence interval (95% CI) is in the range of (-1.32, -0.11), and the P-value is 0.02. To further validate the reliability of the research results, we conducted a sensitivity analysis. The analysis found that the main source of heterogeneity is the study conducted by Enteshari Moghaddam in 2019. After excluding this study, heterogeneity was significantly reduced, as evidenced by a P-value of 0.95 and an I^2 value of 0%. Subsequently, we reanalyzed the remaining data using a fixed effects model, and the results showed that both the experimental group and the control group had statistical significance [SMD=-0.38, 95% CI (-0.59, -0.18), P=0.0003]. Moreover, there is no significant difference in clinical significance compared to the analysis results obtained using the random effects model previously.

In this study, three studies focused on hydroxychloroquine (HCQ) were also included. Among them, the experimental group recruited 171 participants, while the control group had 182 participants. The data analysis results indicate a certain degree of heterogeneity among these studies, manifested by a P-value of 0.11 and an I^2 value of 55%. After conducting in-depth analysis using a random effects model, it was found that there was no statistically significant difference between the experimental group and the control group. The detailed data is as follows: the standardized mean deviation (SMD) is -0.19, the 95% confidence interval (95% CI) is (-0.53, -0.15), and the P-value is 0.28. Further sensitivity analysis showed that the heterogeneity between studies was caused by the research conducted by JOKAR in 2013 [25]. After removing this study, the P-value remained stable at 0.61 and the I^2 value decreased to 0%. At this point, the fixed effects model was used to reanalyze the data, resulting in an SMD of -0.06, 95% CI of (-0.28, 0.17), and a P-value of 0.61. However, no statistically significant differences were observed.

In addition, this study also included three articles focusing on TNF - α inhibitors (including adalimumab and etanercept). Among them, the experimental group included 102 subjects, while the control group had 105 subjects. After analyzing the collected data, it was found that there was no heterogeneity among the studies, as evidenced by a P-value of 0.41 and an I^2 value of 0%. Using a fixed effects model for in-depth analysis, the results showed that there was no statistically significant difference between the experimental group and the control group. The detailed data is as follows: the standardized mean deviation (SMD) is -0.09, the 95% confidence interval (95% CI) is (-0.37, 0.18), and the P-value is 0.50. Please refer to Table 2 for specific data. When conducting further sensitivity analysis, after excluding any study, the remaining data were re integrated and analyzed, and no statistical differences were found, which fully indicates that the research results have extremely high stability.

In addition, this study also involved three different types of IL receptor antagonists, including Orthokin, Anakinra, and tocilizumab. In this study, there were 188 participants in the experimental group and 182 participants in the control group. The data analysis results indicate that there is no heterogeneity among the studies, as evidenced by a P-value of 0.80 and an I^2 value of 0%. Through fixed effects model analysis, it was found that there was no statistically significant difference between the experimental group and the control group. The specific data is: SMD=-0.01, 95% CI (-0.22, 0.19), P=0.91. The relevant data can be found in Table 2. In further sensitivity analysis, the method of deleting each study one by one was adopted, and then

the effect size of the remaining studies was analyzed. The results showed that there was no statistically significant difference, which strongly proves that the research results are stable and reliable.

4.3.3 Different types of OA pain relief

In this research process, 8 research papers focusing on the field of hand osteoarthritis were carefully selected and ultimately included. Among them, the experimental group included 375 subjects, while the control group had 383 subjects. After analyzing the collected data, the results showed that there was no heterogeneity among the studies, with a P-value of 0.70 and an I^2 value of 0%. Through in-depth analysis using a fixed effects model, it was found that there was no statistically significant difference between the experimental group and the control group. The detailed data is as follows: the standardized mean deviation (SMD) is -0.12, the 95% confidence interval (95% CI) is (-0.26, 0.02), and the P-value is 0.10.

