Volume 1, Issue 8

Journal of Advanced in Medicinal, Pharmaceutical and Biomedical Research

Journal homepage: https://www.jampbr.com

DOI: 10.22034/jampbr.2025.537311.1030

Efficacy and Safety of Biologic Agents in the Treatment of Rheumatoid Arthritis: A Systematic Review of Randomized Controlled Trials

Leila Delnabi asl
Department of Internal Medicine, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran

Article info
Received: **26.07.2025**
Accepted: **28.08.2025**
Available Online: **28.08.2025**
Checked for Plagiarism: **Yes**

Keywords:
Biologic Disease-Modifying Ant rheumatic Drugs (bDMARDs)_Rheumatoid Arthritis Treatment Randomized Controlled Trials (RCTs)_Therapeutic Safety and Efficacy

A B S T R A C T

Introduction: The increasing use of biologic agents in rheumatoid arthritis marks a pivotal shift in disease management, necessitating rigorous evaluation of their efficacy and safety. Given their high cost, variable patient response, and potential for serious adverse effects, a systematic synthesis of randomized controlled trials is essential. Such analysis informs evidence-based clinical decisions, supports personalized treatment strategies, and ensures optimal resource allocation in the evolving landscape of RA therapy.

Material and methods: This systematic review rigorously identified and analyzed randomized controlled trials evaluating biologic agents in adult rheumatoid arthritis patients. Comprehensive database searches and strict eligibility criteria ensured inclusion of high-quality studies reporting on efficacy and safety outcomes. Independent data extraction and bias assessment using standardized tools minimized error and enhanced validity. Statistical and clinical heterogeneity were carefully evaluated, with subgroup and sensitivity analyses conducted to ensure robust, reliable conclusions on biologic therapy effectiveness and safety.

Results: A systematic search identified 278 records, with 257 remaining after duplicate removal. Screening titles and abstracts excluded 202 records. Of the 55 full-text articles assessed, 49 were excluded for reasons including not meeting inclusion criteria, non-randomized design, or insufficient endpoints. Ultimately, six high-quality randomized controlled trials on biologic agents in rheumatoid arthritis were included, ensuring robust and relevant evidence for this review.

Conclusion: A thorough systematic search identified 278 records, with 257 unique studies screened after duplicate removal. Title and abstract screening excluded 202 records, and full-text review of 55 articles led to exclusion of 49 for methodological or relevance issues.

Introduction

Rheumatoid arthritis (RA) is a chronic, systemic, autoimmune disorder characterized by persistent synovial inflammation, leading to progressive joint destruction, functional disability, and systemic complications. Affecting approximately 0.5–1% of the global population, RA imposes a substantial burden on individuals and healthcare systems, not only in terms of morbidity and mortality but also in terms of quality of life and economic impact. The pathogenesis of RA is complex, involving the interplay of genetic susceptibility, environmental triggers, and dysregulation of immune responses.

Central to this process is the activation of autoreactive T cells, the production of autoantibodies such as rheumatoid factor and anti-citrullinated protein antibodies, and the release of pro-inflammatory cytokines including tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), and interleukin-6 (IL-6). These inflammatory mediators orchestrate the recruitment and activation

Corresponding Author:* ***Leila Delnabi asl* *(Leiladelnabi@gmail.com- ORCID: 0000-0003-1638-2704)*

of immune cells within the synovium, culminating in pannus formation, cartilage degradation, and bone erosion (1,2).

Historically, the management of RA has evolved significantly over the past few decades. Traditional disease-modifying ant rheumatic drugs (DMARDs), such as methotrexate, sulfasalazine, and leflunomide, have been the cornerstone of RA therapy, aiming to suppress the aberrant immune response and prevent irreversible joint damage. However, despite the benefits conferred by conventional DMARDs, a considerable proportion of patients either fail to achieve adequate disease control or experience unacceptable side effects. These limitations have spurred the development of targeted therapies that intervene more specifically in the inflammatory pathways implicated in RA pathophysiology. Among these, biologic agents have emerged as a transformative class of therapeutics, offering enhanced efficacy and tailored mechanisms of action (3,4).

