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Comparative efficacy and safety of monoclonal antibodies in rheumatoid arthritis

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Abstract

Rheumatoid arthritis (RA), as the most commonly diagnosed systemic inflammatory arthritis, affects 0.5 – 1% of the population worldwide. Over the recent decades, there has been extensive research on disease-modifying antirheumatic drugs (DMARDs), including biological DMARDs (bDMARDs), which emerged as an alternative treatment option for conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) nonresponding RA patients. Some of the promising drug groups are the monoclonal antibodies, including tumor necrosis factor--alpha (TNF-α) inhibitors, interleukin 6 (IL-6) inhibitors, blockers of IL-6 receptors (IL-6R), and agents targeting B-cell reduction. This study aims to review the existing knowledge about the efficiency and safety of monoclonal antibodies used in the treatment of rheumatoid arthritis. The bDMARDs monotherapy has been proven effective, as evidenced by reductions in the American College of Rheumatology (ACR) and Disease Activity Score 28 (DAS28) scores, leading to decreased RA disease activity and symptom alleviation. Also, the bDMARDs can serve as a treatment agent for csDMARDs therapy, achieving a higher remission rate. There is extensive research on tocilizumab as it presents promising treatment effects, safety profile, and cost per clinical response among bDMARDs. Thanks to still developing RA medication, patient therapy can be tailored to specific needs, achieving personalized treatment. *(Farm Współ 2025; 18: 3-9) doi: 10.53139/FW.20251806*

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Introduction

Rheumatoid arthritis (RA) is one of the most common autoimmune inflammatory diseases affecting the joints [1]. It affects approximately 0.5-1% of the population, with women being 2-3 times more likely to suffer from that disease. It can present symptoms in many organs, though its hallmark feature is inflammation of joints, leading to their irreversible deformation [2,3]. Along with arthritis being a clinical manifestation, autoantibodies play a key role. The two most common include - rheumatoid factor (RF), with a sensitivity of 70% and a specificity of 80%, and anti-citrullinated peptide antibodies (ACPAs), with a sensitivity of 74% and a specificity of 94% [4–6]. According to the EULAR 2022 recommendations, the treatment of RA should focus on the disease activity, patient comorbidities, and the patient's individual, medical, or societal costs. As low disease activity might take months to achieve, the physician and patient's shared decisions are crucial overreaching principles [7]. The effectiveness of RA treatment is commonly measured using the American College of Rheumatology (ACR) response criteria with improvement thresholds established as 20%, 50%, and 70% (ACR20, ACR50, ACR70) [8]. Another frequently used scale is the Disease Activity Score 28 (DAS28). It provides a score to assess disease activity according to specific numbers: remission (<2.6), low activity (2.6-3.2), moderate activity (3.2-5.1), and high activity (>5.1) [9].

Upon diagnosing RA, the primary treatment strategy involves the early initiation of conventional synthetic disease-modifying antirheumatic drugs (csDMARDs). First-line agents typically include methotrexate (MTX), leflunomide, and sulfasalazine, which are administered to mitigate disease progression and alleviate the symptoms [7]. Among patients treated

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with MTX, approximately 20-40% achieve an ACR70 response rate, indicating substantial improvement in disease symptoms and function. When combined with biological DMARDs (bDMARDs), remission is achieved in about 40% of RA patients. Since combination therapy with a single bDMARD may not achieve low disease activity, there is still a 10-15% chance that switching to another bDMARD could be beneficial. [10]. The use of csDMARDs in RA treatment is steadily declining, with the MTX dropping from 40% in 2016 to 34% in 2021, whereas bDMARDs utility has increased in that time. Nevertheless, csDMARDs are still the most prescribed medications for RA, ranging from 77.2 to 79.2% [11].

Taking into consideration the possible second- and third-line utility of the bDMARDs in patients diagnosed with rheumatoid arthritis, this review aims to examine the safety and comparative efficacy of the monoclonal antibodies, a class of biological disease--modifying antirheumatic drugs (bDMARDs), which are becoming more commonly used in RA treatment.

Target points of monoclonal antibodies in RA

Monoclonal antibodies currently used in the treatment of RA are classified into three main groups – Tumor necrosis factor alpha (TNF-α) inhibitors, blockers of IL-6 receptors (IL-6R), and agents targeting B-cell reduction [12].

