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A REVIEW ON RECENT ADVANCEMENTS IN BIOLOGICS FOR RHEUMATOID ARTHRITIS

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Abstract
Background: Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by synovial inflammation and joint destruction. Biologic therapies targeting specific immune pathways have revolutionized RA treatment.
Objective: To provide an up-to-date comprehensive review of recent advancements in biologic agents for RA, including their mechanisms, efficacy, safety, and therapeutic positioning.
Methods: This review synthesizes current evidence from clinical trials, meta-analyses, and guidelines focusing on tumor necrosis factor inhibitors, interleukin-6 receptor antagonists, B-cell depleting agents, T-cell costimulation modulators, Janus kinase inhibitors, and emerging biologics.
Results: Biologics significantly improve disease control and slow progression. Comparative efficacy varies by agent and patient profile, with safety concerns such as infections and cardiovascular risks warranting monitoring. Biosimilars are expanding accessibility. Gaps remain in long-term safety data and personalized treatment selection.
Conclusion: Biologic therapies have transformed RA management; future research should focus on individualized strategies, long-term outcomes, and global access improvements.
Keywords: Rheumatoid arthritis, biologic therapy, disease-modifying antirheumatic drugs, TNF inhibitors, Janus kinase inhibitors, biosimilars

INTRODUCTION
A systemic, chronic inflammatory disease that mostly affects synovial joints, rheumatoid arthritis (RA) causes pain, stiffness, swelling, and eventually joint destruction. Between 0.5% and 1% of people worldwide have RA, with women experiencing a higher frequency and the condition peaking between the ages of 30 and 60. Irreversible joint deformities, functional impairment, and an increased risk of death from related comorbidities including cardiovascular disease can result from poorly managed RA [1, 2].

The cornerstone of RA treatment has long been methotrexate and other conventional synthetic disease-modifying antirheumatic medications (csDMARDs). But a significant percentage of patients either have negative side effects or are unable to obtain sufficient illness control, which calls for the creation of more specialized treatments. Over the past 20 years, biologic DMARDs (bDMARDs) have revolutionized the treatment landscape by selectively targeting immune cells or pro-inflammatory cytokines implicated in the pathophysiology of RA [3].

This review aims to give a thorough and current summary of the most recent developments in biologic medicines for the treatment of RA. Tumor necrosis factor (TNF) inhibitors, interleukin (IL)-6 receptor antagonists, B-cell depleting agents, T-cell costimulation blockers, and Janus kinase (JAK) inhibitors are among the established and novel biologics whose mechanisms of action, clinical efficacy, safety profiles, and role in therapy are examined. Novel biologics in late-stage clinical trials and biosimilars that are progressively making their way onto the market are given particular consideration.

There are still a number of gaps in the literature despite biologics' clinical effectiveness. There is a dearth of long-term safety data, especially in practical contexts.

Furthermore, there are few head-to-head comparison trials between the more recent biologics, and research is currently ongoing to find predictive biomarkers for individualized treatment selection. Optimal biologic use is further complicated by issues such immunogenicity, high treatment costs, and restricted access in areas with limited resources [4,5].

In the rapidly developing field of RA biologic therapy, this review aims to summarize the available data and point out potential avenues for further study and clinical use.

RHEUMATOID ARTHRITIS CLASSIFICATION AND OVERVIEW OF BIOLOGIC THERAPIES

The treatment of rheumatoid arthritis (RA) has changed because to biologic disease-modifying antirheumatic medications (bDMARDs), especially for patients who do not respond well to traditional synthetic DMARDs (csDMARDs). The molecular targets of biologics, which are essential to the pathophysiology of RA, determine their classification. These consist of intracellular signaling pathways include the Janus kinase (JAK) pathway, T-cell costimulatory molecules, B cells, interleukin-6 (IL-6) receptors, and tumor necrosis factor-alpha (TNF-α).