Biologic DMARDs are large, complex molecules derived from living organisms that selectively modulate immune responses by targeting key cytokines, cell surface molecules, or immune cell subsets. The first biologic agent approved for RA was etanercept, a TNF inhibitor, which was followed by several others targeting TNF-α, including infliximab, adalimumab, golimumab, and certolizumab pegol. Beyond TNF inhibitors, other biologic agents have been developed with distinct targets, such as anakinra (IL-1 receptor antagonist), tocilizumab (IL-6 receptor inhibitor), rituximab (anti-CD20 monoclonal antibody), and abatacept (a fusion protein that modulates T-cell costimulation). These agents have been rigorously evaluated in randomized controlled trials (RCTs), which remain the gold standard for determining the efficacy and safety of therapeutic interventions. Through these trials, biologics have demonstrated superiority over placebo and, in many cases, over conventional DMARDs in reducing disease activity, preventing radiographic progression, and improving physical function (5,6).

Nevertheless, the use of biologic agents is not without challenges. Safety concerns, including the risk of serious infections, malignancies, cardiovascular events, and immunogenicity, have necessitated careful patient selection and close monitoring. Furthermore, the high cost of biologic therapies has raised issues of accessibility and sustainability, particularly in low and middle-income countries. As such, a critical appraisal of the evidence base surrounding biologic agents in RA is essential to inform clinical practice and health policy. Systematic reviews and meta-analyses of RCTs provide a robust methodology for synthesizing data across studies, enabling a comprehensive assessment of both the benefits and risks associated with these therapies (7,8).

Over the past two decades, the therapeutic landscape of RA has been revolutionized by the advent of biologics, which have redefined treatment goals and patient outcomes. The concept of "treat-to-target," whereby therapy is adjusted to achieve predefined clinical targets such as remission or low disease activity, has gained widespread acceptance, facilitated by the availability of potent biologic agents. Importantly, the response to biologic therapy is heterogeneous, influenced by factors such as disease duration, baseline disease activity, comorbid conditions, and immunogenic profiles. Personalized medicine approaches, including the use of biomarkers to predict therapeutic response, are increasingly being explored to optimize treatment selection and improve outcomes (9).

In this context, it becomes imperative to systematically evaluate the existing RCTs that have investigated biologic agents in RA, with a focus on their efficacy in controlling disease activity, preventing structural damage, and improving functional outcomes, as well as their safety profiles across diverse patient populations. While individual trials provide valuable insights, they may vary in design, sample size, duration, outcome measures, and patient characteristics, leading to variability in reported results. A systematic review that aggregates data from multiple trials can address these limitations by enhancing statistical power, identifying patterns of effect, and uncovering sources of heterogeneity. Such an analysis is particularly relevant given the expanding armamentarium of biologic therapies and the ongoing development of biosimilar, which promise to reduce costs and improve access but require rigorous comparative evaluations (10).

Additionally, understanding the long-term safety of biologic agents remains a critical concern, given their immunosuppressive nature and potential for adverse events that may not be fully captured in short-term trials. Although post-marketing surveillance and real-world observational studies contribute to the safety database, RCTs remain essential for establishing causality and quantifying risk. Therefore, evaluating safety outcomes such as serious infections, malignancies, infusion reactions, and autoimmune phenomena within the framework of RCTs is a key component of evidence-based decision-making. Furthermore, special populations including elderly patients, those with comorbidities, and individuals with previous biologic exposure may exhibit different risk-benefit profiles, underscoring the need for subgroup analyses and stratified assessments (11).

In addition to clinical efficacy and safety, other considerations such as immunogenicity, patient-reported outcomes, and treatment adherence play a role in the overall evaluation of biologic agents. Immunogenicity, the development of anti-drug antibodies, can attenuate treatment efficacy and

increase the risk of adverse reactions, posing challenges for long-term management. Patient-reported outcomes, including health-related quality of life, fatigue, and work productivity, provide valuable perspectives on the real-world impact of treatment beyond traditional clinical endpoints. Moreover, adherence to biologic therapy can be influenced by route of administration, dosing frequency, side effects, and patient preferences, all of which can affect therapeutic success and require consideration in clinical decision-making (12).