Monoclonal antibodies, classified as TNF-α inhibitors, such as infliximab and adalimumab, are used to help control the inflammatory process [12]. TNF-α is a kind of glycoprotein mainly produced by activated macrophages. This protein binds with specific receptors on cells, triggering an inflammatory response. It activates synovial fibroblasts, which produce enzymes, like matrix metalloproteinases (MMPs), that destroy cartilage and bone. Therapies targeting TNF-α aim to discontinue this process, reduce inflammation, and slow disease progression [13–15].

The other group consisted of monoclonal antibodies that target the IL-6 pathway. Tocilizumab specifically targets the IL-6 receptor [12]. Similar to TNF-α, IL-6 is mainly produced by activated macrophages. This interleukin has pleiotropic effects: it activates synovial fibroblasts, stimulates B-cells to produce antibodies, and plays a role in osteoclast activation, contributing to bone erosion. IL-6 also promotes the predominance of Th17 over Treg cells and stimulates the overproduction of vascular endothelial growth factor (VEGF), leading to disease progression. By blocking the IL-6 receptor, monoclonal antibodies aim to stop the inflammation and slow synovial and bone damage [16–18].

The last type of monoclonal antibodies mentioned above, which includes Rituximab, targets the reduction of B cells [12]. They are binding to the CD20 antigen present on the surface of B lymphocytes, leading to their death. B cells, functioning as antigen-presenting cells (APCs), activate T cells and promote the production of pro-inflammatory cytokines. This process is further enhanced by synthesizing autoantibodies (RF, ACPA) that stimulate synovial fibroblasts and macrophages, contributing to the inflammation. Rituximab can interrupt these mechanisms by effectively depleting B cells, inhibiting disease progression [19,20].

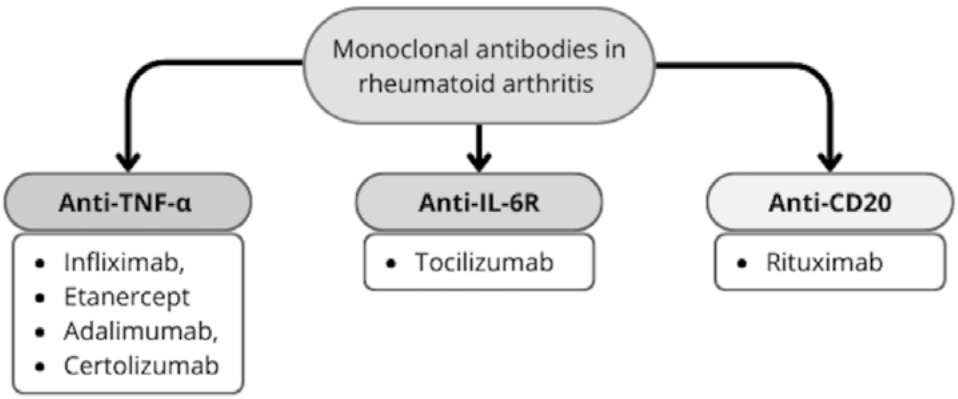

Figure 1. Monoclonal antibodies used in the rheumatoid arthritis treatment [12]

