BIOLOGIC DISEASE-MODIFYING ANTIRHEUMATIC DRUGS (BDMARDS) IN THE TREATMENT OF RHEUMATOID ARTHRITIS: EFFICACY, SAFETY, AND MODERN APPROACHES

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Abstract:

Background: Rheumatoid arthritis (RA) is a chronic autoimmune disease in which biologic and targeted synthetic disease-modifying antirheumatic drugs (bDMARDs/tsDMARDs) have become an integral stage of care when conventional synthetic DMARDs (csDMARDs), primarily methotrexate, fail to achieve adequate control. These agents act at defined points in the immunopathogenic cascade, reducing disease activity and preventing structural damage.

Methods: This narrative review synthesizes current evidence on the mechanisms of action, clinical efficacy, safety profile, and modern selection strategies for bDMARDs/tsDMARDs, drawing on the 2022/2023 EULAR recommendations and major randomized controlled trials.

Results: TNF inhibitors, IL-6 receptor inhibitors, the T-cell costimulation blocker abatacept, the B-cell depleting agent rituximab, and JAK inhibitors act at distinct points in the immune cascade and produce comparable ACR20/50/70 response rates. Safety profiles differ by class: infection risk is common to all bDMARDs, while JAK inhibitors carry particular concern for venous thromboembolism and cardiovascular risk, IL-6 inhibitors for gastrointestinal perforation and lipid changes, and rituximab for hepatitis B reactivation. Modern practice emphasizes individualized selection based on comorbidities, cost reduction through the availability of biosimilars, and gradual dose tapering once sustained remission is achieved.

Conclusion: Biologic and targeted synthetic DMARDs represent a qualitative advance in RA treatment, but their safe and effective use requires thorough screening, regular monitoring, and individualized patient selection — an approach that, with the expanding availability of biosimilars, is increasingly feasible even in resource-constrained systems such as Uzbekistan's.

Keywords: Rheumatoid arthritis, biologic DMARD, TNF inhibitors, IL-6 inhibitors, rituximab, abatacept, JAK inhibitors, biosimilars, safety.

Methods

This work was prepared as a narrative literature review. A literature search was conducted in September 2026 using PubMed, the ACR and EULAR publication databases, and the websites of major rheumatology societies, with the search terms “rheumatoid arthritis,” “biologic DMARD,” “TNF inhibitor,” “tocilizumab,” “rituximab,” and “JAK inhibitor safety,” restricted to sources published in English between 2004 and 2026. Priority was given to the 2022/2023 EULAR management recommendations, major randomized controlled trials (ATTRACT, ARMADA, COMET, RADIATE, REFLEX, ATTAIN, AMPLE, ORAL Surveillance), and systematic reviews. Case reports and articles without accessible full text were excluded. A total of twelve sources meeting these criteria were selected and synthesized for this review.

Introduction

Rheumatoid arthritis is a chronic autoimmune polyarthritis characterized by synovial inflammation, autoantibody production (rheumatoid factor and anti-citrullinated protein antibodies), and progressive cartilage and bone destruction. First-line therapy conventionally remains methotrexate-based conventional synthetic DMARDs; however, a substantial proportion of patients fail to achieve the target disease activity (remission or low disease activity) with this therapy alone.

Over the past 25 years, the introduction of biologic DMARDs has transformed RA management: these agents act selectively at defined molecular points in the immunopathogenic cascade — TNF-α, IL-6, T-cell costimulation, or the B-cell population. They have been joined by targeted synthetic DMARDs such as JAK inhibitors, oral small molecules with comparable efficacy but a distinct safety profile.

The aim of this review is to summarize the mechanisms of action of biologic and targeted synthetic DMARDs, the evidence base for their clinical efficacy, their safety profile, and modern selection and sequencing strategies, and to consider their relevance to rheumatology practice in Uzbekistan.

