Allergologia et immunopathologia
Sociedad Española de Inmunología Clínica, Alergología y Asma Pediátrica
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REVIEW ARTICLE

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The efficacy and safety of biologic or targeted synthetic DMARDs in rheumatoid arthritis treatment: one year of review 2024

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Received 28 November 2024; Accepted 25 January 2025
Available online 1 May 2025

KEYWORDS
b/ts DMARDs;
JAK;
IL-6;
rheumatoid arthritis;
TNF-α

Abstract
Background: Both articular and extra-articular structures are affected by rheumatoid arthritis (RA), a chronic inflammatory rheumatic illness that results in severe joint destruction, disability, and death. To increase the response rate and provide RA patients more options, there is an unmet need for the development of innovative treatment drugs. Evaluation of cellular, cytokine, genomic, and transcriptome profiles that would predict therapeutic response to biologic or targeted disease-modifying anti-rheumatic drugs (DMARDs) with various action modes is necessary for a customized therapy plan in RA. Owing to the development of new biologic medicines that target distinct mechanisms of action, the treatment algorithm for RA has undergone significant modification during the last one to two decades. More patients are now able to undergo biologic therapy early in the progression of their illness, thanks to the availability of less expensive biosimilars.
Objective: To summarize the efficacy and safety of biologic or targeted syntheticb/ts DMARDs in RA treatment based on the publications in the past year.
Material and Methods: We compiled the most recent findings from original research publications of 2024 about the effects of b/tsDMARDs on the treatment of RA. In addition, this review article also concluded the recent findings from original research publications of the year 2024 about the effects of b/tsDMARDs biosimilars for treating RA.
Conclusion: This article summarizes the evidence and safety of biologic DMARDs (bDMARDs) or targeted synthetic DMARDs (tsDMARDs) in the management of RA, including those that target tumor necrosis factor alpha, interleukin (IL)-6, B cells, T-cell co-stimulation, and Janus kinase (JAK) from original research articles published in 2024.

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https://doi.org/10.15586/aei.v53i3.1278

Introduction

Inflammation is a hallmark of rheumatoid arthritis (RA), a chronic autoimmune illness. Patients with RA frequently experience bilateral joint stiffness, swelling, and discomfort.[1] The etiology and pathophysiology of RA are unknown and incredibly complex. They include epigenetic changes, environmental stimuli, and inheritance.[2] RA is a global health issue that affects around 240 out of every 100,000 individuals. Furthermore, since the world's population is aging quickly, the prevalence of RA is increasing globally.[3] Moreover, when RA progresses, harm to extra-articular organs and systems may happen. According to epidemiological data, people with RA have a 3–10 years lower life expectancy than people in the general population because they are more likely to experience cardiovascular (CV) effects, infections, pulmonary diseases, and various types of cancers.[4,5] Thankfully, early detection of the condition, and the significant progress in managing RA over the past 10 years, can result in better health outcomes, quicker attainment of treatment objectives, and preservation of joint functions.[6]

The first-line management options for RA are disease-modifying anti-rheumatic drugs (DMARDs), which help to attenuate clinical manifestations as well as slow the course of joint deterioration. A significant percentage of patients are either nonresponders or insufficient responders to conventional synthetic DMARDs (csDMARDs), despite the fact that these medications are linked with better results.[7] In the last one to two decades, the development of biologic DMARDs (bDMARDs) or targeted synthetic DMARDs (tsDMARDs) has completely changed the way RA is treated. According to the updated 2022 European Alliance of Associations for Rheumatology (EULAR) guidelines, short-term bridging glucocorticoids (GCs) and a single csDMARD, such as methotrexate (MTX), should be used to treat RA.[8] In cases where methotrexate is contraindicated or intolerant, other csDMARDs include leuflunomide or sulphasalazine. bDMARDs or tsDMARDs may be appended as the second phase of therapy in patients with unfavorable prognostic factors if clinical improvement is not observed at 3 months or if the treatment goal (remission or state of low disease activity [LDA]) is not reached at 6 months.

The first class of bDMARDs to be licensed for the management of RA was anti-tumor necrosis factor (TNF) biologics. Several biologic agents that target interleukin (IL)-6, B cells, and co-stimulation of T cells were studied in RA. In the arsenal of RA treatment, there are now a number of specific tsDMARDs that mark the Janus kinase–signal transducer and activator of transcription (JAK-STAT) pathways. In this review article, we compiled the most recent findings from original research publications of 2024 about the effects of b/tsDMARDs on the treatment of RA (Figure 1). Besides, biosimilar drugs are potentially low-cost versions that have been used in RA treatment and have the potential to improve access to therapy.[9,10] Moreover, several systematic reviews have compiled evidence on similar efficacy and safety between biosimilars and reference products for RA at both qualitative and quantitative levels.[11,12] International guidelines and consensus recommend biosimilars for RA management.[8,13-16] Thus, this review article also concluded the recent findings from original research publications of the year 2024 about the effects of b/tsDMARD biosimilars for treating RA.

TNF-α inhibitors (TNFi)

TNF-α is essential to the pathophysiology of RA. Both synovium and synovial fluid are discovered to contain it.[17] The pathophysiology of inflammatory osteolysis, osteoclast recruitment, and bone destruction are dependent on TNF-α; thus, it is essential for bone deterioration.[18] The addition of TNF-α inhibitors to the RA therapy regimen has considerable improved the quality of life, joint injury prevention, and recovery of physical functions. Additionally, it is now easier to maintain control over RA manifestations.[19] TNFi may weaken the immune system and raise the risk of severe infections, although it prevents TNF-α from stimulating proinflammatory pathway.[20] For instance, JAK inhibitors (JAKi) and TNFi were used to treat a 59-year-old male with RA who developed iatrogenic Kaposi sarcoma.[21] According to a case series, TNFi caused systemic lupus erythematosus in RA patients, suggesting that systemic lupus erythematosus should be monitored in RA patients receiving TNFi treatment.[22] Although each TNFi had a unique positive adverse drug event (ADE), a real-world analysis based on the US Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) database revealed that there were four common ADEs among TNFi: infection, pulmonary TB, hypersensitivity, and herpes zoster.[23] TNFi administered to RA patients were linked to the development of Merkel cell cancer.[24] As a result, TNFi are now the first option for RA patients who are intolerant of or do not respond to bDMARD treatment with csDMARDs. So far, six TNF-α targeted biologic agents—adalimumab, golimumab, certolizumab, etanercept, infliximab, and ozoralizumab—have received global approval for managing moderate-to-severe RA.