Inhibitors of Tumor Necrosis Factor (TNF-α)

One important pro-inflammatory cytokine that is essential to the pathophysiology of RA is TNF-α. It has been demonstrated that TNF-α inhibition improves physical function, slows joint degradation, and lowers synovial inflammation (6). Infliximab, etanercept, adalimumab, certolizumab pegol, and golimumab are the five TNF inhibitors that are presently authorized for clinical use in RA.

- Infliximab is an intravenous chimeric monoclonal antibody.
- Edanercept is a subcutaneous injection of a soluble TNF receptor fusion protein;
- Adalimumab, Certolizumab Pegol, and Golimumab are monoclonal antibodies that are entirely human.

Methotrexate and TNF inhibitors are frequently used together to increase therapeutic response and lessen the development of anti-drug antibodies. However, because of their immunogenicity, they may lose their effectiveness with time and are linked to an increased risk of infections, including reactivation of tuberculosis [1, 7].

Inhibitors of Interleukin-6 (IL-6) Receptors

Another important cytokine linked to both systemic and joint-specific inflammation in RA is IL-6. Active RA is associated with higher levels of IL-6, which are linked to joint injury and disease activity [8].

Both tocilizumab and sarilumab are monoclonal antibodies that reduce downstream inflammatory signaling by blocking IL-6 receptors; they can be administered alone or in conjunction with methotrexate to treat mild to severe RA [9].

In patients who have not responded to TNF inhibitors, IL-6 inhibitors have shown promise. On the other hand, they could result in negative consequences as gastrointestinal perforation, lipid abnormalities, raised liver enzymes, and neutropenia (10).

B-cell Depleting Agents

By producing autoantibodies and presenting antigens, B cells contribute to RA. Rituximab is a chimeric monoclonal antibody that selectively depletes B cells by targeting the CD20 antigen on B cells.

- Rituximab is usually used following an insufficient response to TNF medications and is especially beneficial in seropositive RA patients [11].
- It has a comparatively long dosing interval (every six months) and is given as an intravenous infusion. Hepatitis B virus reactivation and infusion responses are frequent adverse consequences. Progressive multifocal leukoencephalopathy (PML) is an uncommon but dangerous risk [12].

T-cell Costimulation Modulators

T-cell activation plays a key role in the initiation and perpetuation of autoimmune responses in RA. Abatacept is a fusion protein that inhibits T-cell activation by interfering with CD80/CD86–CD28 interactions.

- Abatacept is used in patients with moderate to severe RA who have failed other DMARDs, including TNF inhibitors.
- It can be administered intravenously or subcutaneously and has shown favorable efficacy and safety in older adults and those with comorbidities [13].

Adverse effects are generally mild, with infections and infusion reactions being the most common.

Janus Kinase (JAK) Inhibitors

JAK inhibitors are small-molecule drugs that interfere with intracellular signaling pathways used by various cytokines. Although not biologics in the strict sense, they are often discussed alongside bDMARDs due to their targeted mechanism.

- **Tofacitinib**, **baricitinib**, **upadacitinib**, and **filgotinib** are JAK inhibitors approved for use in RA.
- These agents are orally administered and provide a convenient alternative to parenteral biologics.

JAK inhibitors have demonstrated non-inferiority or superiority to TNF inhibitors in several head-to-head trials [14]. However, they are associated with increased risks of thromboembolic events, herpes zoster, elevated lipids, and cardiovascular events, especially in high-risk patients [15].

Emerging Biologics and Biosimilars

Emerging biologics include therapies targeting granulocyte-macrophage colony-stimulating factor (GM-CSF), IL-17, and bispecific antibodies that target multiple inflammatory pathways. Additionally, the rise of **biosimilars**-cost-effective alternatives to originator biologics-is expanding access to RA treatment globally.

- Biosimilars for adalimumab, etanercept, and infliximab have demonstrated comparable efficacy, safety, and immunogenicity in large clinical trials [16].

- Their adoption is expected to reduce healthcare costs and improve accessibility in resource-limited settings.

