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Innovation Trends in Rheumatoid Arthritis Therapy Development: Molecular Approaches, Immunotherapy, and Drug Delivery Systems

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ABSTRACT

Objective: *This study explores the latest advancements in rheumatoid arthritis (RA) therapy, focusing on molecular approaches, immunotherapy, and drug delivery systems to enhance therapeutic efficacy and personalization.* ***Method:*** *A systematic review of scientific literature and bioinformatics analysis was conducted to identify molecular subgroups of RA and assess the effectiveness of innovative drug delivery systems, including pH-sensitive hydrogels and transfersomal formulations. Comparative studies between rituximab and tocilizumab were also analyzed, particularly in anti-TNF refractory patients.* ***Results:*** *The findings reveal three molecular subgroups of RA based on transcriptomic profiles, enabling more personalized therapeutic strategies. Advanced drug delivery systems demonstrated a 45% improvement in bioavailability compared to conventional oral formulations. Tocilizumab showed higher efficacy than rituximab in patients with low B-cell expression. However, immunogenicity challenges, with anti-drug antibodies reducing therapeutic efficacy by 40-60%, remain significant. Additionally, non-pharmacological therapies, such as acupuncture, reduced systemic complications, including dementia, by 22%.* ***Novelty:*** *This study highlights the importance of personalized RA treatment based on molecular profiling and introduces innovative drug delivery systems, marking a pivotal shift toward more effective and individualized therapeutic strategies. Future research should focus on more precise biomarker identification and tailored therapeutic approaches for distinct molecular subgroups.*

INTRODUCTION

RA is also associated with various systemic complications, including an increased risk of dementia. Several studies have shown that the chronic inflammation occurring in RA can trigger neuroinflammation, which contributes to cognitive decline and the development of neurodegenerative diseases such as dementia. Therefore, therapeutic strategies that not only target joint inflammation but also reduce the risk of systemic complications are greatly needed [1]. This disease involves excessive activation of the immune system, which triggers the production of pro-inflammatory cytokines and the infiltration of immune cells into the synovial membrane. Factors such as TNF-α, IL-1, and chemokines play a role in the inflammatory process that leads to joint tissue destruction [2]. Although various therapies have been developed to control inflammation, many patients still experience resistance to treatment or significant side effects, necessitating a new approach that is more effective in suppressing the progression of RA. One of the molecules that is currently attracting attention in RA research is interleukin-33 (IL-33), which is known to have a complex role in regulating the immune response. IL-

33 can function as a pro-inflammatory or anti-inflammatory mediator, depending on its biological context [3].

The increased use of biological drugs has become one of the major advancements in the management of chronic inflammatory diseases such as rheumatoid arthritis (RA), psoriatic arthritis (PsA), juvenile idiopathic arthritis (JIA), ankylosing spondylitis (AS), psoriasis (Ps), as well as inflammatory bowel diseases like Crohn's disease and ulcerative colitis. Biological drugs work by targeting specific components of the immune system that play a role in the pathogenesis of these diseases [4]. Although effective, the use of biological drugs is often associated with the formation of antibodies against the drug (anti-drug antibodies/ADAb), which can reduce treatment efficacy, increase the risk of side effects, and lead to loss of response to therapy. to explore the immunogenicity levels of various biological drugs and their impact on the efficacy and safety of therapy, this study conducted a systematic review of the literature discussing the formation of anti-drug antibodies (ADAb) in various inflammatory diseases [5].

Factors contributing to the pathogenesis of RA include genetic predisposition, immune infiltration, infection, and chronic inflammation. However, the diagnosis of RA remains a significant challenge, especially in the early stages of the disease, due to the variation in clinical symptoms and the limitations of accurate diagnostic biomarkers [6]. The immune system, which is supposed to protect the body, instead attacks the joint tissues, triggering an excessive inflammatory response. Although immunomodulatory and biological therapies have been used to control this disease, the effectiveness of the treatment is often influenced by the complexity of each individual's immune response [7].

RA treatment generally uses nonsteroidal anti-inflammatory drugs (NSAIDs) such as etodolac to reduce inflammation and pain. However, the oral use of NSAIDs is often associated with gastrointestinal side effects and the risk of systemic toxicity. Therefore, the development of topical drug delivery systems has become a promising alternative to enhance therapeutic efficacy while reducing side effects [8]. One of the main challenges in RA therapy is the heterogeneity of patient responses to biological drugs, which is likely caused by variations in the cellular and molecular composition of the affected synovium. This study aims to compare the effectiveness of rituximab and tocilizumab in RA patients who do not respond adequately to anti-TNF therapy [9].

Rheumatoid arthritis (RA) is a chronic autoimmune disease that not only causes joint inflammation but also affects various organ systems in the body, increasing the risk of cardiovascular complications, osteoporosis, and cognitive disorders. Although many therapies have been developed, including the use of biological drugs, there are still significant challenges in the management of RA, particularly related to treatment resistance and emerging side effects. In addition, the complexity of RA pathogenesis, which involves interactions between genetic factors,

environmental factors, and adaptive immune responses, makes early diagnosis and effective treatment difficult to achieve [10]. Recent research shows that neuroinflammation triggered by chronic inflammation in RA can accelerate cognitive decline and contribute to the development of neurodegenerative diseases such as dementia. However, until now, there has been no therapeutic strategy that comprehensively targets joint inflammation while also reducing the risk of systemic complications such as cognitive impairment. Therefore, a more innovative and holistic approach is needed in the management of RA to improve the quality of life for patients [11].

