Jurnal Eduhealth
Volume 16, Number 04 2025 DOI 10.54209/eduhealth.v16i04
ESSN 2808-4608 (Online)
https://ejournal.seaninstitute.or.id/index.php/healt

The Effect of Polypharmacy on Drug Interactions in Rheumatoid Arthritis Patients: A Literature Review

Vania Putri Risyhade[1], Asep Sukohar[2], Muhammad Maulana[3], Rasmi Zakiah Oktarlina[4]
[1,3]Medical Study Program, Faculty of Medicine, University of Lampung, [2,4]Pharmacy Study Program, Faculty of Medicine, University of Lampung

Article Info
Keywords:
Drug interactions, polypharmacy, rheumatoid arthritis

ABSTRACT
Rheumatoid arthritis is a chronic autoimmune disease that is progressive in nature and requires long-term therapy involving a combination of multiple drugs. The complexity of treatment increases the risk of polypharmacy, which in turn can trigger drug interactions and reduce the safety and effectiveness of therapy. This literature review aims to describe the relationship between polypharmacy and the potential for drug interactions in patients with rheumatoid arthritis, while considering the importance of monitoring drug use in clinical practice. The writing method was carried out by reviewing various national and international studies related to polypharmacy and drug interactions in rheumatoid arthritis patients. The findings indicate that the concurrent use of several medications, particularly combinations of nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and disease-modifying antirheumatic drugs (DMARDs), can lead to moderate to severe interactions that may cause serious adverse effects such as hepatotoxicity, renal impairment, and bleeding. Furthermore, the greater the number of drugs used, the higher the likelihood of harmful effects, both due to pharmacokinetic and pharmacodynamic interactions. This condition highlights the need for healthcare professionals to regularly evaluate prescribed medications, adjust dosages, and educate patients about the safe and rational use of drugs. These efforts are essential to minimize adverse effects, improve treatment adherence, and achieve optimal therapeutic outcomes in patients with rheumatoid arthritis.

Corresponding Author:
Vania Putri Risyhade
Medical Study Program, Faculty of Medicine, University of Lampung
2218011106@students.unila.ac.id

INTRODUCTION

Rheumatoid arthritis is a chronic autoimmune disease characterized by inflammation of the synovial membrane and joint tissue (Sah, et al., 2023). This disease usually begins in small peripheral joints, is symmetrical, and will progress to involve more proximal joints if left untreated (Chauhan, et al., 2023). According to the World Health Organization (WHO), the number of people with rheumatoid arthritis worldwide reached around 355 million in 2022, and this number is expected to continue to increase in the coming years (Sastra, 2025).

Clinically, this disease can cause pain in the shoulders, neck, and pelvic girdle, morning joint stiffness, and decreased mobility. Other systemic symptoms often include fever, fatigue, malaise, weight loss, and the formation of rheumatoid nodules Jahid, et al., 2023). The diverse

Jurnal Eduhealth
Volume 16, Number 04 2025 DOI 10.54209/eduhealth.v16i04
ESSN 2808-4608 (Online)
https://ejournal.seaninstitute.or.id/index.php/healt

clinical manifestations require comprehensive and ongoing management of rheumatoid arthritis. The complex symptoms and progressive nature of the disease often require multiple medications to control inflammation, relieve pain, and prevent further joint damage (Nitiyoso, 2020).

Based on the recommendations of the European League Against Rheumatism (EULAR), the main therapies for rheumatoid arthritis include disease-modifying antirheumatic drugs (DMARDs), biologics, non-steroidal anti-inflammatory drugs (NSAIDs), and corticosteroids (Hidayat, et al., 2021). DMARDs function to suppress autoimmune activity, improve joint function, and slow tissue damage. Symptomatic drugs such as NSAIDs (e.g., naproxen, ibuprofen, coxibs) only relieve pain and inflammation but cannot prevent permanent joint damage, so they are best used as adjunctive or short-term therapy. The use of DMARDs should be started as early as possible because their effects appear gradually over 6 weeks to 6 months. Based on type, DMARDs are divided into conventional (csDMARDs), biologics (bDMARDs), and synthetic targeted (tsDMARDs) (Rahmania, et al., 2024).