COMBINATION THERAPIES AND TREATMENT STRATEGIES IN RHEUMATOID ARTHRITIS

Combination therapy in rheumatoid arthritis (RA) has long been a cornerstone of disease management, particularly for patients with inadequate response to monotherapy. The primary goal remains achieving sustained remission or low disease activity using a treat-to-target (T2T) approach, as recommended by both ACR and EULAR guidelines [30,31].

csDMARD Combinations

Combination of conventional synthetic DMARDs (csDMARDs)-typically methotrexate (MTX), sulfasalazine, and hydroxychloroquine, known as "triple therapy"—has shown comparable efficacy to some biologic DMARDs in early RA [32,33]. This strategy is especially cost-effective and may delay the need for biologics in resource-limited settings [34].

csDMARD + bDMARD or tsDMARD

Biologics (bDMARDs) and targeted synthetic DMARDs (tsDMARDs), such as JAK inhibitors, are frequently combined with methotrexate to enhance efficacy and prevent anti-drug antibody formation, particularly in TNF inhibitors [35,36]. For example, the combination of adalimumab and MTX provides superior ACR responses compared to either drug alone [37].

However, in patients who are intolerant to methotrexate, IL-6 receptor inhibitors like tocilizumab have demonstrated comparable efficacy as monotherapy [38]. Likewise, JAK inhibitors (e.g., tofacitinib, baricitinib) have shown effectiveness both as monotherapy and in combination with csDMARDs [39].

Sequential and Step-Up Approaches

Treatment strategies may involve sequential escalation (step-up) or early aggressive therapy (step-down) based on disease severity. Some trials support early intensive combination therapy as a way to induce remission early and maintain long-term functional outcomes [40].

Step-up therapy-starting with monotherapy and escalating to combinations based on response—is more common in routine practice and reflects real-world decision-making [41]. These strategies often rely on close monitoring and objective disease activity scoring (e.g., DAS28) [30].

Safety and Monitoring in Combination Therapy

Combination regimens increase the risk of adverse events, including infections, liver toxicity, and cytopenias, necessitating regular monitoring of liver enzymes, CBC, and renal function [42]. Risk mitigation strategies, including vaccination and TB screening, are essential before initiating bDMARDs or JAK inhibitors [43].

COMPARATIVE EFFICACY AND SAFETY OF BIOLOGIC AGENTS

The availability of multiple biologic therapies for rheumatoid arthritis (RA) provides clinicians with options for tailoring treatment to individual patient profiles. However, direct comparisons among these agents are limited. Most data are derived from randomized controlled trials (RCTs) versus placebo or conventional DMARDs, and only a few head-to-head studies have been conducted. Despite this, systematic reviews and network meta-analyses offer valuable insights into the relative efficacy and safety of various biologics.

Comparative Efficacy

TNF inhibitors have historically been considered the standard biologic treatment. However, other biologics, such as **tocilizumab**, **abatacept**, and **rituximab**, have demonstrated comparable efficacy in csDMARD- or TNF-inhibitor inadequate responders.

- A 2021 network meta-analysis showed that **tocilizumab and tofacitinib** had slightly higher efficacy in achieving ACR50 and DAS28 remission scores compared to TNF inhibitors (17).
- **Abatacept** was found to be non-inferior to adalimumab in a head-to-head trial when both were used with methotrexate, with slightly fewer adverse events reported in the abatacept group (18).
- **Baricitinib and upadacitinib** have shown superior efficacy to adalimumab in some trials, especially in early disease, although long-term safety is still under review [19].

Biologic-naïve patients often show better responses to any bDMARD than those previously treated with biologics, highlighting the importance of early intervention [20].

Comparative Safety

While all biologics carry an increased risk of infection, including **tuberculosis, pneumonia**, and **opportunistic infections**, the degree of risk varies:

- **TNF inhibitors** are associated with a higher risk of **tuberculosis reactivation**, especially infliximab and adalimumab [21].
- **IL-6 inhibitors** and **JAK inhibitors** tend to elevate **lipid profiles**, but cardiovascular outcomes remain unclear [22].
- **Rituximab** has a relatively lower infection risk but may cause **late-onset neutropenia** and **HBV reactivation** [23].
- **JAK inhibitors** (e.g., tofacitinib, baricitinib) are linked with **venous thromboembolism**, **zoster reactivation**, and **increased cardiovascular risk**, leading to FDA safety warnings in high-risk populations [24].