In addition, this study also included 6 articles exploring knee osteoarthritis (KOA). In this study, there were 360 participants in the experimental group and 365 participants in the control group. The data analysis results indicate that there is a high degree of heterogeneity among various studies, specifically reflected in P values less than 0.00001 and I^2 values as high as 96%. After using a random effects model for analysis, it was found that the research results have statistical significance. The specific data is: SMD=-0.88, 95% CI (-1.65, -0.11), P=0.02, and the relevant data is recorded in Table 2. Further subgroup analysis was conducted on different types of DMARDs (disease modified anti rheumatic drugs) interventions, and the results showed that the cDMARDs intervention group exhibited statistically significant results, with specific data as follows: SMD=-1.33, 95% CI (-2.27, -0.39), P=0.006.

4.3.4 Overall improvement of the joint

In this study, a total of 7 relevant literature were selected for comprehensive analysis. Among them, the experimental group included 458 participants, while the control group had 463 participants. Through data analysis, it was found that there is a high degree of heterogeneity among the studies (P<0.00001, I^2=97%). According to the data presented in Table 2, after analyzing using a random effects model, the results showed that the study had statistically significant effects, with standardized mean deviation (SMD)=-0.90, 95% confidence interval (95% CI) of (-1.73, -0.08), and a P-value of 0.03.

After further subgroup analysis, it was found that there was no statistically significant difference in the intervention of methotrexate in this subgroup. The specific data are: SMD=-1.80, 95% CI (-4.52, 0.92), P=0.20; The intervention subgroup of hydroxychloroquine also did not show statistically significant effects, and the specific data are: SMD = -0.41, 95%CI(-1.11, 0.29),P = 0.25; However, the intervention subgroup with IL-1 receptor antagonists did not show statistical significance.

Table 2: Main results of meta-analysis

Outcome indicators	Number of documents	P-value	12-value effect model	Effect size SMD (95% CI)	P-value
DMARDs relieve the pain of OA	E:771 C:784	<0.0000190%	REM	-0.44(-0.78, -0.10)	0.01
cDMARD relieve thepain ofosteoarthritis	E:481 C:497	0.000193%	REM	-0.71(-1.23, 0.20)	0.007
bOMARDsrelievethepain ofosteoarthritis	E:290 C:287	0.78	FEM	0.04(0.20, 0.12)	0.62
MTX alleviates the pain of OA	E:225 C:233	0.0000189%	REM	0.71(-132, 0.11)	0.02
HCQ alleviates the pain of OA	E:171 C:182	0.1%	REM	0.19(-0.53 0.15)	0.28
TF-alleviates the pain ofosteoarthritis	E:102 C:105	0.41%	FEM	0.09(0.37,0.18)	0.50
IL-RA alleviates the pain of OA	E:188 C:182	0.80%	FEM	0.01(0.2, 0.19)	0.91
Relief of pain by HOA	E:375 C:383	0.70%	FEM	0.12(0.26, 0.02)	0.10
Pain relief of KOA	E:360 C:365	<0.000196%	REM	0.88(1.65.0.23)	0.02
Overallimprovement of the joints	E:458 C:463	0.000197%	REM	-0.90(-1.73, -0.08)	0.03

Based on the comprehensive analysis of the data in Table 2, the effects of different drugs and treatment methods on relieving pain in osteoarthritis were deeply explored, and the following important conclusions were drawn.

DMARDs have shown overall effectiveness in relieving pain in osteoarthritis (OA). Using a random effects model (REM) analysis, the effect size SMD was -0.44 (95% CI: -0.78, -0.10), with a P-value of 0.01, indicating that DMARDs have a statistically significant relieving effect on OA pain. Further subdivision, REM analysis of cDMARDs showed an effect size SMD of -0.71 (95% CI: -1.23, 0.20), with a P-value of 0.007, which is also statistically significant, indicating that cDMARDs can effectively alleviate OA pain. However, according to the fixed effects model (FEM) analysis, the effect size SMD of bDMARDs was 0.04 (95% CI: 0.20, 0.12), with a P-value of 0.62, which was not statistically significant, indicating that bDMARDs are not effective in relieving OA pain.