Adalimumab

A critical component of the biologic treatment of RA is adalimumab, a TNFi that binds to TNF-α and prevents TNF-mediated cellular inflammation. Globally, it is among the most commonly prescribed biologic drugs.[25] Adalimumab, either by itself or in conjunction with csDMARDs, such as methotrexate, has been shown in clinical trials and real-world investigations to considerably lower disease activity and improve patient outcomes.[26,27]

Fifty-six RA patients who did not respond to methotrexate were treated with adalimumab according to established therapeutic guidelines in a prospective, observational, single-center research. Twenty-four (42.9%) patients failed the American College of Rheumatology (ACR) 20 response after receiving continuous adalimumab treatment for 12 weeks.[28] According to a retrospective analysis of 105 RA patients that received either adalimumab or etanercept, adalimumab outperformed etanercept in terms of a numerically higher response rate and comparable adverse effects.[29] Tripterygium wilfordii Hook F could be an alternative management for the RA patients intolerant to methotrexate, according to the results of a multicenter, open-label, randomized controlled clinical trial that treated 64 RA patients with inadequate response to

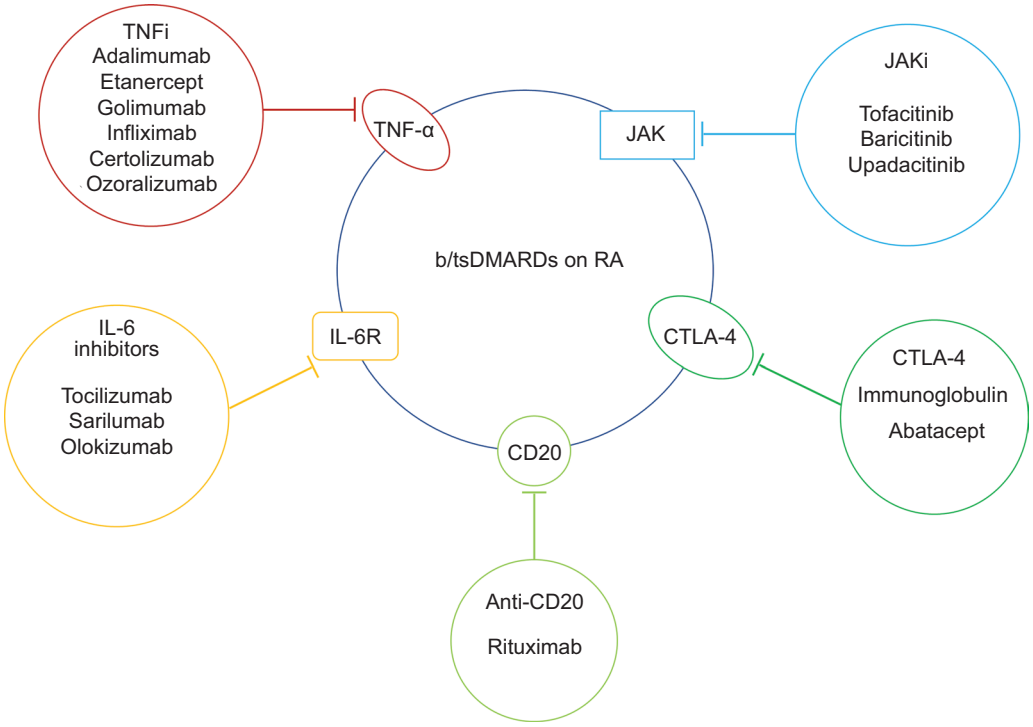

Figure 1 b/tsDMARDs for RA treatment. TNFis (i.e., adalimumab, etanercept, golimumab, infliximab, certolizumab, and ozoralizumab), IL-6 inhibitors (i.e., tocilizumab, sarilumab, and olokizumab), anti-CD20 (rituximab), CTLA-4 immunoglobulin (abatacept), and JAKis (i.e., tofacitinib, baricitinib, and upadacitinib) were summarized in this mauscript for the treatment of RA.

methotrexate with either adalimumab in combination with tripterygium wilfordii Hook F or methotrexate with tripterygium wilfordii. No significant differences in efficacy and safety was observed between adalimumab combined with tripterygium wilfordii Hook F and adalimumab combined with methotrexate.[30] According to a population-based cohort research, adalimumab and infliximab were linked to the longest drug survival periods among late-onset RA patients, compared to early-onset patients when it came to drug survival on first biologic therapy.[31] Adalimumab-treated RA patients had a decreased incidence of dyslipidemia than tofacitinib-treated RA patients, according to a real-world cohort research involving 7580 patients; however, there were no differences in major adverse CV events (MACEs) or all-cause mortality.[32] A 47-year-old female with RA who was diagnosed with multiple sclerosis was treated with adalimumab for 2 years.[33] According to Shirah et al., a patient with RA experienced demyelination of the central nervous system because of adalimumab.[34]

Additionally, a few biosimilars of adalimumab have also shown promising results in treating RA because of their lower cost, bioequivalence efficacy, and safety. Phase I and III clinical trials, pre-clinical and analytical data, and proof of similar efficacy, pharmacokinetics, safety, and immunogenicity profiles of the reference adalimumab were the basis for the 2017 European approval of adalimumab biosimilar SB5.[35] Patients with RA who started routine SB5 medication as their first adalimumab (naïve) or when they switched from another adalimumab (switched) were the subjects of a 12-month observational, multi-center cohort trial. The results showed that naïve patients' 12-month remission/low-activity proportions for RA were 58%, significantly higher than baseline, while switched patients' remission proportions were constant between baseline and month 12 (M12) for all reasons.[36] With a safety profile in keeping with the one reported for other biosimilars, a retrospective and multicenter investigation demonstrated that adalimumab biosimilar MSB11022 preserved the efficacy advantages offered by prior adalimumab therapies.[37] Adalimumab and biosimilar (GP2017) patient groups did not differ in disease activity levels, according to Colina et al.[38] During the first 18 months of treatment, all scores dropped dramatically across all treatments. They hit a low point at 24 months, which persisted for as long as 48 months, suggesting that adalimumab biosimilars were just as effective as their original medications over an extended period.