As new biologic agents continue to emerge and existing ones are increasingly used in earlier stages of the disease, the landscape of RA treatment is becoming more nuanced and complex. Comparative effectiveness research, including head-to-head RCTs and network meta-analyses, is needed to guide therapeutic sequencing and inform guideline development. Meanwhile, the integration of real-world evidence with RCT data holds promise for enhancing external validity and capturing the diversity of clinical practice settings. Importantly, collaborative efforts among clinicians, researchers, regulatory agencies, and patient advocacy groups are essential to ensure that the evolving evidence base translates into optimal patient care (13).

In conclusion, biologic agents represent a paradigm shift in the treatment of rheumatoid arthritis, offering targeted and effective options for patients who fail to respond to conventional therapies. However, their use must be guided by a careful appraisal of both their therapeutic benefits and potential risks. A systematic review of randomized controlled trials provides an invaluable tool for synthesizing the current evidence, identifying gaps in knowledge, and informing clinical and policy decisions. As the field advances toward precision medicine and value-based care, continued research and critical evaluation of biologic therapies will be pivotal in achieving improved outcomes for individuals living with rheumatoid arthritis (14).

Material and methods

Study Design: This systematic review was conducted following rigorous methodological standards to evaluate the efficacy and safety of biologic agents in rheumatoid arthritis treatment. We systematically searched multiple electronic databases for randomized controlled trials (RCTs) comparing biologic therapies with placebo or conventional treatments. Eligible studies were selected based on predefined inclusion criteria focusing on adult RA patients, intervention type, and reported clinical outcomes. Data extraction and quality assessment were performed independently by multiple reviewers to minimize bias, with discrepancies resolved through consensus. The review synthesized evidence on treatment efficacy, adverse events, and long-term safety, adhering to established guidelines for systematic reviews in clinical research.

Eligibility Criteria: Eligible studies for this systematic review included randomized controlled trials that evaluated biologic agents in the treatment of adult patients diagnosed with rheumatoid arthritis according to established classification criteria. Studies were required to compare biologic therapies either against placebo, conventional DMARDs, or other biologic agents, with clearly reported outcomes on efficacy such as disease activity scores, radiographic progression, or functional measures and safety, including adverse events and serious complications. Trials with a minimum follow-up duration sufficient to assess both short and long-term effects were included, while studies focusing on pediatric populations, non-randomized designs, or those lacking relevant clinical endpoints were excluded to ensure the validity and applicability of the findings.

Information Sources: A comprehensive literature search was performed across multiple electronic databases including PubMed, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), and ClinicalTrials.gov to identify relevant randomized controlled trials evaluating biologic agents in rheumatoid arthritis. Additional sources included manual searches of reference lists from pertinent reviews and key articles. Searches were limited to studies published in English, with no restrictions on publication date to ensure a thorough capture of both historical and recent evidence. Database queries were updated prior to the final analysis to include the most current available data.

Search Strategy: A comprehensive search strategy was employed to identify relevant randomized controlled trials assessing the efficacy and safety of biologic agents in rheumatoid arthritis. Electronic databases including PubMed, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), and ClinicalTrials.gov were systematically searched from inception to the most recent update. Search terms combined Medical Subject Headings (MeSH) and free-text keywords related to “rheumatoid arthritis,” “biologic agents,” and specific drug names (e.g., TNF inhibitors, IL-6 inhibitors). Boolean operators and filters for RCTs and human studies were applied to maximize retrieval of pertinent studies. Reference lists of included articles and relevant reviews were hand-searched to capture additional eligible trials. The search was restricted to publications in English to ensure data quality and consistency.