Knowledge of biologic DMARDs is relevant to several areas of clinical practice, including:

- Rheumatology (drug selection, sequencing, monitoring)
- Infectious disease (tuberculosis and hepatitis reactivation screening)
- Oncology (long-term surveillance of malignancy risk)
- Cardiology (assessment of JAK-inhibitor-associated cardiovascular risk)
- Health-system management and pharmacoeconomics (cost reduction through biosimilars)

Mechanisms of Action and Classes of Biologic DMARDs

The pathogenesis of RA begins with activation of T cells by antigen-presenting cells through CD28–CD80/86 costimulation, followed by B-cell activation and the production of autoantibodies such as rheumatoid factor and anti-CCP. Activated immune cells release pro-inflammatory cytokines, principally TNF-α and IL-6, driving synovial inflammation, osteoclast activation, and cartilage/bone destruction.

Each class of biologic DMARD acts at a defined point in this cascade: abatacept blocks T-cell costimulation, rituximab depletes CD20+ B cells, TNF inhibitors neutralize free TNF-α or block its receptor binding, and IL-6 receptor inhibitors interrupt IL-6 signaling. JAK inhibitors, although not biologics, achieve a comparable end effect by blocking the intracellular signaling pathway downstream of cytokine receptors. These sites of action are shown in Figure 1, and a comparative summary of the classes is provided in Table 1.

Figure 1. Sites of Action of Biologic DMARD Classes in the RA Immunopathogenic Cascade

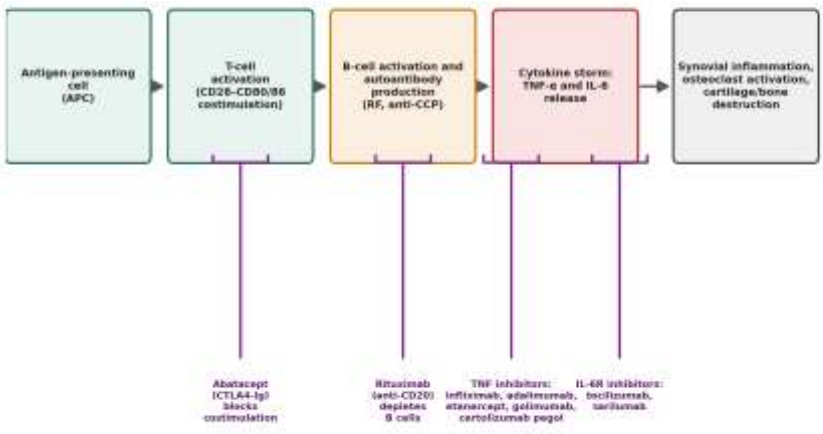

Figure 1. Sites of action of biologic DMARD classes in the RA immunopathogenic cascade: each stage, from T-cell costimulation through cytokine release, is blocked by a specific class of agent.

Table 1. Comparative Overview of Biologic and Targeted Synthetic DMARD Classes

Class	Target	Representative Agents	Route / Frequency
● **TNF inhibitors**	Tumor necrosis factor-alpha (TNF-α)	Infliximab, adalimumab, etanercept, golimumab, certolizumab pegol	IV (infliximab) or SC; every 2–4 weeks
● **IL-6 receptor inhibitors**	Interleukin-6 receptor	Tocilizumab, sarilumab	IV or SC; every 1–2 weeks
● **T-cell costimulation blocker**	CD28–CD80/86 costimulatory signal	Abatacept	IV or SC; SC — weekly
● **B-cell depleting agent**	CD20+ B lymphocytes	Rituximab	IV; 2 infusions (days 0 and 15), repeated every 6–12 months
● **JAK inhibitors (tsDMARD)**	Janus kinase (JAK1/JAK2/JAK3) signaling pathway	Tofacitinib, baricitinib, upadacitinib	Oral (tablet); once or twice daily

Clinical Efficacy: The Evidence Base

The efficacy of biologic DMARDs has been established in numerous large randomized, placebo-controlled trials. The ATTRACT trial showed that infliximab combined with methotrexate substantially slowed radiographic progression compared with methotrexate monotherapy. The ARMADA trial demonstrated that adding adalimumab significantly increased ACR20/50/70 response rates over methotrexate monotherapy. The COMET trial showed that etanercept combined with methotrexate in early, active disease achieved higher remission rates than methotrexate monotherapy.