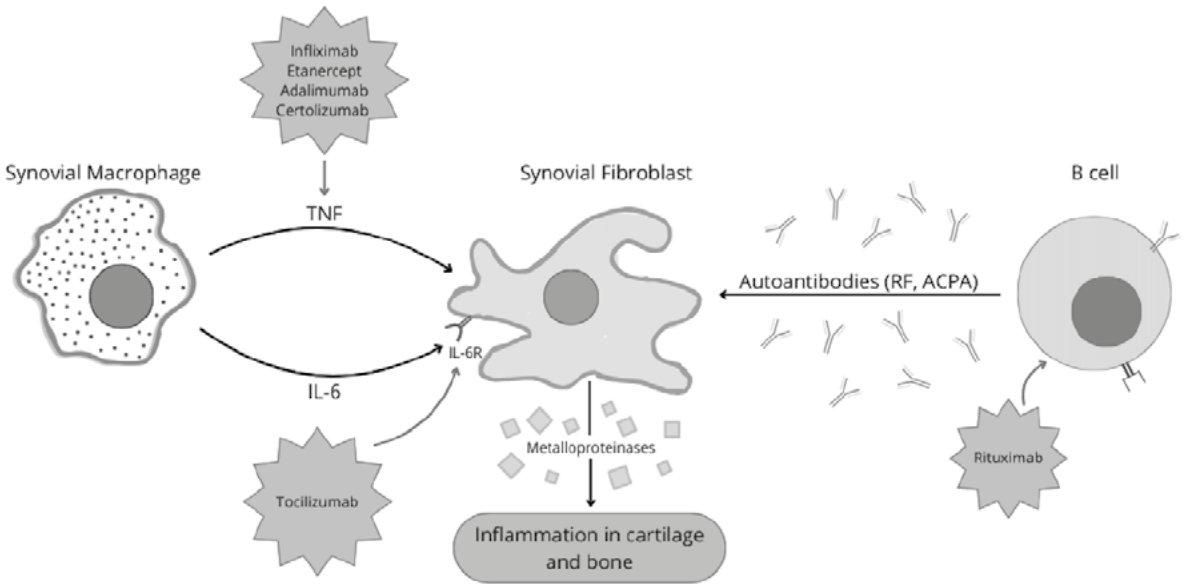

Figure 2. The points of action of bDMARDs [3]

Efficacy comparison among antibodies

The comparative study published in the year 2013 by Gabay et al. examined the efficacy of tocilizumab (TCZ) and adalimumab (ADA) monotherapy in RA treatment. The results were measured using DAS28, which revealed a significant decrease in disease activity in both TCZ patients (–3.3) and ADA patients (–1.8); the difference between the drug's efficiency was found significant with the difference –1.5 (95% Confidence interval (CI) –1.8 to –1.1; P<0.0001) favoring the TCZ treatment [21]. The REBONE study, which compared TCZ monotherapy vs. ADA + methotrexate (MTX) for 52 weeks, confirmed the superior effect of TCZ on bone erosion repair (P<0.001), concluding that targeting IL-6 is a crucial aspect for managing bone homeostasis in patients with RA, both treatment group significantly reduced the disease activity with TCZ [22]. The 2-year study comparing the efficacy of three bDMARDs revealed that tocilizumab had a significantly greater improvement of DAS28 score when compared to infliximab (P = *0.0005)* and abatacept *(*P < *0.0001)* [23]. The retrospective study comparing the tumor necrosis factor inhibitors (TNFi) vs. TCZ in a patient group of prior inadequate response to csDMARDs has shown that the therapy involving the TCZ and DMARDs + TCZ result in significantly more patients achieving remission (DMARD-IR, TCZ 44.0 % vs. TNFi 29.6 % P < 0.001) (TCZ 37.2 % vs. TNFi 30.2 % P < 0.001) [24]. The 1488 patient TNFi head-to-head comparison of certolizumab pegol + MTX versus adalimumab + MTX reported no significant differences in either ACR20 response at week 12 (0.467) or DAS28 at week 104 (P=0.532) indicating similar efficiency between those TNF inhibitors [25]. The study comparing IL-6 receptor inhibitors and TNF inhibitors in high-disease activity RA patients who experienced prior treatment with MTX or other bDMARDs found no significantly different outcomes [26]. The MONARCH study from 2016 compared the monotherapy of sarilumab and adalimumab for 24 weeks. The research found a significantly higher decline in DAS28-ESR in the sarilumab group than in the adalimumab group (–3.28 vs. –2.20; P<0.0001). Also, there was a significant difference in American College of Rheumatology 20/50/70 response rates between those drugs favoring the sarilumab: 71.7%/45.7%/23.4%, adalimumab: 58.4%/29.7%/11.9%; all P≤0.0074 [27]. Patients diagnosed with RA categorized with knee joint involvement were more likely to benefit from anti-IL-6 receptor antibodies rather than other bDMARDs (TNF-i CTLA4Ig) (P=0.006); however, the results in elbow and shoulder involvement did not present any significant differences between drugs [28]. The cotreatment effect of bDMARDs and MTX has been associated with a 55% higher likelihood of DAS28