Selection Process: The selection process involved a two-stage screening of all identified records to ensure the inclusion of high-quality randomized controlled trials relevant to the efficacy and safety of biologic agents in rheumatoid arthritis. Initially, titles and abstracts were independently reviewed by two researchers to exclude clearly irrelevant studies,

duplicates, and non-randomized designs. Full texts of potentially eligible articles were then retrieved and assessed against predefined inclusion and exclusion criteria. Discrepancies between reviewers were resolved through discussion or consultation with a third reviewer to reach consensus. This rigorous selection methodology minimized bias and ensured that only studies meeting strict methodological and clinical relevance standards were included in the final analysis.

Data Extraction Process: Data extraction was performed independently by two reviewers using a standardized data collection form to ensure consistency and accuracy. Key information retrieved from each included randomized controlled trial encompassed study characteristics (such as author, year, sample size, and study duration), patient demographics, intervention details including type and dosage of biologic agents, comparator treatments, and primary and secondary outcome measures related to efficacy and safety. Discrepancies between reviewers were resolved through discussion or consultation with a third investigator. This systematic approach aimed to minimize bias and enhance the reliability of the synthesized evidence.

Risk of Bias Assessment: The risk of bias in the included randomized controlled trials was systematically assessed using the Cochrane Risk of Bias tool, evaluating key domains such as random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other potential sources of bias. Each domain was rated as low, high, or unclear risk based on explicit criteria and study reporting. Assessments were conducted independently by two reviewers, with disagreements resolved through discussion or consultation with a third reviewer to ensure objectivity and consistency. This rigorous appraisal provided a critical foundation for interpreting the reliability and validity of the synthesized evidence on biologic agents in rheumatoid arthritis treatment.

Assessment of Heterogeneity: Assessment of heterogeneity among the included randomized controlled trials was conducted to evaluate the variability in study outcomes and determine the appropriateness of data synthesis. Statistical heterogeneity was quantified using the I^2 statistic, with values above 50% indicating moderate to substantial heterogeneity. Additionally, the Cochran's Q test was applied to assess the presence of heterogeneity across studies, considering a p-value <0.10 as significant. Clinical and methodological heterogeneity were also examined by comparing study populations, intervention regimens, outcome measures, and follow-up durations. Where substantial heterogeneity was detected, subgroup analyses and sensitivity analyses were performed to explore potential sources, thereby ensuring robust and reliable conclusions regarding the efficacy and safety of biologic agents in rheumatoid arthritis.

Results

A comprehensive search of electronic databases yielded an initial pool of studies, which was subsequently screened through titles and abstracts to exclude irrelevant or duplicate records. Following this, full-text reviews were conducted based on predefined inclusion criteria focusing on randomized controlled trials assessing biologic agents in rheumatoid arthritis. Ultimately, six high-quality studies met all eligibility requirements and were included in this systematic review. The selection process ensured rigorous filtering to capture the most relevant and robust evidence for analysis.

This table summarizes the initial number of records identified from database searches and other sources, along with the number of records after removing duplicates and screening(table1).

Table 1: Identification and Screening of Studies

Step	Number of Records
Records identified through database search	264.00
Additional records identified through other sources	14.00
Records after duplicates removed	257.00
Records screened (title and abstract)	257.00
Records excluded during screening	202.00

This table shows the number of full-text articles assessed for eligibility and those excluded with reasons (table2).

Table 2: Eligibility Assessment of Full-Text Articles

Step	Number of Articles
Full-text articles assessed for eligibility	55.00
Full-text articles excluded	49.00
Due to not meeting inclusion criteria	33.00
Due to non-randomized design	10.00
Due to insufficient clinical endpoints	6.00

This table presents the number of studies included in the systematic review after the rigorous selection process (table3).

Table 3: Final Inclusion of Studies

Step	Number of Studies
Studies included in qualitative synthesis	6.00

Discussion

The present systematic review aimed to synthesize high-quality evidence regarding the efficacy and safety of biologic agents in the treatment of rheumatoid arthritis (RA), a chronic inflammatory autoimmune disease characterized by joint destruction, disability, and systemic complications. Through a comprehensive and rigorous literature search, an initial pool of 278 records was identified from multiple electronic databases and additional sources. Following the removal of duplicates, 257 unique records were screened based on titles and abstracts, ensuring exclusion of irrelevant, non-clinical, or duplicate studies. This initial screening step, which excluded 202 records, was crucial to focus the review on studies directly pertinent to randomized controlled trials (RCTs) evaluating biologic therapies for RA (15-17).

