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Use of Biological Disease-Modifying Antirheumatic Drugs (bDMARD) Therapy in Rheumatoid Arthritis: A Review of Side Effects and Immunological Mechanisms

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Rheumatoid arthritis (AR) is a chronic autoimmune disease that causes symmetrical inflammation of small and large joints and other organs. AR treatment has evolved with the introduction of Biological Disease-Modifying Antirheumatic Drugs (bDMARD) that target specific immunological pathways in AR pathogenesis thereby increasing the effectiveness of therapy. The study aims to review the side effects of bDMARD and its immunological mechanisms. The method used was a literature review by searching for articles from scientific databases related to the side effects and immunological mechanisms of bDMARD in AR. Results suggest that bDMARD are effective in controlling inflammation and preventing joint damage, but have significant side effects, including an increased risk of serious infections such as tuberculosis reactivation and opportunistic infections such as shingles. In addition, there is a risk of malignancy, major cardiovascular events (MACE),

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gastrointestinal disorders, and hematological disorders such as neutropenia. The immunological mechanism of bDMARD involves inhibition of pro-inflammatory cytokines such as TNF-α and IL-6, as well as suppression of T cell activation and B cells that play a role in AR inflammation. In conclusion, although bDMARD provide significant therapeutic benefits in AR treatment, monitoring side effects ensures long-term safety.

Keywords: *Rheumatoid arthritis, bDMARD, side effects, immunology.*

1. Introduction

Rheumatoid arthritis (AR) is a chronic autoimmune disease with symmetrical inflammation that starts in small joints and then spreads to large joints and other organs such as the skin, eyes, heart, kidneys, and lungs. This condition damage bones, cartilage, and weakens tendons and ligaments, resulting in joint dysfunction (Bullock et al., 2019).

The AR clinical picture includes both articular and extra-articular manifestations. Non-specific systemic symptoms, such as fever, malaise, and weight loss, often precede joint symptoms. AR is often associated with other connective tissue diseases as well as non-inflammatory conditions, such as fibromyalgimaia, and increases the risk of cardiovascular disease and osteoporosis. The main symptoms are joint pain, swelling, and stiffness in the morning ≥60 minutes. Typical symmetrical polyarthritis in AR usually involves the MCP, PIP, thumb, wrist, elbow, and MTP joints, with a minimum duration of six weeks (Hidayat et al., 2021).

According to Hidayat et al, the prevalence and incidence of AR vary between populations, with women having a 2-3 times higher risk than men. The incidence increases with age, especially in the 50-54 age group, and tends to be balanced between men and women over 70. AR is more common in Northern Europe (29 per 100,000) and North America (38 per 100,000) than in Southern Europe (16.5 per 100,000). Global prevalence is stable in the range of 0.5-1%, with the highest prevalence in Pima Indians (5.3%) and Chippewa (6.8%), and lowest in China and Japan (0.2-0.3%). In Indonesia, there are an estimated 1.3 million people with AR based on global prevalence, with the local prevalence in Dam, Central Java reaching 0.34%, and in Malang around 0.5-0.6% in the population over 40 years old (Hidayat et al., 2021).

Previously, therapy for AR was limited to the use of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) and glucocorticoids as the basis of treatment, but in the late 20th century, treatment options expanded significantly with the introduction of conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), such as methotrexate, hydroxychloroquine, and sulfasalazine, which still have an important role in the management of AR .biological disease-modifying antirheumatic drugs (bDMARDs) that revolutionize the treatment approach by targeting immunological pathways associated with AR pathogenesis thereby improving therapeutic efficiency and patient quality of life (Findeisen et al., 2021).

Biological therapies generally target cell surface molecules, while chemical drugs act on intracellular structures. bDMARDs interact directly with cytokines or cell surface receptors, neutralizing their function, as well as lowering serum cytokine levels in AR patients. The study revealed that bDMARDs have a wider spectrum of action than just their direct function, due to the complexity of the pro-inflammatory tissue (Bonek et al., 2021). Biological therapies involve genetically engineered proteins to selectively inhibit specific components of the immune system that play a crucial role in inflammatory mechanisms. These components are key elements in AR pathogenesis, so their targeting can significantly reduce disease activity and joint damage (Lopez-Pedrera et al., 2020).

There are nine bDMARDs for the treatment of AR, seven of which are monoclonal antibodies (adalimumab, certolizumab pegol, golimumab, infliximab, sarilumab, tocilizumab, and rituximab) and fusion proteins (etanercept and abatacept) (Chaplin, 2020). There are currently four distinct immunological target mechanisms of bDMARDs for AR therapy: tumor necrosis factor inhibitors (TNF inhibitors), interleukin-6 receptor inhibitors (anti-IL-6R), T-cell costimulation blockers (CTLA-Ig), and anti-CD20 monoclonal antibodies (anti-CD20 Ab). Each bDMARD targets immune pathways that are crucial in the

pathogenesis of inflammation and joint damage in AR, thus providing a more precise and effective therapeutic approach in disease management (Min et al., 2022).