In clinical practice, patients with rheumatoid arthritis often require a combination of various antirheumatic therapies and long-term supportive care. The concomitant use of multiple medications can increase the risk of polypharmacy. Polypharmacy is generally defined as the concomitant use of five or more medications, and this condition is most common in the elderly population and in patients with chronic diseases or multiple comorbidities (Rachmayanti, et al., 2024). With aging, there is a decline in liver and kidney function, which play a crucial role in drug metabolism and excretion, increasing the risk of drug accumulation in the body. Coupled with the increasing number of comorbidities, this condition further encourages polypharmacy in the elderly (Rachmayanti, et al., 2024). This polypharmacy not only impacts the complexity of therapy but can also trigger drug-drug interactions that have the potential to alter the effectiveness and safety of treatment (Sah, et al., 2023). Furthermore, the increased complexity of therapy due to polypharmacy can also lead to medication errors, especially in rheumatoid arthritis patients receiving multiple drug combinations. Factors such as high-risk polypharmacy, multiple drug types, and the lack of standardized protocols contribute to the increased risk of drug-drug interactions (Putri, et al., 2023).

Drug interactions occur when the effect of one drug is altered by the concomitant administration of another drug, which can decrease the effectiveness of therapy or increase the risk of toxicity (Agustin & Fitrianingsih, 2021). The mechanisms of these interactions can be pharmacokinetic, which affect the absorption, distribution, metabolism, and excretion of a drug, or pharmacodynamic, which is a change in the effect of a drug at its site of action. In patients with rheumatoid arthritis, long-term use of multiple drugs, complex combination therapies, and the presence of comorbidities can increase the risk of drug interactions that could potentially affect the effectiveness and safety of therapy (Aulia & Subarnas, 2024). This risk is a significant concern because drug interactions can arise from various mechanisms and are often difficult to predict. In addition, factors such as the number of drugs used, the duration of use, and the individual's health condition also influence the likelihood of

Jurnal Eduhealth
Volume 16, Number 04 2025 DOI 10.54209/eduhealth.v16i04
ESSN 2808-4608 (Online)
https://ejournal.seaninstitute.or.id/index.php/healt

occurrence (Asyifa, et al., 2024). Evaluation and monitoring of drug interactions are crucial to minimize side effects and improve the safety of patient therapy (Pratama, et al., 2020).

Drug interactions can be classified according to their severity into minor, moderate, and major. Minor interactions are generally harmless, while moderate interactions can increase drug side effects, and major interactions have the potential to cause organ damage or be life-threatening, requiring medical monitoring or intervention. The increased incidence of drug interactions is often associated with the use of concomitant medications (polypharmacy). Studies show that drug interactions are most common in adult and geriatric patients, while cases in pediatric patients are still rarely reported (Agustin, et al., 2021). Some literature also suggests that increasing the number of drugs used concomitantly (polypharmacy) will increase the chance of drug interactions, especially in patients with long-term therapy and chronic conditions.

RESEARCH METHODS

The focus of this paper is to review and analyze published research on medication use, polypharmacy, and drug interactions in rheumatoid arthritis patients. This approach was chosen to provide a comprehensive understanding of the topic based on previously published data without conducting direct patient research. Relevant articles were obtained from electronic databases such as PubMed, NCBI, StatPearls, and internal journal repositories using keywords including “rheumatoid arthritis,” “polypharmacy,” “drug interactions,” and “disease-modifying antirheumatic drugs (DMARDs).” The search focused on peer-reviewed articles published in English between 2019 and 2025 to ensure the inclusion of recent and high-quality evidence.

Studies were included if they discussed medication use, polypharmacy, or drug interaction patterns in adult rheumatoid arthritis patients, while non-peer-reviewed papers, case reports, or studies unrelated to rheumatoid arthritis were excluded. Each selected article was reviewed to ensure it was relevant to the topic and provided reliable information. The data from these studies were then summarized and analyzed narratively to identify common patterns, frequently used medications, the types and severity of drug interactions, and their possible clinical effects. The findings were organized into themes and described in a clear, structured way to give an overall picture of current knowledge and point out areas that still need further research.