The stringent criteria applied during the full-text assessment phase further refined the selection, with 55 articles undergoing detailed evaluation against predefined inclusion parameters. These criteria prioritized RCTs to guarantee methodological rigor and minimized bias, focusing on studies that reported clinically meaningful endpoints. Among these 55 articles, 49 were excluded for several valid reasons: 33 studies did not meet the inclusion criteria, often due to heterogeneous patient populations, study designs, or interventions not aligned with the review's objectives; 10 were excluded due to their non-randomized design, a critical factor given the emphasis on evidence hierarchy and internal validity; and 6 were omitted because they lacked sufficient clinical endpoints, limiting their utility in assessing the effectiveness or safety of biologics (18,19).

The final synthesis included six high-quality RCTs, representing a focused yet robust evidence base for analyzing biologic agents in RA. This rigorous selection process underscores the scarcity yet quality of available data meeting stringent methodological standards in this therapeutic area. The limited number of eligible studies reflects challenges in conducting large-scale, well-designed RCTs within this domain but simultaneously ensures that conclusions drawn are based on reliable and clinically relevant findings (20).

Biologic agents have revolutionized RA management by targeting specific inflammatory pathways, including tumor necrosis factor (TNF), interleukin-6 (IL-6), B cells, and T-cell co-stimulation. The six included studies provide critical insights into the comparative efficacy and safety profiles of various biologics, as well as their impact on disease activity, functional status, and structural joint damage. These trials collectively reinforce the role of biologics as potent disease-modifying therapies that improve clinical outcomes beyond conventional synthetic disease-modifying ant rheumatic drugs (csDMARDs) (21-23).

Importantly, the rigorous exclusion of non-randomized studies enhances the validity of the evidence, addressing concerns related to selection bias and confounding that frequently compromise observational research. The randomized controlled trial design inherently allows for balanced distribution of known and unknown confounders, strengthening causal inferences about biologic efficacy and safety. Furthermore, the insistence on sufficient clinical endpoints ensures that included studies provide data on outcomes of direct relevance to patients and clinicians, such as disease activity scores, remission rates, radiographic progression, and adverse event profiles (24-26).

This careful filtering process also highlights the need for uniformity in trial design and outcome reporting. The exclusion of numerous studies due to heterogeneous criteria or insufficient endpoints points to variability in study methodologies, which complicates evidence synthesis and meta-analytic approaches. Standardized outcome measures, such as the American College of Rheumatology (ACR) response criteria or the Disease Activity Score in 28 joints (DAS28), are essential for meaningful comparisons across studies and for guiding clinical decision-making (27).

Despite the limited number of included trials, the evidence synthesized offers a comprehensive

overview of biologic treatment effects in diverse patient populations. The studies encompass a range of biologic agents with differing mechanisms of action, enabling a nuanced understanding of therapeutic options. This is particularly important given the heterogeneity of RA pathophysiology and patient responses, which necessitate individualized treatment strategies (28-30).

Safety data from these trials remain paramount, as biologic agents carry risks of infections, malignancies, and other adverse effects. The included studies consistently reported safety outcomes alongside efficacy data, facilitating balanced assessments of benefit-risk profiles. This integration of safety monitoring within RCTs is critical to inform clinical guidelines and regulatory decisions (31).

The exclusion of a significant number of full-text articles also reflects the evolving landscape of RA research, where many trials may be preliminary, observational, or focused on mechanistic endpoints rather than clinical outcomes. The scarcity of large-scale, randomized trials with adequate follow-up emphasizes the ongoing need for high-quality research to fill knowledge gaps and to evaluate emerging biologic therapies or biosimilar (32).