Etanercept

The recombinant human TNF receptor p75Fc fusion protein etanercept, which binds to either soluble or transmembrane TNF-α, is the first TNFi approved by the US FDA for rheumatic diseases.[39] According to a population-based cohort research comparing the drug survival on first biologic therapy among late-onset RA patients to those with early-onset RA, etanercept was linked to the longest drug survival period of the first biologic in early-onset patients.[31] According to the propensity score-matched analysis from the Czech ATTRA registry, patients with RA treated with etanercept had a longer median survival period than those treated with monoclonal antibody tumor necrosis factor-α

inhibitors.[40] A two-year pragmatic, randomized CareRA2020 trial assessing the efficacy of methotrexate and bridging glucocorticoids with or without early introduction of a 6-month course of etanercept in early RA discovered that adding etanercept for 6 months did not improve disease control over 104 weeks, compared to adding leflunomide first in early insufficient responders. However, etanercept's brief introduction resulted in better disease management immediately following randomization and fewer patients on b/tsDMARDs at 104 weeks.[41]

Regarding safety, a 68-year-old RA patient experienced aseptic meningitis during etanercept and methotrexate treatment, according to Kassabian et al.[42] A 35-year-old female with RA since the age of 18 years developed clinical manifestations similar to multiple sclerosis as a result of using etanercept.[43] Ramsay Hunt syndrome was identified in a 38-year-old RA patient receiving etanercept.[44] A 67-year-old male with RA on etanercept therapy developed pulmonary embolism (PE).[45] One patient using methotrexate and etanercept for RA developed multifocal leukoencephalopathy.[46] According to a population-based cohort study on the incidence and risk factors of stopping tofacitinib and bDMARDs (etanercept, adalimumab, golimumab, tocilizumab, or abatacept) in RA patients, etanercept had the highest proportion (43.27%), while tofacitinib had the lowest proportion (21.8%) of drug discontinuation. Higher steroid dosage and concurrent connective tissue diseases were identified as risk factors for stopping the medication.[47]

Numerous etanercept biosimilars have been used in clinical settings. According to an open-label, randomized, comparative, multicenter report evaluating biosimilar etanercept's efficacy, safety, and immunogenicity in RA patients, compared to the reference formulation of original etanercept, the American College of Rheumatology 20 (ACR20) response proportions in the biosimilar etanercept and etanercept groups were 82.3% and 90.9%, respectively, with no significant difference. Furthermore, there were no appreciable variations in the frequency of adverse responses or incidents, regardless of their intensity, between the two groups. According to the findings, the reference formulation and biosimilar etanercept were identical.[48]

According to a retrospective 12-month follow-up research, RA patients who used the original etanercept to achieve remission were able to keep it going even after switching to biosimilar YLB113.[49] Following the release of etanercept biosimilar, a 49-year-old female with RA acquired antimelanoma differentiation-associated gene 5 antibody-positive dermatomyositis.[50] Etanercept biosimilar LBEC0101 and reference were compared for safety and efficacy in RA patients using the Kyoto University Rheumatoid Arthritis Management Alliance (KURAMA) cohort. According to the results, LBEC0101 and the reference product were comparable in terms of continuation rate, introduction efficacy, and impact permanence both before and after switching in clinical practice.[51]

According to Colina et al.,[38] no variations in disease activity levels were observed between patient groups receiving etanercept and biosimilars (GP2015/SB4). During the first 18 months of treatment, all scores dropped dramatically across all treatments. The scores hit a low point at 24 months, which persisted for as long as 48 months, suggesting that biosimilars are just as effective as their original medications over an extended period. Owing to the relative efficacy of etanercept originator and biosimilar in treating RA, treatment persistence was comparable when taking either one of the two.[52] The European Commission has approved SDZ ETN as an etanercept biosimilar for the same indications as the reference etanercept, including RA, axial-spondyloarthritis (axSpA), psoriatic arthritis (PsA), and juvenile idiopathic arthritis (JIA). SDZ ETN has been approved by the US FDA to treat ankylosing spondylitis (AS), RA, PsA, and JIA.[53] According to a multi-country COMPACT research, At 12 months, patients with PsA, axSpA, or RA receiving SDZ ETN demonstrated good treatment persistence.[54] According a matched-analysis of the BSRBR-RA, among terms of disease activity and treatment persistence, individuals who transitioned from etanercept originator to etanercept biosimilar among 1024 RA patients appeared to perform similarly, compared to those who remained on originator.[55] In a JET observational study carried out in Japanese clinical practice, the treatment continuity, utility, and nocebo effect of transferring from the original etanercept to its biosimilar in patients with RA were investigated. Even in ordinary clinical practice at rheumatology clinics in Japan, the results showed that moving from etanercept to biosimilar was successful, and no nocebo effects were observed.[56]