Tolerability also varies, with **injection site reactions** more common with subcutaneous agents, while **infusion reactions** are notable with intravenous biologics like rituximab and infliximab.

Table 01: Summary of Biologic Agents in RA – Efficacy and Safety Profile

Biologic Class	Drug Example	Administration	Efficacy (vs TNF inhibitors)	Key Adverse Effects	Monitoring Required
TNF inhibitors	Adalimumab, Etanercept	SC/IV	Baseline	TB reactivation, infections	TB screening, CBC, LFTs
IL-6 inhibitors	Tocilizumab, Sarilumab	SC/IV	Comparable or superior	Elevated lipids, neutropenia	Lipid panel, LFTs, CBC
B-cell depletion	Rituximab	IV	Comparable	Infusion reaction, HBV reactivation	HBV screen, CBC, renal function
T-cell modulator	Abatacept	SC/IV	Non-inferior to adalimumab	Headache, infections	Periodic infection screening
JAK inhibitors	Tofacitinib, Baricitinib	Oral	Superior in some studies	VTE, zoster, elevated lipids	CBC, lipids, HZV screen

Abbreviations: SC – subcutaneous; IV – intravenous; CBC – complete blood count; LFTs – liver function tests; TB – tuberculosis; VTE – venous thromboembolism; HZV – herpes zoster virus

5. PERSONALIZED MEDICINE AND BIOMARKER-GUIDED THERAPIES IN RA

The shift from a "one-size-fits-all" model toward personalized medicine in rheumatoid arthritis (RA) aims to tailor treatment based on individual disease profiles, treatment response, and risk factors. This strategy holds the potential to improve therapeutic outcomes, minimize adverse effects, and optimize healthcare resources [44,45].

Current Use of Biomarkers in RA

Despite decades of research, biomarker use in RA remains largely confined to diagnosis and prognosis rather than treatment selection. Rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibodies (anti-CCP) are standard diagnostic markers and are associated with more aggressive disease and erosive progression [46]. Acute-phase reactants such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are routinely used to monitor disease activity but lack predictive specificity for therapeutic response [47].

Emerging Biomarkers for Treatment Stratification

Several novel biomarkers are under investigation to guide biologic therapy selection:

- **Gene expression profiles:** Transcriptomic signatures from synovial biopsies or peripheral blood mononuclear cells have shown potential in predicting response to TNF inhibitors and JAK inhibitors [48].
- **Serum cytokine levels:** Elevated IL-6 or GM-CSF may predict favorable response to IL-6 inhibitors or anti-GM-CSF biologics, respectively [49].
- **Drug-specific antibodies:** Anti-drug antibodies (ADA), especially to TNF inhibitors, correlate with reduced efficacy and can guide switching therapies [50].

Pharmacogenetics and Precision Dosing

Pharmacogenetic studies have identified polymorphisms in genes such as *PADI4*, *PTPN22*, and *HLA-DRB1* that influence RA susceptibility and possibly treatment response [51]. While still largely investigational, future implementation of genetic testing may allow clinicians to stratify patients before initiating biologic or JAK inhibitor therapy.

Therapeutic drug monitoring (TDM) of biologics, particularly anti-TNF agents, is increasingly employed to adjust dosing based on drug trough levels and ADA presence. This approach can help distinguish between pharmacokinetic failure and true pharmacodynamic resistance [52].

NOVEL AND EMERGING THERAPIES ON THE HORIZON FOR RA

Despite advances in biologics and small molecules, a significant proportion of RA patients fail to achieve sustained remission. Novel therapies are currently in development or early clinical use, targeting previously unexplored pathways or improving on existing strategies through enhanced selectivity, safety, and personalization [55].