For patients who fail to respond to TNF inhibition, alternative mechanisms have proven effective: the RADIATE trial showed significant clinical improvement with tocilizumab and the REFLEX trial with rituximab in patients refractory to anti-TNF

therapy, while the ATTAIN trial demonstrated the efficacy of abatacept in TNF-inhibitor-refractory RA. The AMPLE trial — a large head-to-head comparison of abatacept and adalimumab — found comparable efficacy and safety for both agents in combination with methotrexate, confirming that class selection often hinges on patient-specific factors such as comorbidities, convenience, and cost rather than on differences in efficacy.

Safety Profile and Monitoring

A risk common to all biologic DMARDs is serious infection due to immunosuppression, in particular reactivation of latent tuberculosis; consequently, QuantiFERON or tuberculin skin testing, chest radiography, and hepatitis B/C and HIV screening are mandatory before initiating therapy. Each class also carries additional, distinct risks: IL-6 receptor inhibitors may raise the lipid profile and, particularly in patients with a history of diverticulitis, increase the risk of gastrointestinal perforation; rituximab carries a risk of hepatitis B reactivation and, rarely, hypogammaglobulinemia; and JAK inhibitors, based on the findings of the ORAL Surveillance trial, are associated with an increased risk of venous thromboembolism, major cardiovascular events, and malignancy — particularly in patients aged 50 years or older with cardiovascular risk factors — which led the FDA to issue a boxed warning for this class. The principal risks and recommended screening by class are summarized in Table 2.

Table 2. Safety Profile of Biologic and Targeted Synthetic DMARD Classes

Class	Principal Risks	Pre-initiation Screening / Monitoring
● **TNF inhibitors**	Tuberculosis reactivation, serious infections, demyelinating disease, may worsen heart failure	QuantiFERON/tuberculin skin test, chest radiograph, hepatitis B/C, HIV screening
● **IL-6R inhibitors**	Elevated lipid profile, elevated liver enzymes, neutropenia, risk of gastrointestinal perforation (particularly with diverticulitis)	Lipid panel, liver enzymes, neutrophil/platelet counts; ask about diverticulitis history
● **Abatacept**	Infection risk (somewhat lower than TNFi), infusion reactions	TB and hepatitis screening (same as TNFi)

Class	Principal Risks	Pre-initiation Screening / Monitoring
● **Rituximab**	Infusion reactions, hypogammaglobulinemia, rare progressive multifocal leukoencephalopathy (PML)	Hepatitis B screening (higher reactivation risk), immunoglobulin levels
● **JAK inhibitors**	Increased venous thromboembolism, major cardiovascular events, and malignancy risk (ORAL Surveillance findings), herpes zoster	Assess cardiovascular and VTE risk; caution in patients ≥ 50 years or smokers

Modern Approaches: Individualized Selection, Sequencing, and Biosimilars

When methotrexate fails to achieve the treatment target, selection of the first bDMARD/tsDMARD is recommended based on the patient's comorbidities: TNF inhibitors should be avoided in patients with heart failure or a history of demyelinating disease, JAK inhibitors avoided in those with high cardiovascular or thromboembolic risk, and rituximab preferred in patients with a history of lymphoma. If the target is not achieved with the first agent, both switching to another molecule within the same mechanism and switching to a different mechanism entirely have been shown to be effective as second-line therapy; the choice often depends on the reason for the first therapy's failure (secondary versus primary non-response). This sequencing process is shown in Figure 2.