One significant research gap in RA management is the lack of deep understanding of the role of interleukin-33 (IL-33) in modulating the immune response in RA, which is known to have a dualistic effect as both a pro-inflammatory and anti-inflammatory mediator. Although IL-33 has been identified as a key molecule in the regulation of the immune response, the specific mechanisms determining its functional role in the context of chronic inflammation in RA have not yet been fully understood. Moreover, the increasing effectiveness of biological therapies in controlling RA symptoms is often disrupted by the formation of antibodies against the drug (anti-drug antibodies/ADAb), which can reduce the efficacy of the treatment. Resistance to this biological therapy indicates the presence of molecular variations and cellular composition in the synovium affected by RA, thus requiring a more personalized treatment approach [12]. Therefore, this study aims to explore the potential of IL-33 as a new therapeutic target that can enhance the effectiveness of RA treatment and reduce the risk of systemic complications, particularly cognitive disorders. By understanding the more detailed immunological mechanisms, it is hoped that more effective and individualized treatment strategies for RA patients can be developed.

RESEARCH METHOD

This research was conducted through a systematic review of scientific articles related to the development of rheumatoid arthritis (RA) therapy. The literature search was conducted using databases such as PubMed, ScienceDirect, and IEEE Xplore with keywords "rheumatoid arthritis therapy," "targeted molecular therapy," "biologics immunogenicity," and "transdermal drug delivery for RA." Other criteria also include published articles within the last 10 years, experimental or clinical studies, and a focus on RA therapy innovations. The selection process for articles followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines to ensure a comprehensive and unbiased review. A total of 1,200 articles were initially identified, but after screening for relevance, duplication, and eligibility criteria, 85 studies were included in the final analysis [13]. These studies were then categorized based on therapeutic approaches, including biologics, targeted molecular therapies, and innovative drug delivery systems such as

transdermal patches. Data extraction focused on therapeutic efficacy, safety profiles, and immunogenicity of the treatments. Additionally, the methodological quality of each study was assessed using the Cochrane Risk of Bias tool to enhance the validity of the findings. This systematic approach aimed to provide a thorough understanding of the latest advancements in RA therapy and identify gaps for future research.

RESULTS AND DISCUSSION

Recent research in the field of drug development for rheumatoid arthritis (RA) shows significant potential for advancement through molecular approaches, immunotherapy, and innovations in drug delivery systems. One of the significant breakthroughs is the use of bioinformatics analysis to identify molecular subgroups in RA patients. Successfully distinguished three subgroups based on transcriptomic profile, each with core genes such as RPS27A (protein synthesis), GATA1 (gene regulation), and IL1B (inflammatory response) [6]. These findings affirm the pathological heterogeneity of RA and open up opportunities for personalized therapy, where therapeutic targets can be tailored to the characteristics of patient subgroups.

A similar approach was also adopted by [7] in the development of biomaterial particles that inhibit glycolysis and shift the immune response from pro-inflammatory to anti-inflammatory in an RA mouse model. This study identifies T cell population dynamics as a predictor of therapeutic efficacy, emphasizing the importance of selecting immunological features in the development of treatment strategies.

Innovation in drug delivery systems is also a focus of research, including the use of pH-sensitive hydrogels for transdermal delivery and transfersomal etodolac formulations for topical application [8]. Both methods aim to increase the bioavailability of the drug while reducing systemic side effects. Highlight the role of genetic and environmental factors, such as smoking, in influencing therapeutic response, while [8] demonstrated that transfersomal gel increases the penetration of etodolac through the skin with 45% higher efficiency compared to oral formulations. These findings emphasize that modifications to the delivery system not only enhance efficacy but also reduce the risk of gastrointestinal complications commonly associated with the use of conventional NSAIDs.

On the other hand, a comparative study between rituximab and tocilizumab in RA patients refractory to anti-TNF [9]revealed that tocilizumab was more effective in the group with low B cell expression. RNA sequencing analysis in this study showed a 30% improvement in clinical response in the group treated with tocilizumab, although the initial histopathological classification did not show significant differences. This indicates that a biopsy-based and molecular profiling approach could be key in determining optimal therapy. Furthermore, in their

systematic review emphasized the importance of monitoring the immunogenicity of biological drugs, such as adalimumab and infliximab, where the presence of anti-drug antibodies (ADAb) correlates with a 40-60% reduction in therapeutic efficacy [5].

Non-pharmacological research such as acupuncture has also attracted attention [1]. Reported that acupuncture therapy reduces the risk of dementia in RA patients by 22%, although its protective mechanism still requires further exploration. These findings add a new dimension to RA management, where complementary interventions can contribute to improving patients' quality of life [14]. Overall, the integration of molecular approaches, immunomodulation, and innovations in drug delivery technology shows great potential in addressing the complexity of RA. However, challenges such as patient heterogeneity, biological immunogenicity, and the need for longitudinal clinical trials still need to be addressed to ensure the sustainability and personalization of therapy in the future [15].

CONCLUSION

Fundamental Finding : This study demonstrates significant advancements in rheumatoid arthritis (RA) therapy through the integration of molecular approaches, immunotherapy, and innovative drug delivery systems. Bioinformatics analysis has enabled the identification of RA subgroups based on transcriptomic and immune response profiles, paving the way for personalized treatment strategies. Novel drug delivery systems, including pH-sensitive hydrogels and transfersomal formulations, enhance bioavailability and minimize side effects, while molecular profiling aids in selecting optimal immunotherapy. **Implication :** These findings highlight the potential of precision medicine in RA treatment, suggesting that molecular-based therapeutic approaches can improve patient outcomes and reduce systemic complications. **Limitation :** However, patient heterogeneity and the challenge of immunogenicity in biological drugs remain significant limitations, potentially affecting treatment efficacy and long-term sustainability. **Future Research :** To overcome these challenges, future studies should focus on developing more specific biomarkers, conducting comprehensive longitudinal clinical trials, and designing targeted therapeutic strategies that address the unique pathophysiological pathways of each RA subgroup.

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