remission and better objective clinical outcome [29]. The retrospective study comparing the tumor necrosis factor inhibitors (TNFi) vs. TCZ in a patient group of prior inadequate response to csDMARDs has shown that the therapy involving the TCZ and DMARDs + TCZ result in significantly more patients achieving remission (DMARD-IR, TCZ 44.0 % vs. TNFi 29.6 % P < 0.001) (TCZ 37.2 % vs. TNFi 30.2 % P < 0.001) [24]. The 1488 patient TNFi head-to-head comparison of certolizumab pegol + MTX versus adalimumab + MTX reported no significant differences in either ACR20 response at week 12 (0.467) or DAS28 at week 104 (P=0.532) indicating similar efficiency between those TNF inhibitors [25]. However, the study comparing IL-6 receptor and TNF inhibitors in high-disease activity RA patients who experienced prior treatment with MTX or other bDMARDs did not find significantly different outcomes between groups [26]. Moreover, it was found that there is no significant difference in terms of the Clinical Disease Activity Index (CDAI) and mACR20 or mACR50 response between the TCZ group vs. TNFi + MTX group. This study highlighted the similar efficiency of those two treatment schemes in 6-month follow-up [30]. This outcome was also confirmed in a study by Finzel et al., where there was no significant difference in DAS28, SDAI, and CDAI between TCZ and ADA+MTX groups during a 52-week follow-up [22]. A large pan-European study involving seven countries concluded that there is a highly similar effect of TCZ monotherapy (mono), TCZ combination with csDMARDs (combo), and TNFi combo effect in RA treatment in terms of CDAI, achieving low disease activity (LDA) and remission corrected for attrition. Authors also suggested a treatment combination of

Table I. Comparative efficiency of bDMARDs monotherapy and combinations

Author, reference	Drug comparison	Comparative effect
Gabay et al. [21]	TCZ vs. ADA	TCZ had a better effect on the DAS28 score decline –1.5 (95% CI –1.8 to –1.1; P<0.0001).
Finzel et al. [22]	TCZ vs. ADA+MTX	TCZ effect on bone erosion repair was more significant (P<0.001), ADA+MTX (P=0.77). The DAS28, SDAI, and CDAI remain similar, with no statistical difference between groups.
Diep et al. [23]	TCZ vs. INF vs. ABA	TCZ had significantly greater improvement in DAS28 score vs INF (P = 0.0005) vs. ABA (P< 0.0001).
Backhouse et al. [24]	TCZ vs. TNFI	The greater remission rate for TCZ 37.2 % vs. TNFi 30.2 % P < 0.001.
Smolen et al. [25]	ADA+MTX vs. CZP+MTX	No significant differences in ACR20 response at week 12 (P=0.467) or DAS28 at week 104 (P=0.532).
Sebba et al. [26]	TNFI vs. IL-6Ri	No significant differences in high disease activity RA in a population previously treated with b/tsDMARDs.
Harrold et al. [30]	TCZ vs. TNFi+MTX	No significant difference in CDAI, mACR20, or mACR50 between groups in the 6-month treatment.
Lauper et al. [30]	TCZ vs. TCZ+csDMARDs vs. TNFi *vs* TNFi+csDMARDs	No significant difference in CDAI, low disease activity, and remission was corrected for attrition between TCZ, TCZ+csDMARDs, and TNFi+csDMARDs.
Burmester et al. [27]	ADA vs. SAR	SAR had better effect on DAS28-ESR than ADA (−3.28 vs. −2.20; P<0.0001) and on ACR 20/50/70 (71.7%/45.7%/23.4% vs. 58.4%/29.7%/11.9%; P≤0.0074).
Maeda et al. [28]	IL-6Ri vs. TNFi/CTLA4ig	Greater benefit from IL-6Ri among patients with knee joint involvement (P=0.006).
Gaujoux-Viala et al. [29]	bDMARDs + MTX	Cotreatment has been associated with a 55% higher likelihood of DAS28 remission and better objective clinical outcomes.