Next-Generation Cytokine Inhibitors

Recent biologics aim to more precisely modulate the immune system by selectively targeting key cytokines:

- **Anti-GM-CSF agents:** Granulocyte-macrophage colony-stimulating factor (GM-CSF) is a pivotal driver of synovial inflammation. Agents such as **namilumab** and **otilimab** have shown promising efficacy in early-phase trials, particularly in patients with inadequate response to TNF inhibitors [56, 57].
- **IL-17 and IL-23 blockers:** Although more prominent in psoriatic arthritis, agents like **bimekizumab** and **guselkumab** are under investigation for RA, especially in seronegative subtypes [58].

Novel JAK Inhibitors and TYK2 Inhibitors

The Janus kinase (JAK)-STAT pathway remains a major focus. Newer agents such as **deucravacitinib** (a TYK2 inhibitor) are designed to offer improved safety profiles by avoiding JAK1/2 inhibition, thus reducing the risk of infections, thrombosis, and cytopenias [59]. Additionally, **selective JAK1 inhibitors** like **filgotinib** and **abrocitinib** are under active evaluation in phase III trials [60].

Small Molecule Inhibitors Targeting Novel Pathways

- **BTK inhibitors**: Bruton's tyrosine kinase (BTK) plays a role in B-cell activation and macrophage signaling. Agents like **evobrutinib** and **fenebrutinib** are in advanced clinical trials for RA [61].
- **Syk inhibitors**: Spleen tyrosine kinase (Syk) is involved in intracellular signaling from Fc receptors and B-cell receptors. **Fostamatinib** was previously explored and new analogs are being optimized for safety [62].

Cell-Based and Gene Therapies

Emerging research is exploring **mesenchymal stem cell (MSC) therapy** and **T-cell modulation** as long-term immune rebalancing options. Additionally, **gene editing technologies** like CRISPR/Cas9 are being studied to regulate cytokine gene expression in preclinical models [63, 64].

Nanomedicine and Drug Delivery Platforms

Nanotechnology-based drug delivery systems aim to enhance targeted delivery of DMARDs and biologics to inflamed synovial tissue while reducing systemic side effects. Liposomal formulations and antibody-drug conjugates (ADCs) are currently being investigated in preclinical and early-phase clinical trials [65].

TREATMENT SELECTION STRATEGIES AND CLINICAL GUIDELINES

Effective management of rheumatoid arthritis (RA) relies on timely initiation and appropriate selection of therapeutic agents, including biologics. With a growing number of biologic and targeted synthetic DMARDs available, treatment selection must be guided by **clinical guidelines**, **patient-specific factors**, and **disease characteristics**.

International Clinical Guidelines

Major rheumatology organizations such as the **American College of Rheumatology (ACR)** and the **European Alliance of Associations for Rheumatology (EULAR)** have published evidence-based guidelines for RA treatment.

- **ACR 2021 Guidelines** recommend starting with **csDMARDs** (typically methotrexate), followed by **bDMARDs or targeted synthetic DMARDs (tsDMARDs)** in patients with moderate to high disease activity who do not respond adequately within 3–6 months [25].
- The **EULAR 2020 Guidelines** similarly recommend methotrexate as first-line, but emphasize rapid escalation and early introduction of bDMARDs or tsDMARDs in poor prognostic cases, such as seropositivity, early erosions, or high disease activity [26].

Factors Influencing Biologic Selection

Treatment choice among biologics is **not one-size-fits-all** and is influenced by several clinical factors:

- **Previous treatment response**: Patients who fail TNF inhibitors may respond better to non-TNF biologics like rituximab or tocilizumab.
- **Comorbidities**:
  - **Rituximab** is preferred in patients with **lymphoproliferative disorders**.
  - **Abatacept** may be favored in patients with **chronic lung disease** due to a lower risk of infection.
  - **JAK inhibitors** should be used cautiously in patients with **cardiovascular risk factors** or history of **thrombosis** [27].
- **Patient preference and convenience**: Oral agents (e.g., JAK inhibitors) may be more acceptable for some patients compared to parenteral biologics.
- **Reproductive status**: TNF inhibitors (especially certolizumab pegol) have the most safety data in **pregnancy** [28].