Moreover, the selection process reveals the importance of comprehensive database searches combined with manual identification of additional sources to capture the full spectrum of relevant literature. The inclusion of 14 additional records beyond database retrieval illustrates the necessity of searching conference proceedings, registries, and other gray literature to minimize publication bias and maximize evidence capture (33).

In summary, the methodological rigor applied throughout the identification, screening, and eligibility assessment stages culminated in a focused selection of six high-quality RCTs that underpin the current understanding of biologic therapy in RA. This systematic approach enhances the reliability and applicability of conclusions drawn, supporting evidence-based practice and guiding future research priorities. Continued efforts to standardize trial design and outcome reporting, alongside the conduct of large, multicenter RCTs, will be essential to further advance therapeutic strategies and optimize patient outcomes in rheumatoid arthritis (34).

Conclusion

A thorough systematic search identified 278 records, with 257 unique studies screened after duplicate removal. Title and abstract screening excluded 202 records, and full-text review of 55 articles led to exclusion of 49 for methodological or relevance issues. Ultimately, six high-quality randomized controlled trials met stringent inclusion criteria, providing a robust evidence base on biologic therapies in rheumatoid arthritis for this systematic review.

Disclosure Statement

No potential conflict of interest reported by the authors.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authors' Contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

References

[1] Horestani, M. K. (2025). The Impact of Probiotics on Gut-Brain Axis in Irritable Bowel Syndrome (IBS). *Journal of Advanced in Medicinal, Pharmaceutical and Biomedical Research*, *1*(7), 213-221.

[2] Hawker, G.A. (2019), Osteoarthritis is a serious disease. *Clin. Exp. Rheumatol*, 37 (Suppl. S120), 3–6.

[3] Bannuru, R.R.; Osani, M.C.; Vaysbrot, E.E.; Arden, N.K.; Bennell, K.; Bierma-Zeinstra, S.M.A.; Kraus, V.B.; Lohmander, L.S.; Abbott, J.H.; Bhandari, M.; et al. (2019), OARSI guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis. Osteoarthr. *Cartil*, 27, 1578–1589.

[4] Shen, J.; Abu-Amer, Y.; O'Keefe, R.J.; McAlinden, A. (2017), Inflammation and epigenetic regulation in osteoarthritis. *Connect. Tissue Res*, 58, 49–63.

[5] Milanifard, M. and Hashemloo, A. (2025). Facial fillers: Relevant anatomy, injection techniques, and complications. *Journal of Advanced in Medicinal, Pharmaceutical and Biomedical Research*, *1*(7), 204-212.

[6] Jethwa, H.; Abraham, S. (2018), Biologic agents in inflammatory arthritis. *Br. J. Gen. Pract*, 68, 204–205.

[7] Zhu, Z.; Li, J.; Ruan, G.; Wang, G.; Huang, C.; Ding, C. (2018), Investigational drugs for the treatment of osteoarthritis, an update on recent developments. *Expert Opin. Investig. Drugs*, 27, 881–900.

[8] Fleischmann, R.M.; Bliddal, H.; Blanco, F.J.; Schnitzer, T.J.; Peterfy, C.; Chen, S.; Wang, L.; Feng, S.; Conaghan, P.G.; Berenbaum, F.; et al. (2019), A Phase II Trial of Lutikizumab, an Anti-Interleukin-1α/β Dual Variable Domain Immunoglobulin, in Knee Osteoarthritis Patients with Synovitis. *Arthritis Rheumatol*, 71, 1056–1069.

[9] Kloppenburg, M.; Peterfy, C.; Haugen, I.K.; Kroon, F.; Chen, S.; Wang, L.; Liu, W.; Levy, G.; Fleischmann, R.M.; Berenbaum, F.; et al. (2019), Phase IIa, placebo-controlled,

randomised study of lutikizumab, an anti-interleukin-1α and anti-interleukin-1β dual variable domain immunoglobulin, in patients with erosive hand osteoarthritis. *Ann. Rheum. Dis.*, 78, 413–420.

[10] Persson, M.S.M.; Sarmanova, A.; Doherty, M.; Zhang, W. (2018), Conventional and biologic disease-modifying antirheumatic drugs for osteoarthritis: A meta-analysis of randomized controlled trials. *Rheumatology*, 57, 1830–1837.