Golimumab

Approved to treat rheumatic illnesses, golimumab is a fully humanized monoclonal IgG1κ antibody with a high affinity for TNF-α.[57,58] The GO-BEYOND study, which was conducted from 2017 to 2019, involved 39 RA patients who were started on golimumab following the failure of a first-line TNFi. Of these patients, 80% achieved at least LDA, with 60% achieving complete remission, and 88.2% showed a good/moderate EULAR response after a 12-month follow-up.[59] A pooled analysis of European prospective observational studies showed improvements in disease activity, quality of life, and treatment persistence rate without any new safety signals when golimumab was used to treat patients with active RA, PsA, or axSpA who had not responded to treatment with an initial TNFi.[60] A *post hoc* analysis of the GO-FORTH research employing cluster analysis for efficacy of golimumab in RA patients at high risk of a bad prognosis discovered that the drug was efficacious in a subset of RA patients at high risk of poor prognostic characteristics. For this cohort, a dose of 100 mg would be more beneficial in halting radiographic progression.[61] A cohort study of RA patients' self-reported experiences and satisfaction with golimumab and etanercept therapies discovered no differences between the two groups' satisfaction levels with global disease improvement, symptom alleviation, and speed of action. In contrast to the etanercept group, the golimumab group experienced less discomfort, swelling, pain, and burning, and was more satisfied with the global injection experience, injection device, frequency, and convenience.[62] Golimumab has six distinct positive ADEs, such as pneumonia cryptococcal, device failure, pneumonia bacterial, device issue, pneumocystis pneumonia, polyneuropathy, etc., according to a real-world study from the US FAERS database for the safety of TNFi.[23] An 87-year-old female RA

patient who was on golimumab and methotrexate experienced severe pneumocystis pneumonia.[63]

Infliximab

A chimeric monoclonal antibody called infliximab exhibits high affinity for both membrane-bound and soluble forms of TNF-α. According to a population-based cohort research, both adalimumab and infliximab were linked to the longest drug survival periods among late-onset RA patients, compared with early-onset patients when it came to drug survival on first biologic therapy.[31] In a study on the features and 6-month results of RA patients, beginning infliximab biosimilar IFX-dyyb in a real-world setting, the Clinical Disease Activity Index (CDAI) remained constant in patients switching from reference infliximab/IFX biosimilar, but improved in patients switching from a non-IFX b/tsDMARD and in b/tsDMARD-naïve patients.[64] When compared to originators, such as infliximab, etanercept, and adalimumab, an observational analysis on the French National Health Data System revealed that the safety and persistence of biosimilar TNFi were reassuring.[65]

Based on the US FAERS database for safety of TNFi, a real-world study discovered that infliximab has 60 different positive ADEs, such as Hodgkin's disease, metastatic neoplasm, non-Hodgkin's lymphoma, and others.[23] After receiving long-term treatment with methotrexate, leflunomide, and infliximab, a 60-year-old female with more than 10 years of RA developed an actinomycosis infection.[66] Infliximab-induced plaque psoriasis eruption on the palms and soles occurred in a 70-year-old female with a RA history.[67] A 25-year-old female with RA using infliximab was diagnosed with new-onset uveitis after presenting with bilateral impaired vision.[68] A female with RA was suspected of having colitis brought on by rituximab.[69] After receiving treatment with methotrexate, bucillamine, prednisolone, and infliximab for RA, a 73-year-old female was diagnosed with the disease at the age of 60.[70]

Certolizumab

A PEGylated, Fc-free TNFi is certolizumab. Numerous clinical trials that demonstrated a significant and long-lasting reduction in disease manifestations, suppression of illness progression, and improvements in physical performance and quality of life have encouraged the global adoption of certolizumab for the management of RA. Certolizumab pegol's safety and efficacy in Japanese RA patients were confirmed by a post-marketing surveillance trial that lasted for up to 3 years.[71] Certolizumab has 24 distinct positive ADEs, according to a real-world study from the US FAERS database for the safety of TNFi. These include exposure by the mother before becoming pregnant, early rupture of the membranes, exposure through breast milk, erysipelas, low birth weight, herpes virus infection, premature delivery, and staphylococcal sepsis.[23]

Ozoralizumab

The sixth TNF inhibitor approved in Japan, ozoralizumab, was approved in September 2022. It is a ground-breaking next-generation TNFi known as Nanobody®, which has changeable heavy-chain domains of heavy-chain-only antibodies. No new safety issues were discovered in an integrated analysis of the OHZORA, NATSUZORA, and HOSHIZORA studies, and long-term ozoralizumab treatment preserved efficacy in RA patients.[72] An 81-year-old female patient with RA, who had not reacted favorably to previous TNFi, experienced heart failure with reduced ejection fraction following her first dose of ozoralizumab.[73]

IL-6 inhibitors

Interleukin-6 is a key target for therapies that aim to reduce the systemic and local inflammatory features of RA.[74] It plays a significant role in the pathophysiology of RA by regulating the chronic inflammation that underlies both local and systemic clinical manifestations of RA through cell signaling influenced by membrane-bound and soluble IL-6 receptor (IL-6R).[75,76] Significantly elevated IL-6 levels in RA, in conjunction with many growth factors mostly generated by macrophages and synovial-like fibroblasts, are essential for the clinical course of the illness. Because IL-6 is harmful and mediates inflammation and context-driven signaling, blocking it could be a powerful target for RA treatment.

Tocilizumab

By blocking both soluble and membrane-bound IL-6 receptors, tocilizumab, the first IL-6 inhibitor to be approved, lowers the inflammatory cascade. With a low risk of immunogenicity and a flexible administration method (subcutaneous or intravenous), tocilizumab can be self-administered once a week.[77] Tocilizumab-treated 189 RA patients displayed notably lower levels of all disease activity indices than the control group in a prospective observational analytical analysis.[78]

In a Saudi Arabian single-center research, RA patients treated with tocilizumab experienced greater mean decrease in their levels of erythrocyte sedimentation proportion and C-reactive protein (CRP) than those treated with adalimumab and etanercept, although at a higher cost.[79] In a multicenter, post-marketing, non-interventional, observational study of the persistence of subcutaneous tocilizumab as monotherapy or in combination with csDMARDs in RA patients, it was determined that the drug was a very safe and effective treatment option for patients with moderate-to-severe RA in Greece.[80] Real-world experience from the TReasure Registry (a multicentre, web-based registry of RA and spondyloarthritis patients across Turkey), which demonstrated notable decrease in the disease activity score-28 as well as in the simplified disease activity index (SDAI), CDAI, and health assessment questionnaire (HAQ) scores, corroborated the impact of tocilizumab in managing RA with a good safety profile.[81] When tocilizumab, sarilumab, and olokizumab were compared for efficacy and safety in individuals with active RA, they were discovered to be more effective than adalimumab and to have comparable efficacy and safety in RA patients who did not respond well to methotrexate.[82] According to a Korean multi-center registry research involving 893 patients, tocilizumab was discovered to have a considerably lower treatment discontinuation rate than TNFi in biologic-naïve patients with RA, especially those with anemia.[83] Infliximab-induced plaque psoriatic eruption of the palms and soles occurred in a 70-year-old female with a RA history. It recurred after tocilizumab relay and disappeared following tocilizumab interruption.[67]