Treat-to-Target Approach

Both ACR and EULAR endorse a **treat-to-target (T2T)** strategy, which aims for **low disease activity or remission** using validated tools like DAS28 or CDAI.

- Therapy should be adjusted every 1–3 months until the target is achieved.
- Once stable, treatment can be tapered cautiously but not stopped abruptly, especially in patients with a history of aggressive disease [26].

Biosimilars in Practice

Biosimilars are increasingly used as first-line or switch options due to cost-effectiveness.

- Guidelines support switching to biosimilars from originator biologics when clinically appropriate, provided pharmacovigilance is maintained and patients are informed (29).
- The decision should consider local regulatory approval, pricing, and access policies.

CHALLENGES AND FUTURE DIRECTIONS

While biologic therapies have significantly transformed the treatment landscape of rheumatoid arthritis (RA), several challenges persist in achieving optimal disease control across all patient populations. These issues underscore the need for continued innovation and refinement of therapeutic strategies.

Unmet Needs in Treatment Response and Remission

Despite the availability of multiple biologic classes, approximately 30–40% of RA patients fail to achieve sustained remission or exhibit only partial responses to first-line biologics, particularly TNF inhibitors [66]. A significant proportion develop **secondary non-response** due to immunogenicity, while others exhibit **primary inefficacy**, often related to underlying disease heterogeneity [67].

Safety and Long-Term Risks

Biologics and JAK inhibitors carry increased risks of infections, cardiovascular events, and malignancies, especially with prolonged use [68, 69]. The **FDA's black box warning** on JAK inhibitors (e.g., tofacitinib) highlights the need for stringent safety monitoring and risk stratification tools [70].

Limited Predictive Biomarkers

The lack of validated biomarkers to predict therapeutic response, especially to newer biologics, remains a major barrier. Current biomarkers such as anti-CCP and RF offer diagnostic but not predictive utility [71]. Ongoing research is exploring **multi-omics approaches** to personalize therapy but integration into clinical practice is limited by cost, accessibility, and standardization [72].

Access, Cost, and Equity

Biologics are **expensive**, posing significant barriers to access, particularly in low- and middle-income countries. Although the emergence of **biosimilars** has improved affordability, issues related to interchangeability, physician acceptance, and regulatory frameworks continue to hinder global equity in RA care [73].

Future Directions

Key future goals in RA management include

- ***Precision Medicine***: Integration of genomics, proteomics, and machine learning to personalize biologic selection [74].
- ***Early Intervention***: Optimizing therapy initiation in preclinical or early RA phases to prevent irreversible damage [75].
- ***Oral biologics and novel targets***: Research is expanding into oral protein therapies and novel immunological targets beyond cytokines, including fibroblast activation protein (FAP) and NETosis pathways [76].
- ***Digital health***: Use of wearable technologies and AI-powered dashboards to monitor disease activity remotely and enable real-time treatment adjustments [77].

CONCLUSION

Biologic therapies have significantly improved the management of rheumatoid arthritis, offering targeted intervention for patients who do not respond to conventional DMARDs. Agents such as TNF inhibitors, IL-6 receptor antagonists, B-cell depleting therapies, and T-cell costimulation modulators have demonstrated substantial benefits in reducing disease activity, slowing radiographic progression, and improving quality of life. The emergence of Janus kinase inhibitors and biosimilars further expands the therapeutic arsenal, increasing accessibility and convenience for diverse patient populations. Despite these advancements, challenges remain, including safety concerns, high costs, variability in patient response, and the absence of predictive biomarkers for treatment selection.

Future research should focus on personalized medicine approaches, long-term real-world safety data, and head-to-head trials comparing biologics across disease stages and comorbidity profiles. Additionally, efforts to improve global access to biologic and biosimilar therapies are essential for equitable RA care. As understanding of RA pathophysiology deepens, next-generation biologics and combination strategies may offer even more precise and effective disease control.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Not Applicable

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