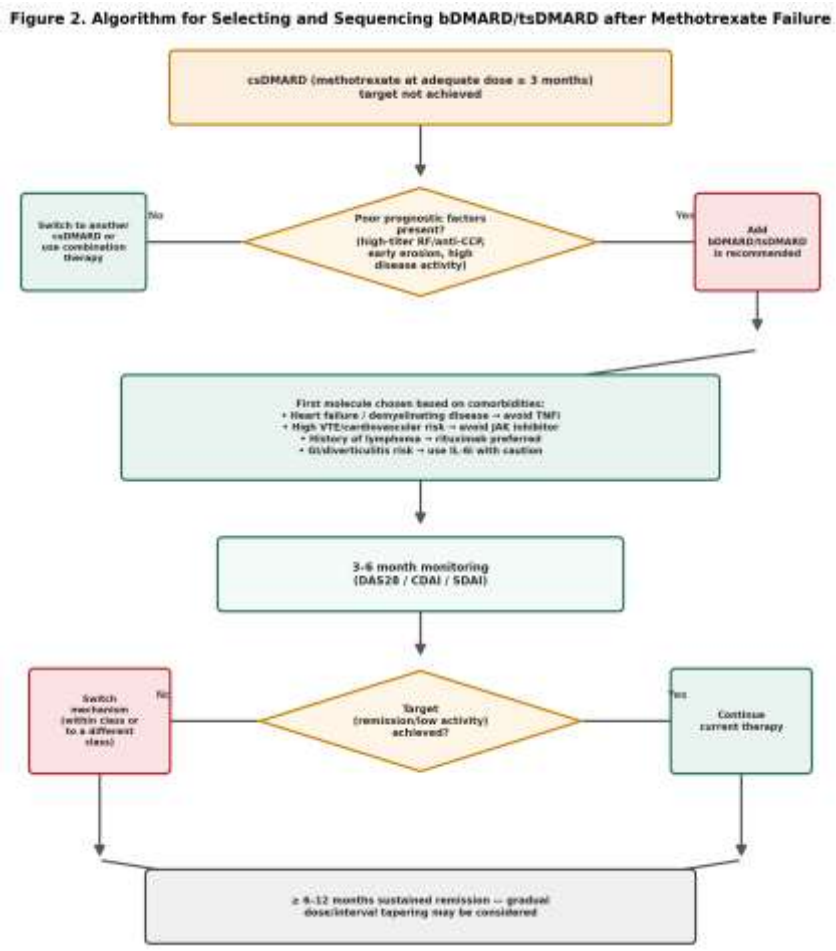

Figure 2. Algorithm for selecting and sequencing bDMARD/tsDMARD after methotrexate failure: comorbidity-based first selection, regular monitoring, mechanism switching, and gradual dose tapering once sustained remission is achieved.

The entry of biosimilars into the market — in particular biosimilars of infliximab, etanercept, and adalimumab — has substantially lowered the cost of this treatment class, an important development for expanding access to bDMARD therapy in resource-constrained healthcare systems such as Uzbekistan's. Once biosimilars pass rigorous comparability studies against the originator molecule, they are considered equivalent in clinical efficacy and safety. In patients who achieve sustained remission (typically 6–12 months), gradual dose or interval tapering may be considered, though this process should be carried out under close monitoring to minimize the risk of disease flare.

Conclusion

Biologic and targeted synthetic DMARDs have fundamentally expanded treatment options for patients with rheumatoid arthritis who fail to respond adequately to methotrexate, achieving high efficacy through selective action at defined points in the immune cascade. However, each class carries a distinct safety profile, and successful, safe

use requires thorough baseline screening, regular clinical and laboratory monitoring, and individualized selection matched to the patient's comorbidities.

For clinical practice, this translates into two practical priorities: matching molecule selection to the patient's risk profile, and maintaining systematic safety monitoring throughout treatment. Broader adoption of biosimilars, including within Uzbekistan's healthcare system, holds substantial potential to expand patient access to this highly effective treatment class, reduce long-term disability, and improve quality of life.

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