After using tocilizumab for 2 years to treat RA, a 75-year-old female was diagnosed with liver dysfunction a year later. Additional investigation revealed that tocilizumab caused iron buildup.[84] Following the administration of methotrexate and tocilizumab, a 59-year-old female RA patient developed medication-related osteonecrosis of the jaw.[85] The safety outcomes of tocilizumab and tofacitinib in RA patients were compared using data from the Taiwan National Health Insurance Research Database. The findings indicated that the incidence proportions of other safety concerns and mortality proportions were similar in both groups, with a lower incident rate of herpes zoster in the tocilizumab group.[86] Prosthetic infections were reported by RA patients treated with tocilizumab.[87] In contrast to TNFi-treated and bDMARD-naïve RA patients, a Danish cohort study discovered that in a real-world setting, treating RA patients with tocilizumab/sarilumab did not increase their chance of acquiring cancer.[88]

In a phase 3 randomized, double-blind, active-controlled clinical trial, individuals with moderate-to-severe RA who did not respond well to methotrexate were compared with the tocilizumab reference product using the tocilizumab biosimilar BAT1806/BIIB800 for analysis of two treatment periods (weeks 24 to 48), the tocilizumab, tocilizumab to BAT1806/BIIB800, and BAT1806/BIIB800 groups were shown to have similar effectiveness, safety, immunogenicity, and pharmacokinetic profiles.[89] A double-blind, randomized phase III study discovered that tocilizumab biosimilar CT-P47 or tocilizumab (8 mg/kg) given every 4 weeks to RA patients demonstrated efficacy equivalence as well as comparable pharmacokinetic, safety, and immunogenicity profiles between CT-P47 and tocilizumab, including after switching from tocilizumab to CT-P47.[90] According to a randomized double-blind study, the suggested biosimilar MSB11456 and the tocilizumab reference product had the same level of safety and efficacy in patients with moderate-to-severe RA.[91] According to a phase 3 randomized, multicenter, double-blind, active-controlled clinical trial, BAT1806/BIIB800 demonstrated similar safety, immunogenicity, and pharmacokinetic characteristics to cilizumab, along with equivalent effectiveness.[92]

Sarilumab

Human monoclonal antibody sarilumab stops IL-6 from binding to membrane-bound and soluble IL-6R-α. It can be used to treat RA in adults either alone or in combination with csDMARDs.[93,94] A 1-year PROspective sarilumab (preFILled syringe/pen) international observational (PROFILE) trial revealed that sarilumab treatment enhanced physical performance and quality of life while lowering the CDAI score. With 66.2% of patients reporting a treatment-emergent adverse event (TEAE) or serious adverse event (SAE), neutropenia was the most frequently reported TEAE of interest.[95] Tocilizumab, sarilumab, and olokizumab were discovered to be more successful than adalimumab when assessed for efficacy and safety in people with active RA. They also showed comparable efficacy and safety in RA patients who did not respond well to methotrexate.[82] In an interim analysis of a post-marketing surveillance for the safety and effectiveness of the medication in Japanese RA patients who had not responded to previous treatments, sarilumab was well tolerated and no new safety signals were discovered.[96] A multicenter, retrospective, inverse probability of treatment-weighted analysis based on the Fukuoka RA Biologics (FRAB) Registry discovered that sarilumab's effectiveness was unaffected by body mass index (BMI), comorbidities, methotrexate use, or the number of prior b/tsDMARDs.[97] Furthermore, there were no apparent additional safety concerns in RA patients. In a Japanese population with RA, data from an interim analysis of a post-marketing monitoring study showed that sarilumab was well tolerated by RA patients, with no new safety signals, regardless of the age group.[98] In contrast to TNFi-treated and bDMARD-naïve RA patients, a Danish cohort study discovered that in a real-world setting, treating RA patients with tocilizumab/sarilumab did not increase their chance of acquiring cancer.[88] According to Tada et al., sarilumab was effective in treating RA without causing a recurrence of lymphoproliferative diseases, and two individuals with RA flared after stopping methotrexate because of these conditions.[99]

Olokizumab

A new IL-6 inhibitor called olokizumab has shown promising results in RA patients.[100] The results of a Clopidogrel for the Reduction of Events During Observation (CREDO) I, a randomized controlled trial (RCT), comparing the effectiveness of olokizumab subcutaneous injections at a dose of 64 mg every 2 and 4 weeks, versus placebo, in 428 RA patients were recently published by Nasonov et al.[101] Compared to a placebo, the treatment with olokizumab (of regimens) produced clinically and statistically significant improvements in all patient-reported outcomes (PRO), including pain, exhaustion, and functional impairment, in a timely and meaningful manner.[101] A total of 183 patients with moderate-to-severe RA activity were included in an open-label observational non-interventional trial. Every 4 weeks, all patients got injections of olokizumab, 64 mg, along with methotrexate. The Disease Activity Score in 28 joints (DAS28)-CRP dropped to 3.3 ± 0.9 ($P < 0.001$) after 6 months, and a statistically significant decrease was observed in fatigue, patient global assessment (PGA), pain intensity, and functional impairment. In 24 weeks, the percentage of patients with Central Sensitization Inventory (CSI) score > 40 dropped from 71.0% to 21.0% ($P < 0.001$), and the percentage of patients with PainDETECT score > 18 dropped from 21.5% to 13.2%. Steroid use dropped from 54.2% to 32.6%, while use of nonsteroidal anti-inflammatory drugs (NSAID) dropped from 70.8% to 33.8% ($P < 0.001$). Three patients experienced serious events, while 14.2% of patients reported adverse effects. Olokizumab is useful in managing chronic pain associated with nociceptive system dysfunction and lowering RA activity.[102] According to Lee et al., olokizumab at 64 mg/kg every 2 or 4 weeks produced a prominent ACR20 response relative to placebo.[103]