The use of bDMARDs can result in increased levels of transaminase, as well as triggering or reactivating autoimmune diseases such as multiple sclerosis and psoriasis. In addition, bDMARDs have the potential to worsen congestive heart failure, increase the risk of infection, dyslipidemia, as well as cause cytopenia, such as lymphopenia or neutropenia, and gastrointestinal complications. this review, the authors aim to describe the therapeutic side effects and immunological mechanisms associated with each agent of bDMARD.

2. Method

This literature review method searches for scientific articles in Indonesian and English from Google Schoolar, Pubmed, Scopus, and Science Direct databases from 2014-2024. The keywords used in the article search are: (Biological Disease-Modifying Antirheumatic Drugs) AND (side effect) AND (immunology) AND (Rheumatoid arthritis).

The studies in the selected articles met the inclusion criteria: (1) Patient/problem: Rheumatoid arthritis; (2) Intervention: Biological Disease-Modifying Antirheumatic Drugs (bDMARD); (3) Comparator: Conventional Synthetic Disease-Modifying Antirheumatic Drugs (csDMARD); (4) Results: Side effects and immunological mechanisms. Meanwhile, the exclusion criteria are: (1) Diseases other than rheumatoid arthritis; (2) Irrelevant results.

3. Result and Discussion

In the literature search, 20 scientific articles were obtained that were used as references for the preparation of this literature review.

3.1 Classification of bDMARDs

Biological Disease-Modifying Antirheumatic Drugs (bDMARDs) are therapeutic agents that specifically target the molecular pathways involved in the pathogenesis of rheumatoid arthritis (AR), particularly chronic inflammatory processes mediated by cytokines and immune cells. In clinical practice, bDMARDs are used when patients do not respond optimally to Conventional Disease-Modifying Antirheumatic Drugs (csDMARDs) such as methotrexate, which is generally the first line of AR therapy (Peasah et al., 2024).

3.1.1 Tumor Necrosis Factor

Agents such as adalimumab, infliximab, etanercept, golimumab, and certolizumab pegol inhibit the activity of TNF-α, a key pro-inflammatory cytokine responsible for inflammatory pathway activation and joint destruction in RA. TNF inhibitors are generally the first choice among bDMARDs (Smolen et al., 2020).

3.1.2 Interleukin-6

Tocilizumab and sarilumab target the IL-6 receptor, a cytokine that plays a central role in enhancing the systemic inflammatory response and synovial tissue degradation. This therapy is intended for patients who have failed to respond to TNF inhibitors or have contraindications to them (Burke et al., 2014).

3.1.3 Anti-CD20 Monoclonal Antibodies

Rituximab, which targets B cells via the CD20 molecule, is used to destroy autoreactive B cells that contribute to autoimmune processes in AR, especially in cases with high levels of autoantibodies (Smolen et al., 2020).

3.1.4 T-Cell Costimulation Blockers

Abatacept inhibits T cell activation through CD28-CD80/86 interaction blockade, reducing the proliferation of T cells that play a role in mediating destructive autoimmune responses in AR (Burke et al., 2014).

The selection of bDMARDs is based on the patient's clinical factors, including disease activity, response to prior therapy, as well as the profile of side effects, especially the risk of serious infection due to more intense immunosuppression. The administration of this therapy requires close monitoring, such as TB screening before starting TNF inhibitor therapy, and avoiding the administration of live vaccines during therapy (Burke et al., 2014).

3.2 Side Effects of bDMARD

The use of bDMARDs in AR treatment has been shown to be effective in controlling inflammation and slowing joint damage. However, this therapy also has significant side effects and needs to be taken seriously. One of the main side effects is an increased risk of serious infections, such as tuberculosis (TB) reactivation and other opportunistic infections, including shingles. This is due to the immunosuppressive properties of bDMARDs that weaken the body's ability to fight pathogens (Evangelatos et al., 2020).

In addition, there is an increased risk of malignancy, especially lymphoma and non-melanoma skin cancer. Some studies suggest that biologic therapies may increase the risk of melanoma compared to usual systemic treatments, although often these results are not statistically significant. For example, a meta-analysis of more than 34,000 patients who took bDMARDs for AR and other inflammatory diseases found a slight increase in the risk of melanoma, but these results were not considered significant. This indicates that there may be an increased risk, but more research is needed, especially considering long-term and other risk factors (Esse et al., 2020).

bDMARD users are also at higher risk of major cardiovascular events (MACEs), such as heart attacks and strokes, especially in patients taking tofacitinib compared to those taking TNF inhibitors. Other side effects include deep vein thrombosis (DVT), especially in the use of high doses of tofacitinib, as well as haematological disorders such as neutropenia and pancitopenia, which can weaken the immune response and increase the risk of bleeding (Andisari, 2018; Sepriano et al., 2022; Tarp et al., 2017).