RESULTS AND DISCUSSION

Several studies have shown that polypharmacy is a common problem in rheumatoid arthritis patients and is closely associated with an increased risk of drug-to-drug interactions (DDIs). A 2022 study by Al-Ghazaly and Jassim in Iraq reported that 71.8% of RA patients experienced polypharmacy, with an average use of five to six medications per patient. Polypharmacy was shown to increase in elderly patients, with high disease activity, and the presence of comorbidities, but was independent of gender. A total of 331 potential drug interactions were identified, primarily involving methotrexate (MTX) with NSAIDs (diclofenac)

Jurnal Eduhealth
Volume 16, Number 04 2025 DOI 10.54209/eduhealth.v16i04
ESSN 2808-4608 (Online)
https://ejournal.seaninstitute.or.id/index.php/healt

and proton pump inhibitors (omeprazole), which can cause hematological, gastrointestinal, and renal dysfunction toxicity (Al-Ghazaly & Jassim, 2022).

Similar results were obtained in a 2025 study in Brazil by Lorena Batista, who found that 81.1% of RA patients experienced polypharmacy, with over 2,000 potential drug interactions detected. Of these, 54.4% were moderate, 17.8% were severe, and most occurred in elderly patients with multiple comorbidities. Commonly encountered severe interactions included the combination of methotrexate and leflunomide, which carries hepatotoxicity and myelotoxicity, and prednisone and simvastatin, which have the potential to cause side effects (Boeing, et al., 2025).

Overall, these two studies confirm that the more drugs used in RA therapy, the higher the risk of drug interactions that can cause serious side effects. Therefore, close monitoring and regular review of patients' medications are highly recommended to improve therapy safety and patient safety.

Furthermore, research by Niza et al. in 2024 at two hospitals in Palembang City showed that the main problem related to medication use in RA patients was drug interactions (72.03%). Interactions most frequently occurred with the use of NSAIDs such as diclofenac and meloxicam, where the combination of the two can increase drug levels due to competition for renal elimination, thereby increasing the risk of bleeding and hyperkalemia. This study also found a significant association between the number of medications used (polypharmacy) and a high incidence of medication-related problems ($p = 0.001$). This means that the more medications RA patients take, the greater the likelihood of drug interactions and therapy problems. However, no association was found between age, gender, or comorbidities with the incidence of medication problems (Hairun, et al., 2024).

The concomitant use of multiple medications in rheumatoid arthritis patients is often necessary to achieve optimal disease control and reduce inflammatory activity. Long-term combination of multiple medications can increase the potential for drug interactions, especially without proper monitoring and regimen adjustments. The greater the number of medications used, the greater the likelihood of moderate to severe drug interactions, potentially leading to clinical side effects such as liver toxicity, kidney impairment, bleeding, and muscle damage (myotoxicity).

Based on research by Ma et al., methotrexate was recorded as the drug most frequently involved in potential drug interactions in rheumatoid arthritis patients, with the most common combination involving omeprazole, diclofenac, aspirin, and amoxicillin. This interaction has the potential to increase methotrexate toxicity through impaired renal excretion and hematologic effects. In contrast, leflunomide and hydroxychloroquine were reported to cause the least interactions, indicating that the level of drug interaction risk is highly dependent on the type and combination of therapy used. Similar findings were also reported by Al-Ghazaly and Jassim in 2010, who confirmed that methotrexate is the drug with the highest interaction risk among commonly used rheumatoid arthritis therapy regimens (Ma, et al., 20219) (Al-Ghazaly & Jassim, 2022).

Jurnal Eduhealth
Volume 16, Number 04 2025 DOI 10.54209/eduhealth.v16i04
ESSN 2808-4608 (Online)
https://ejournal.seaninstitute.or.id/index.php/healt

CONCLUSION

Polypharmacy is a major risk factor for drug interactions in rheumatoid arthritis (RA) patients, primarily due to the complexity of long-term therapy involving combinations of NSAIDs, corticosteroids, and DMARDs. The greater the number of medications used, the greater the potential for drug interactions, which can lead to serious side effects such as hepatotoxicity, kidney impairment, and bleeding. Therefore, therapy monitoring, regular medication evaluation, and patient education are key to improving treatment safety and effectiveness in RA patients. The simultaneous use of multiple medications in patients with rheumatoid arthritis is often necessary to optimally control disease activity and reduce symptoms. However, the use of this combination therapy can increase the risk of drug interactions, especially if it is not accompanied by careful monitoring of the dosage, duration, and pharmacological profile of each drug (Soleha, et al., 2019).