During the COVID-19 epidemic, it was demonstrated that RA patients could safely and effectively switch from rituximab to olokizumab. TJC28 significantly decreased after 8 and 12 weeks of treatment, and TSC28 decreased after 4, 8, and 12 weeks of treatment with olokizumab, according to the findings of a 12-week open-label, non-interventional study on the safety and effectiveness of olokizumab therapy in patients with RA who had switched from rituximab during the SARS-CoV-2 pandemic.[104]

The safety and effectiveness of olokizumab plus methotrexate were examined over 106 weeks of treatment using pooled data from three randomized clinical trials followed by an open-label extension study. The findings demonstrated that the efficacy of olokizumab was sustained through week 106 and that the long-term safety and tolerability of olokizumabin combined with methotrexate remained stable.[105] Tocilizumab, sarilumab, and olokizumab were discovered to be more effective than adalimumab and to have comparable efficacy and safety in RA patients who did not respond well to methotrexate, according to a network meta-analysis of RCTs comparing the efficacy and safety of these medications in RA patients.[106]

Anti-CD20

It's still unclear how exactly B cells enhance RA pathophysiology.[107] The identification of autoantibodies directed against citrullinated peptides (anti-CCPs) was linked to the resurgence of interest in B cells in RA. Because B cells also produce pro-inflammatory cytokines[108] and act as antigen-presenting cells,[109] reduction of B cells has been explored as a potential therapy approach for RA.

Rituximab

The CD20 protein on the surface of B lymphocytes carrying this antigen is the target of rituximab, a mouse/human chimeric monoclonal antibody. B cells in bone marrow and synovial tissue are somewhat depleted with rituximab treatment, while B cells in peripheral blood are temporarily but almost completely reduced.[110] In patients who are not responding to traditional and other bDMARDs, rituximab, an approved and successful medication for the treatment of RA, has been demonstrated to reduce disease manifestations.[111,112] Early RA patients who get repeated management with rituximab + methotrexate report better physical functioning and better clinical results at the 2-year follow-up.[113,114]

A single dose of either 1000-mg rituximab + 100-mg methylprednisolone and antihistamines or a placebo was administered to 78 RA-risk patients in a phase II randomized, double-blind, and placebo-controlled clinical trial. In seropositive RA-risk patients, 1000-mg rituximab demonstrated a considerable delay in the onset of arthritis by up to 12 months;[115] however, there was no appreciable and noteworthy improvement in patient-reported outcomes over a 2-year follow-up period.[116] A 104-week open-label multicenter randomized controlled superiority trial comparing treat-to-target fixed-dose rituximab retreatment and fixed interval retreatment with disease activity-guided rituximab dose optimization for RA patients was described by De Meyst et al.[117] Compared to JAKi, IL6Ri, and TNFi, the patients with difficult-to-treat RA (D2TRA) showed a higher proportion of survival following rituximab treatment.[118] According to 15 years of data from the Quebec registry RHUMADATA, rituximab seems to be the most effective course of treatment for RA patients who did not respond to a first-line TNFi.[119] In clinical practice, the reduced dosage of rituximab is successful for many RA patients and results in relevant reduction in dose, according to a retrospective cohort analysis of RA patients with mild disease activity on rituximab.[120]

Adalimumab medication led to the diagnosis of multiple sclerosis in a 47-year-old RA patient, who subsequently experienced free manifestations after switching to rituximab.[33] In an 83-year-old male, RA and anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis were successfully treated with rituximab.[121] A 31-year-old female patient with RA and TNFi-induced immunoglobulin A (IgA) vasculitis was effectively treated with rituximab and methotrexate.[122] The treatment (rituximab and methotrexate, and hydroxychloroquine) showed good response and resolved anasarca and albuminuria in a 45-year-old female with verified membranous nephropathy and RA.[123]

In RA patients receiving rituximab, a retrospective cohort study was performed to examine the incidence, timing, and dose-dependency of infections. The findings revealed that, among 490 patients, 819 infections occurred over 1254 patient years, with respiratory tract infections being the most common type of infection. Additionally, compared to 500- and 1000-mg rituximab, ultra-low dosages (200 mg) are linked to a decreased incidence of infections in RA.[124] RA patients who responded to conventional doses of rituximab were discovered to benefit from long-term usage of ultralow dosages of the drug, according to the observational extension of the REDO (REtreatment with Rituximab in RhEmatoid arthritis: Disease Outcome after Dose Optimization) study.[125] After 34 patients received 76 infusions, data from a Tertiary Veterans Affairs Center for the analysis of safety in RA patients with the implementation of an accelerated infusion protocol (90-min infusion) of rituximab revealed that only two infusion-related reactions were noted: one was chest pain and dyspnea, and the other was itching and sore throat.[126] According to a Danish cohort research, rituximab treatment for RA patients did not raise their risk of developing cancer in a real-world context, compared to the TNFi-treated and bDMARD-naïve RA patients.[88] According to a retrospective cohort research for the examination of cancer risk following the use of bDMARD or tsDMARD, rituximab was linked to a higher incidence of incident cancer than TNFis.[127]

CTLA-4 immunoglobulins

T cells penetrate the synovial membrane in RA patients, where they activate synovial fibroblasts and macrophages and turn them into effector cells that damage tissues.[128] For complete T-cell activation, first a specific antigen must be recognized by a T-cell receptor, followed by a co-stimulatory signal, such as the binding of cluster of differentiation (CD)80 and/or CD86 on the surface of antigen-presenting cells to the CD28 receptor on T cells. Activated T cells express cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), which binds to CD80 and CD86 more firmly and strongly than CD28, thereby acting as a negative regulator of T cell-mediated immune responses.