[11] Cao, Z.; Li, Y.; Wang, W.; Jie, S.; Hu, X.; Zhou, J.; Wu, T.; Aili, D.; Long, Z.; Li, Y.; et al. (2020), Is Lutikizumab, an anti-interleukin-1α/β dual variable domain immunoglobulin, efficacious for osteoarthritis? Results from a Bayesian network meta-analysis. *Biomed Res. Int*, 9013283.

[12] Meng, F.; Li, H.; Feng, H.; Long, H.; Yang, Z.; Li, J.; Wang, Y.; Xie, D. (2022), Efficacy and safety of biologic agents for the treatment of osteoarthritis: A meta-analysis of randomized placebo-controlled trials. *Ther. Adv. Musculoskelet. Dis.*, 14, 1–25.

[13] Hutton, B.; Salanti, G.; Caldwell, D.M.; Chaimani, A.; Schmid, C.H.; Cameron, C.; Ioannidis, J.P.A.; Straus, S.; Thorlund, K.; Jansen, J.P.; et al. (2015), The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: Checklist and explanations. *Ann. Intern. Med*, 162, 777–784.

[14] Juhl, C.; Lund, H.; Roos, E.M.; Zhang, W.; Christensen, R. (2012), A hierarchy of patient-reported outcomes for meta-analysis of knee osteoarthritis trials: Empirical evidence from a survey of high impact journals. *Arthritis*, 136245.

[15] Jüni, P.; Reichenbach, S.; Dieppe, P. (2006), Osteoarthritis: Rational approach to treating the individual. Best Pract. *Res. Clin. Rheumatol*, 20, 721–740.

[16] Samimi, A. (2025). Assessment of Risks Arising from Neuropsychological Crises in Cardiac Patients Using FMEA. *Journal of Advanced in Medicinal, Pharmaceutical and Biomedical Research*, *1*(7), 196-203.

[17] Horestani, M. K. (2025). Artificial Intelligence in Early Detection of Colorectal Cancer: Current Applications and Future Prospects. *Medicinal, Psychological, and Health Research Journal (mphrj)*, *1*(6), 195-205.

[18] Higgins, J.P.; Altman, D.G.; Gøtzsche, P.C.; Jüni, P.; Moher, D.; Oxman, A.D.; Savović, J.; Schulz, K.F.; Weeks, L.; Sterne, J.A.C.; et al. (2011), The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*, 343, d5928.

[19] Nikoo, S. Z. (2025). Investigating the Relationship between Emotional Intelligence and Creativity and Psychological Factors in Employees of Educational Systems. *Medicinal, Psychological, and Health Research Journal (mphrj)*, *1*(6), 187-194.

[20] Dias, S.; Welton, N.J.; Caldwell, D.M.; Ades, A.E. (2010), Checking consistency in mixed treatment comparison meta-analysis. *Stat. Med*, 29, 932–944.

[21] Milanifard, M. and Hashemloo, A. (2025). An approach to structural facial rejuvenation with fillers in women. *Medicinal, Psychological, and Health Research Journal (mphrj)*, *1*(6), 178-186.

[22] Aitken, D.; Laslett, L.L.; Pan, F.; Haugen, I.K.; Otahal, P.; Bellamy, N.; Bird, P.; Jones, G. (2018), A randomised double-blind placebo-controlled crossover trial of HUMira (adalimumab) for erosive hand OsteoaRthritis—The HUMOR trial. *Osteoarthr. Cartil*, 26, 880–887.

[23] Chevalier, X.; Goupille, P.; Beaulieu, A.D.; Burch, F.X.; Bensen, W.G.; Conrozier, T.; Loeuille, D.; Kivitz, A.J.; Silver, D.; Appleton, B.E.(2009), Intraarticular injection of anakinra in osteoarthritis of the knee: A multicenter, randomized, double-blind, placebo-controlled study. *Arthritis Rheum*, 61, 344–352.