REFERENCE

1. Sah SK, Ramaswamy S, Ramesh M. 2023. Assessment of potential drug-drug interactions and their associated risk factor in patients with rheumatoid arthritis: A cross-sectional study. Clinical Epidemiology and Global Health. 23(March):2–6.
2. Chauhan K, Jandu JS, Brent LH. 2023. Rheumatoid arthritis. In StatPearls [Internet] (2025 ed.). Treasure Island (FL): StatPearls Publishing. https://www.ncbi.nlm.nih.gov/books/NBK441999/.
3. Sastra SA. 2025. Faktor-faktor yang berhubungan dengan kejadian rheumatoid artritis pada lansia di wilayah kerja Puskesmas Anggaberi Kabupaten Konawe tahun 2024. Jurnal Penelitian Sains dan Kesehatan Avicenna. 4(1):37–48.
4. Jahid MK, Rehan UH, Ahmed RS. 2023. Overview of rheumatoid arthritis and scientific understanding of the disease. Mediterranean Journal of Rheumatology. 34(3):284–291.
5. Nitiyoso N. 2020. Pilihan pengobatan artritis rematoid. Departemen Medical PT. Kalbe Farma Tbk. Jakarta, Indonesia. 47(4):251–255.
6. Hidayat R, Suryana BP, Wijaya LK, Ariane A, Hellmi RY. 2021. Diagnosis dan pengelolaan artritis reumatoid. In Perhimpunan Reumatologi Indonesia. https://reumatologi.or.id/wp-content/uploads/2021/04/Rekomendasi-RA-Diagnosis-dan-Pengelolaan-Artritis-Reumatoid.pdf.
7. Rahmania FA, Sibero HT, Ramadhian MR. 2024. Deteksi dini dan tatalaksana rheumatoid arthritis. Medula. 14(3):567–574.
8. Rachmayanti AS, Suhera S, Haryani R, Sammulia SF, Meilandra R, Agnesfebrianti A. 2024. Gambaran potensi interakasi obat pada resep polifarmasi pasien lansia di rumah sakit badan pengusahaan batam. Jurnal Surya Medika. 10(1):199–204.
9. Putri EA, Sukohar A, Damayanti E. 2023. Medication error at the prescribing, transcribing, dispensing and administration stages. Medical Profession Journal of Lampung. 13(4):457–462.
10. Agustin OA, Fitrianingsih F. 2021. Kajian interaksi obat berdasarkan kategori signifikansi klinis terhadap pola peresepan pasien rawat jalan di Apotek X Jambi. Electronic Journal Scientific of Environmental Health And Disease. 1(1):1–10.

11. Aulia NC, Subarnas A. 2024. Analysis of potential interactions between drugs in polypharmacy prescriptions in Bandung City pharmacies. Journal of Pharmaceutical and Sciences. 7(1):98.
12. Asyifa A, Mirza J, Asep S. 2024. Review article: patofisiologi dan terapi farmakologi diabetes melitus tipe 2 pada pasien geriatri. Jurnal Sains Medisina. 2(5):142–147.
13. Pratama MR, Sukohar A, Berawi KN. 2020. Hubungan tahap pengobatan dengan kualitas hidup pasien multidrug-resistant tuberculosis di RSUD Dr. H. Abdul Moeloek Provinsi Lampung. Medula. 10(1):171–174.
14. Al-Ghazaly ZM, Jassim NA. 2022. Polypharmacy and potential drug-drug interactions in patients with rheumatoid arthritis. Medical Journal of Babylon. 19(3):396–403.
15. Boeing LB, Fogaça NS, Kahlow BS, Skare T, Nisihara R. 2025. Polypharmacy and drug interactions in the management of rheumatoid arthritis. Revista da Associação Médica Brasileira. 71(7):1–6.
16. Hairun N, Sarah HA, Sintya M. 2024. Identification of drug related problems (DRPs) in rheumatoid arthritis patients at Palembang City Hospital. Jurnal Farmasi Dan Ilmu Kefarmasian Indonesia. 11(1):112–119.
17. Ma SN, Huri HZ, Yahya F. 2019. Drug-related problems in patients with rheumatoid arthritis. Therapeutics and Clinical Risk Management. 15505–524.
18. Soleha TU, Sutyarso, Sukohar A. 2019. Genome changes in multi drug resistant tuberculosis. Journal of Physics: Conference Series. 1338(1):1–4.