For specific drugs, the effect size SMD in the REM analysis of MTX is 0.71 (95% CI: -132, 0.11), with a P-value of 0.02. Although there is some statistical significance, the confidence interval span is large, and the reliability of the results is questionable. The REM analysis of HCQ showed that the effect size SMD was 0.19 (95% CI: -0.53, 0.15), with a P-value of 0.28, which was not statistically significant, indicating that HCQ did not have a significant effect on relieving OA pain.

In studies targeting specific types of osteoarthritis, FEM analysis of TF - α (presumably TNF - α i) for pain relief in OA showed an effect size SMD of 0.09 (95% CI: 0.37, 0.18) and a P-value of 0.50, with no statistical significance. The FEM analysis of IL-RA showed an effect size SMD of 0.01 (95% CI: 0.2, 0.19) and a P-value of 0.91, which was also not statistically significant, indicating that these two drugs have poor efficacy in relieving OA pain.

For pain relief in hand osteoarthritis (HOA), the effect size SMD of FEM analysis was 0.12 (95% CI: 0.26, 0.02), with a P-value of 0.10, which was not statistically significant. The REM analysis of pain relief in knee osteoarthritis (KOA) showed an effect size SMD of 0.88 (95% CI: 1.65, 0.23) and a P-value of 0.02, which is statistically significant, indicating that relevant treatments have a relieving effect on KOA pain.

In terms of overall joint improvement, the effect size SMD of REM analysis was -0.90 (95% CI: -1.73, -0.08), with a P-value of 0.03, which is statistically significant, indicating that overall treatment has a positive effect on joint improvement.

In summary, there are significant differences in the pain relief and joint improvement effects of different drugs and treatment methods for osteoarthritis. CDMARDs and some treatments targeting KOA have better therapeutic effects, while bDMARDs, HCQ, TF - α, IL-RA, etc. have no significant effect on relieving OA pain. Future research can further optimize treatment plans and provide more effective treatment options for patients with osteoarthritis.

5 Discuss

The meta-analysis indicates that DMARDs are effective in alleviating OA pain overall, but there is significant heterogeneity among the studies. Subgroup analysis suggests that this heterogeneity stems from different interventions. Compared to bDMARDs, cDMARDs show more significant pain relief effects. However, there is a lack of research on tsDMARDs (Targeted Synthesis DMARDs).

Among all cDMARDs, MTX stands out, consistent with the findings of Sylvain Mathieu and colleagues [15]. MTX is a dihydrofolate reductase (DHFR) inhibitor that blocks the conversion of dihydrofolate into active tetrahydrofolate, thereby reducing the production of one-carbon units (formyl groups) in the body. This inhibits DNA and RNA synthesis, leading to cell proliferation inhibition [28]. Initially, it was used in cancer patients, where high doses (>1g per dose) effectively inhibited the growth of malignant cells. However, later studies found that low doses of methotrexate (10-30mg once daily) were highly effective for RA patients [29]. The specific pharmacological mechanisms are not yet fully understood, but they mainly include the following aspects: (1) Immune regulation: Low doses of MTX can upregulate the expression of CD4+CD25+ Treg cells [30], induce the shift from Th1 to Th2, restore the balance of Th1/Th2 ratios, and normalize autoimmune responses; (2) Anti-synovitis: By regulating 5-aminoimidazole-4-carboxylamide ribonucleotide formyltransferase (ATIC), it directly reduces the production of inflammatory factors and simultaneously induces adenosine production, which has an anti-inflammatory effect; (3) Bone protection: Small doses of MTX can inhibit osteoclast formation by modulating the RANKL/RANK/OPG pathway; (4) Cartilage cell protection: It inhibits the activity of matrix metalloproteinase-3 (MMP-3), reducing cartilage cell damage. Synovitis, subchondral bone lesions, and cartilage damage are also important mechanisms leading to pain in patients with OA [5]. Among the 5 MTX studies included, 4 were administered orally, and 1 was administered via intra-articular injection. However, this study did not show significant heterogeneity, and the clinical significance of the results is consistent with other studies, suggesting that intra-articular injection of MTX might be another potential treatment option. Additionally, among the four studies on oral MTX, the types of osteoarthritis (OA) varied, including: refractory hip osteoarthritis (HOA) with X-ray evidence of joint erosion, knee osteoarthritis (KOA) unresponsive to conventional NSAIDs, moderate to severe KOA with a K/L grade of III-IV, and HOA with synovitis confirmed by MRI. Although the four groups of OA patients were not entirely the same, their conditions were all relatively severe, with more pronounced inflammation. Therefore, we believe that MTX can help alleviate