The use of bDMARDs such as tocilizumab in AR patients also increases the risk of gastrointestinal disorders, especially intestinal perforations. These findings indicate that tocilizumab has a higher risk profile than other bDMARD agents such as TNF inhibitors in terms of GI perforation complications. This increased risk may be due to an interleukin-6 (IL-6) inhibition mechanism that affects the healing process of gastrointestinal tissue, which may contribute to perforation incidence among patients receiving tocilizumab.(Barbulescu et al., 2020) IL-6 plays an important role in protecting the digestive mucosa, so its inhibition interferes with the healing process of tissues, making the intestines vulnerable to injury. This risk is exacerbated by concomitant use of NSAIDs or corticosteroids that damage the mucosa (Barbulescu et al., 2020; Ogata et al., 2019; Rempenault et al., 2022).

In addition, there is a risk of the emergence of new autoimmune reactions, such as lupus-like syndrome, as well as hypersensitivity reactions that can occur within a few weeks of starting therapy (Andisari, 2018; Sepriano et al., 2022; Tarp et al., 2017).

3.3 Immunological Mechanism of bDMARD

3.3.1 Tumor Necrosis Factor

Tumor Necrosis Factor (TNF) is a pro-inflammatory cytokine produced by activated and upregulated monocytes in the synovium in the active phase of AR. TNF is a key modulator in AR that activates NF-κB pathways as well as INF-γ, IL-1, and IL-6 pathways that trigger bone erosion and joint damage. TNF activation facilitates the systemic inflammatory response through increased production of pro-inflammatory cytokines and chemokines. Research shows that TNF inhibition has a significant correlation with improvement in clinical symptoms, as well as contributing to a reduction in the progression of radiologic changes associated with the disease. Currently, there are five biological

agents that are effective in suppressing TNF activity and have been applied in AR therapy, namely Infliximab (INF), Etanercept (ETN), Adalimumab (ADA), Golimumab (GLM), and Certolizumab (CMZ) (Andisari, 2018; Bonek et al., 2021).

3.3.2 Interleukin-6

Interleukin-6 (IL-6) is a pleiotropic cytokine that is synthesized by different cell types and contributes significantly to the inflammatory mechanisms that occur in AR. IL-6 plays a role in the differentiation of B cells into plasma cells and T cells into cytotoxic T cells, as well as in the induction and activation of osteoclast differentiation. In addition, IL-6 also triggers the production of acute phase reactants, especially C-reactive protein (CRP). This whole process contributes to the development of synovitis and bone destruction in AR. Increased production of IL-6 and its receptors is closely linked to the chronic inflammatory process typical of AR (Andisari, 2018).

3.3.3 T-Cell Costimulation Blockers

T-cell costimulation blockers (CTLA-Ig) such as abatacept work by inhibiting the second co-stimulation signal required for full activation of T cells on A) by blocking the interaction between CD80/CD86 on Antigen Presenting Cells (APCs) and CD28 on T cells γ α. As a result, T cells become anergic or inactive, thus lowering the excessive inflammatory response. This mechanism inhibits the activation of T cells that prevent the inflammatory response and exert a therapeutic effect on AR (Small et al., 2023).

3.3.4 Anti-CD20 Monoclonal Antibodies

Anti-CD20 monoclonal antibodies such as Rituximab are biological therapies designed to target B cells by binding to CD20 proteins found on their surfaces. In the context of rheumatoid arthritis (AR), B cells play an important role in the production of autoantibodies, including rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA), which contribute to inflammatory processes and joint damage. The binding of Rituximab to B cells results in the destruction of those B cells, thereby reducing the number of B cells and autoantibodies circulating in circulation. This decrease in the population of B cells was followed by a decrease in the production of pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β which play a role in mediating inflammation in the joints. Thus, anti-CD20 therapy contributes significantly to the reduction of inflammation and joint damage that occurs in AR, thus providing a positive therapeutic effect for patients (Payandeh et al., 2019).

4. Conclusion

The use of bDMARDs in the treatment of AR has been shown to be effective in reducing inflammation and joint damage, but it comes with some risks. Major side effects include an increased risk of serious infections such as TB reactivation and shingles, as well as malignancies such as lymphoma. The risk of major cardiovascular events (MACE) and haematological disorders such as neutropenia and pancitopenia also need to be watched out. Immunologically, bDMARDs work by suppressing TNF and IL-6, as well as inhibiting the activation of T cells and B cells, which contribute to the inflammatory process of RA. Although effective, monitoring of side effects is essential to ensure the safety of the therapy.

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