Abatacept

By preventing co-stimulation, the CTL4-Fc fusion protein abatacept prevents T-cell activation.[129] Abatacept binds specifically to CD80 and CD86, thereby inhibiting T-cell activation.[130] DAS28-CRP significantly decreased in 53 RA patients who received continuous abatacept medication

for 3 months or a longer period, and the decline in DAS28 was age-related.[131] After 274 patients received abatacept, their CDAI scores after 4, 12, 24, and 52 weeks were considerably lower than their baseline scores. At 4, 12, and 24 weeks, however, the impact of abatacept on CDAI scores was noticeably greater than that of the baricitinib group.[132] According to a retrospective cohort trial, abatacept, when used as a first-line biologic for patients with RA that is anti-citrullinated protein antibody (ACPA)- and rheumatoid factor-positive, improved clinical outcomes and remission rates at 3, 6, and 12 months.[133] According to a population-based cohort research, abatacept was linked to a longer medication survival period for patients with early onset as opposed to those with late onset.[31] Comparing the performance of abatacept and TNFi in RA patients who are anti-citrullinated protein antibodies and shared epitope positive, analyses revealed that abatacept outperformed TNFi in terms of efficacy results.[134] In order to assess the effectiveness and safety of abatacept in preclinical RA, Asif et al. implemented a systematic review and meta-analysis of RCTs.[135] Their findings indicated that abatacept is a promising treatment option for delaying the onset of RA in high-risk individuals with a positive safety profile.

A 3-year efficacy and safety was validated by the interim findings of ORIGAMI, a long-term observational multicenter research conducted in Japan. Additionally, the study identified potential determinants linked to J-HAQ remission in biologic-naïve RA patients receiving abatacept in actual clinical settings.[136] According to a study on the drug's clinical effectiveness and retention in RA patients, the 24-month retention rate of abatacept was 59.9%. Abatacept was also linked to better clinical results and was well-tolerated in Taiwan's real-world environment.[137] When methotrexate is not used at the beginning of the treatment, abatacept is the most commonly used medication, followed by IL-6 receptor inhibitor, according to a retrospective hospital-based administrative claims database study for the disease-modifying antirheumatic drug selection in Japanese patients with RA treated with biologics or JAK inhibitors without methotrexate.[138] A 6-month, multinational, multicenter, double-blind, placebo-controlled trial discovered that abatacept medication lowers MRI inflammation, clinical manifestations, and the risk of RA in high-risk individuals.[139] The intervention's effects last for a year-long drug-free observation period. A randomized, double-blind, multicentre, parallel, placebo-controlled, phase 2b clinical trial discovered that blocking T-cell co-stimulation with abatacept for a year slows the development of RA. Following the course of treatment, there is evidence of continued efficacy and no new safety concerns.[140]

Hypervirulent *Klebsiella pneumoniae* was detected in a 79-year-old male with RA using abatacept.[141] Abatacept was used for 7 months to treat RA in a female in her seventies who was diagnosed with eruptions similar to Mycosis fungoides.[142] According to a retrospective cohort study, in the first 2 years following the start of biologic or tsDMARDs, RA patients starting abatacept, rituximab, and JAKis showed higher incidence rates and statistically significant higher risks of incident cancers than those starting TNFis.[127] According to a Danish cohort research, in a real-world scenario, RA patients treated with abatacept did not have higher cancer risks than those treated with TNFi or bDMARD-naïve RA patients.[88] Comparing patients treated with abatacept to those treated with csDMARDs or other b/tsDMARDs, the results of a 10-year international post-marketing research did not reveal a statistically significant increase in the risk of total malignancies in pooled data.[143] However, relative to csDMARDs, a thorough assessment of observational data and RCTs revealed a possible increase in the incidence of nonmelanoma skin cancer with abatacept treatment.[144]

JAK inhibitors

tsDMARDs known as JAK inhibitors prevent certain cytokines from signaling intracellularly.[145,146] TYK2, JAK1, JAK2, and JAK3 are the four JAK isoforms. While JAK3 is mostly expressed in vascular smooth muscles, endothelial, and hematopoietic cells, JAK1, JAK2, and TYK2 are present in nearly all cells. Different JAK proteins are connected to the corresponding signal transducers and transcription activators (STAT1–STAT6). Different JAK-STAT combinations determine which immunological activities are mediated and which cytokine signaling pathways these molecules are involved in.[145-147] Common γ-chain cytokines, including IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21, for instance, mediate lymphocyte growth, proliferation, and homeostasis via signaling through JAK1 and JAK3. IL-6, IL-11, IL-12, IL-27, leukemia inhibitory factor, and oncostatin M use JAK1, JAK2, and TYK2 in the development of T cells and inflammation. Common ß-chain cytokines, such granulocyte, granulocyte–monocyte colony-stimulating factors, erythropoietin, thrombopoietin, IL-3, and IL-5, only entail JAK2 signaling. These cytokines are involved in myelopoiesis, erythropoiesis, thrombopoiesis, and allergy reactions. Type I interferons, which signal through JAK1 and TYK2, include IFNα and IFNß, IL-10, IL-20, IL-22, and IL-28. They mainly mediate autoimmunity, B cell development, and innate immune responses. Finally, through IFNγ, IL-12, and IL-23 signaling, JAK1 and JAK2 contribute to inflammation and antiviral immunity.[145,147] These details are important because the safety and efficacy characteristics of different JAK inhibitors may be determined by their unique cytokine inhibition patterns.[145-147]