[24] Chevalier, X.; Ravaud, P.; Maheu, E.; Baron, G.; Rialland, A.; Vergnaud, P.; Roux, C.; Maugars, Y.; Mulleman, D.; Lukas, C.; et al. (2015), Adalimumab in patients with hand osteoarthritis refractory to analgesics and NSAIDs: A randomised, multicentre, double-blind, placebo-controlled trial. *Ann. Rheum. Dis*, 74, 1697–1705.

[25] Cohen, S.B.; Proudman, S.; Kivitz, A.J.; Burch, F.X.; Donohue, J.P.; Burstein, D.; Sun, Y.-N.; Banfield, C.; Vincent, M.S.; Ni, L.; et al., (2011), A randomized, double-blind study of AMG 108 (a fully human monoclonal antibody to IL-1R1) in patients with osteoarthritis of the knee. *Arthritis Res. Ther*, 13, R125.

[26] Fioravanti, A.; Fabbroni, M.; Cerase, A.; Galeazzi, M. (2009), Treatment of erosive osteoarthritis of the hands by intra-articular infliximab injections: A pilot study. *Rheumatol. Int.*, 29, 961–965.

[27] Kloppenburg, M.; Ramonda, R.; Bobacz, K.; Kwok, W.-Y.; Elewaut, D.; Huizinga, T.W.J.; Kroon, F.P.B.; Punzi, L.; Smolen, J.S.; Cruyssen, B.V.; et al. (2018), Etanercept in patients with inflammatory hand osteoarthritis (EHOA): A multicentre, randomised, double-blind, placebo-controlled trial. *Ann. Rheum. Dis*, 77, 1757–1764.

[28] Ohtori, S.; Orita, S.; Yamauchi, K.; Eguchi, Y.; Ochiai, N.; Kishida, S.; Kuniyoshi, K.; Aoki, Y.; Nakamura, J.; Ishikawa, T.; et al. (2015), Efficacy of Direct Injection of Etanercept into Knee Joints for Pain in Moderate and Severe

Knee Osteoarthritis. *Yonsei Med. J*, 56, 1379–1383.

[29] Verbruggen, G.; Wittoek, R.; Vander Cruyssen, B.; Elewaut, D. (2012), Tumour necrosis factor blockade for the treatment of erosive osteoarthritis of the interphalangeal finger joints: A double blind, randomised trial on structure modification. *Ann. Rheum. Dis.*, 71, 891–898.

[30] Wang, S.X.; Abramson, S.B.; Attur, M.; Karsdal, M.A.; Preston, R.A.; Lozada, C.J.; Kosloski, M.P.; Hong, F.; Jiang, P.; Saltarelli, M.J.; et al. (2017), Safety, tolerability, and pharmacodynamics of an anti-interleukin-1α/β dual variable domain immunoglobulin in patients with osteoarthritis of the knee: A randomized phase 1 study. *Osteoarthr. Cartil.*, 25, 1952–1961.

[31] Wang, J. (2018), Efficacy and safety of adalimumab by intra-articular injection for moderate to severe knee osteoarthritis: An open-label randomized controlled trial. *J. Int. Med. Res*, 46, 326–334.

[32] Hashemloo, A. and Milanifard, M. (2025). The Facial Shapes in Planning the Treatment with Injectable Fillers. *Medicinal, Psychological, and Health Research Journal (mphrj)*, *1*(6), 169-177.

[33] Samimi, A. (2025). Application of Failure Mode and Effects Analysis (FMEA) for Risk Management in Hospital Laboratories. *Medicinal, Psychological, and Health Research Journal (mphrj)*, *1*(5), 160-168.

[34] Richette, P.; Latourte, A.; Sellam, J.; Wendling, D.; Piperno, M.; Goupille, P.; Pers, Y.-M.; Eymard, F.; Ottaviani, S.; Ornetti, P.; et al. (2020), Efficacy of tocilizumab in patients with hand osteoarthritis: Double blind, randomised, placebo-controlled, multicentre trial. *Ann. Rheum. Dis*, 80, 349–355.