pain symptoms in patients with moderate to severe or significant synovitis. However, in clinical practice, the adverse reactions of MTX remain a significant concern; the benefits and risks of MTX for OA patients need to be carefully evaluated.

Another type of cDMARD, Alemoide, is a small molecule targeted drug independently developed in China. It inhibits multiple inflammatory cytokines, including IL-1, IL-6, IL-8, and TNF, and selectively inhibits COX-2, thereby reducing inflammation and pain. In a study by Zhang Yujing that combined Alemoide with glucosamine, the results indicated that KOA patients experienced significant pain relief. However, since glucosamine has been shown to be effective for KOA, further research is needed to determine whether Alemoide alone can effectively alleviate KOA pain. HCQ reduces the production of pro-inflammatory cytokines (IL-1, IL-6, TNF-γ) by inhibiting phospholipase A2 activity and affecting Toll-like receptors (TLRs), which in turn reduces the generation of nucleic acid receptors and improves synovitis. However, a Meta-analysis of three related studies suggested that HCQ does not significantly relieve OA pain.

In bDMARDs, this Meta-analysis indicates that TNF-α inhibitors (adalimumab, etanercept) and IL-RA (Orthokin, Anakinra, tozilumab) do not significantly alleviate joint pain. Unlike cDMARDs, which have multiple targets, bDMARDs target relatively fewer sites. TNF-α, IL-1, and IL-6 are key inflammatory mediators in synovitis but fail to effectively relieve the pain of OA patients. We consider the following possibilities: (1) Synovitis is not the sole factor contributing to OA pain; peripheral pain stimulation, central nervous system sensitization, and psychological depression can all influence the patient's pain response [5]; (2) The degree of synovitis in the OA population included in the study varies, with some patients having mild synovitis, which is not significant, leading to less effective treatment outcomes.

The meta-analysis showed that DMARDs, especially cDMARDs, were more effective in relieving pain in KOA patients than HOA, while methotrexate, hydroxychloroquine and IL-1 receptor antagonists had no statistically significant results for overall joint improvement.

Limitations and shortcomings of this study: (1) The inclusion of literature was limited to English and Chinese, which may result in incomplete coverage; (2) There are still few high-quality clinical trials on DMARDs for the treatment of OA, particularly bDMARDs and tsDMARDs, which limits our ability to conduct subgroup analyses; (3) The severity of the disease among the included OA patients varies significantly, which could introduce bias into the results.

6 Conclusions and outlook

Different DMARDs have varying effectiveness in alleviating OA pain. For patients with moderate to severe OA or those with significant synovitis, MTX is a potential option, especially for patients with KOA. However, HCQ, adalimumab, etanercept, tozilumab, Orthokin, and anakinra have not shown significant relief of OA joint pain. In terms of overall joint improvement, MTX, HCQ, and IL-1 receptor antagonists have not demonstrated significant efficacy. However, the current studies generally have small sample sizes and include a wide range of OA patients, which limits their generalizability. More large-scale, high-quality studies are needed to verify the effectiveness of DMARDs in treating OA.

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