ABA- abatacept, ADA – adalimumab, CZP – certolizumab, csDMARDs – conventional disease-modifying drugs, CDAI - Clinical Disease Activity Index, DAS28 – disease activity score 28, INF – infliximab, MTX – methotrexate, TCZ – Tocilizumab, TNFi - tumor necrosis factor inhibitors.

csDMARDs (if tolerated) with either TNFi or TCZ or just TCZ in monotherapy [30]. The MONARCH study from 2016 compared the monotherapy of sarilumab and adalimumab during the 24 weeks. The research found a significantly higher decline in DAS28-ESRc in sarilumab than in adalimumab (–3.28 vs. –2.20; P<0.0001). Also, there was a significant difference in American College of Rheumatology 20/50/70 response rates between those drugs favoring the sarilumab: 71.7%/45.7%/23.4%, adalimumab: 58.4%/29.7%/11.9%; all P≤0.0074 [27]. Patients diagnosed with RA categorized with knee joint involvement were more likely to benefit from anti-IL-6 receptor antibodies than other bDMARDs (TNFi, CTLA4Ig) (P=0.006). However, the results in elbow and shoulder involvement did not present significant differences between drugs [28]. The cotreatment effect of bDMARDs and MTX has been associated with a 55% higher likelihood of DAS28 remission and better objective clinical outcome [29]. The efficiency comparison is summarized in table I.

Safety of treatment and frequent adverse effects

The main concern when introducing biological DMARDs is the potential for adverse effects (AEs), which may be life-threatening or reduce the patient's overall quality of life. The most common AEs of bDMARDs treatment are elevated liver enzyme levels such as ALT or AST, gastrointestinal problems, leukopenia, and upper respiratory tract infections (URTIs) - reported as the most frequent type of issue [31]. During the median of 23 months, the study done by Barbieri et al. on 1155 patients reported 216 AEs; 25,5% of them were severe, including leukopenia or lymphocytosis, and 21.8% of them were infections. The authors highlighted still undetected long-term issues of bDMARDs treatment [32]. Interestingly, RA treatment with biological DMARDs has been confirmed to be safe for patients during COVID-19. Although immunosuppressed, they did not experience worse infection outcomes than the general population [33]. According to the systematic review from 2019, there is an increased risk of tuberculosis events after TNFi treatment. However, the data was confounded and requires further research as results from studies are equivocal [34].

The safety profile of monoclonal antibodies during pregnancy has been under continuous research; recent studies have suggested anti-TNFα agents as safe medication during the pregnancy; some antibodies, however, are recommended to be discontinued: Tocilizumab – 3 months before pregnancy, rituximab – discontinued before pregnancy or exceptionally discontinued after 1st trimester [35].

Cost-effectiveness of bDMARDs

Although some of the patients who are non-responsive to synthetic DMARDs might benefit from the bDMARDs treatment, it is still an expensive medication regime. In the 2018 meta-analysis, the total RA-specific cost was calculated to be $3723 for any treatment option, whereas the DMARDs users' treatment cost was estimated to be $20262 [36]. The treatment cost varies within the bDMARDs. The cost-effective analysis examining the cost per successful clinical response of TCZ monotherapy and ADA monotherapy highlighted that tocilizumab was more cost-effective than adalimumab in clinical reemission DAS28 < 2.6: $45,868 – TCZ vs. $244,174 – ADA. Also, mean hospital stay in the TCZ group was shorter (32 vs. 43) [37]. The STRATEGE study, though, has highlighted the importance of initial MTX treatment optimization before initiating biological treatment, showing that properly managed MTX treatment can achieve similar results, improving disease activity [29]. One of the possible solutions for the high economic cost of bDMARDs treatment is the introduction of cheaper biosimilars, which can be offered for a broader spectrum of patients due to lower prices [38]. The currently available biosimilars of bDMARDs (adalimumab, infliximab, and etanercept) were associated with clinically similar effects of the RA treatment regarding ACR20 and patient-reported outcomes [39]. One of the most noteworthy recently registered biosimilars of TCZ is CT-P47, which has been confirmed to have comparable efficacy endpoints, pharmacokinetics, safety, and immunogenicity in RA treatment [40].

Conclusion

The treatment of rheumatoid arthritis (RA) with the use of biologic disease-modifying antirheumatic drugs (bDMARDs) is a promising alternative option for non-responding methotrexate (MTX) patients both in terms of monotherapy and cotreatment. Among these agents, tocilizumab, an interleukin-6 receptor antagonist, stands out as a particularly effective monoclonal antibody in terms of its efficacy profile in RA treatment. However, the economic burden and safety

profile of long-term bDMARDs use leave room for further research in this area, including biosimilars of currently used bDMARDs. Expanding access to more affordable biologic treatments would enable a broader population of RA patients to benefit from modern, targeted therapies, improving patients' quality of life.

Conflict of interest
None

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