A total of 18 RCTs totaling 21,432 patients and 57,040 patient-years were included in a traditional and Bayesian network meta-analysis of randomized clinical trials to report on the CV safety of JAKi or tocilizumab class in comparison to TNFi in RA patients. Findings demonstrated that, in comparison to TNFi, JAKi was associated with a non-statistically significant increase in the risk of severe adverse CV events and all-cause deaths. According to Bayesian analysis, the JAKi group had a higher clinical probability of experiencing significant adverse CV events and all-cause deaths more frequently than the TNFi group.[148] JAK drugs (upadacitinib, baricitinib, tofacitinib, and filgotinib) helped 48.89% of patients reach remission and 26.67% achieve low activity in a single-center observational, descriptive, retrospective study of RA patients. There have been reports of adverse effects or consequences, including herpes zoster infection, increased transaminase levels, and minor upper respiratory tract infections (pharyngitis/pharyngotonsillitis).[149] Colonization of *Pneumocystis jirovecii* is about six times

more likely to occur in RA patients taking bDMARDs (such as TNFi [etanercept, adalimumab, and golimumab], IL-6 inhibitors [tocilizumab], CTLA-4 inhibitors [abatacept], and anti-CD20 Ab [rituximab]) or JAKi (tofacitinib, baricitinib, and upadacitinib).[150]

In patients with D2TRA and those without D2TRA, JAKi significantly decreased CDAI-LDA.[151] JAKi effectively decreased disease activity in D2TRA patients up to the same degree as active non-D2TRA patients, and tolerability profiles were comparable, according to a real-world evaluation of the efficacy and tolerability profile of JAKi in D2TRA patients. The results were primarily influenced by the presence of age and/or CV risk factors.[152]

According to a propensity score-matched study comparing creatine kinase elevation brought on by JAKi and IL-6 inhibitors in RA patients, mild creatine kinase elevations with JAK inhibitors were not a specific clinical issue, and creatine kinase elevation may be unique to JAK inhibitors.[153] Remission rates with JAKi were significantly greater in RA patients who did not respond well to methotrexate, according to a network meta-analysis comparing the relative remission proportions of JAK inhibitors and adalimumab in patients with active RA.[154]

Tofacitinib, baricitinib, upadacitinib, filgotinib, and peficitinib are the five JAK inhibitors approved for the treatment of RA. Upadacitinib and filgotinib mostly inhibit JAK1, while tofacitinib preferentially inhibits JAK1 and JAK3, and baricitinib inhibits JAK1 and JAK2, and so on.[146,147]

Tofacitinib

The first JAK inhibitor approved for the treatment of autoimmune illnesses was tofacitinib (JAK1/JAK3, with limited efficacy against JAK2). For this reason, maximum information is available for the medication. According to study findings, tofacitinib is safe and effective if used in conjunction with other csDMARDs to treat PsA, SpA, and RA.[155,156]

In comparison to the reference strategy, which included the four classes of biologics commonly used in France (TNFi, tocilizumab, abatacept, and rituximab), a multistate Markov model analysis revealed that the introduction of tofacitinib was a dominant strategy. This strategy also produced maximum cost savings and increased quality-adjusted life period by 0.29 years.[157] According to a study on the safety and effectiveness of tofacitinib in RA, 9 years of real-world data showed that the drug was consistently successful, with notable decrease in disease activity indices at 3 and 6 months after beginning tofacitinib.[158]

According to the Oral Surveillance clinical trial, tofacitinib was shown to have a higher risk of major adverse cardiovascular event (MACE) and malignancies (apart from nonmelanoma skin cancer [NMSC]) than TNFi. A multicenter, observational, prospective cohort trial (CANTORAL) included 504 adult Canadian patients with moderate-to-severe RA starting tofacitinib. These patients were separated into cardiovascular (CV), risk-enriched (CV+), and CV- cohorts. The findings demonstrated that CDAI-LDA and remission rates in CV+ and CV- cohorts were 51.5%/54.6% and 12.0%/19.6%, respectively, at month 6; DAS28-4(CRP) $< 3.2/ < 2.6$ rates were 44.0%/39.3% and 31.5%/28.8%, respectively; and the efficacy was mostly sustained through month 18. In both cohorts, the side effects included safety, TEAEs, SAEs, fatalities, serious infections, herpes zoster, MACE, malignancies (not including NMSC), NMSC, and venous thromboembolism (VTE).[159]

According to a retrospective research, tofacitinib in combination with bDMARDs was discovered to be both safe and effective for RA patients not responding well to bDMARDs.[160] According to clinical trials and real-world data, tofacitinib monotherapy showed clinically significant responses/persistence in RCT/LTE analyses, with effectiveness and persistence comparable to combo therapy.[161]

According to the Tofacitinib in Rheumatoid Arthritis a Real-Life experience in Italy (ToRaRI), there were advantages in adopting tofacitinib as first-line therapy, demonstrating that the drug was safe, efficacious, and could increase remission rates in patients who were unfamiliar with bDMARDs.[162] The interim analysis of post-marketing surveillance in Japan showed that disease activity improved over a 6-month period, and safety was consistent with the characteristics of RA patients receiving tofacitinib.[163] Regardless of the regimen, line of therapy, period of beginning, or dose, tofacitinib efficacy (CDAI-LDA) was demonstrated in a real-world US patient scenario with RA, according to results from the CorEvitas Rheumatoid Arthritis Registry.[164]

According to a prospective observational analysis, the remission rates of tofacitinib and TNFi groups at 12 months did not differ significantly. Regarding safety, tofacitinib had more adverse events (AEs) than TNFi; however, both groups experienced SAEs at similar proportions.[165] Tofacitinib was associated with greater proportions of PE and VTE than TNFi, and these proportions were mostly stable across time.[166] Patients with RA receiving tofacitinib and baricitinib were more likely to become infected than those receiving subcutaneous bDMARDs.[167] A *post hoc* analysis of a phase 3b/4 randomized safety study discovered no difference between tofacitinib and TNFi in terms of the risk of composite CV endpoints, which comprise all ischemic CV events and heart failure.[168] Patients on tofacitinib experienced higher proportion of AEs, such as major adverse CV events and malignancies other than nonmelanoma skin cancer, than those on TNFi, according to a *post hoc* analysis of the ORAL surveillance trial.[169] Comparing generic tofacitinib to its original manufacturer, a prospective longitudinal cohort trial in RA patients revealed that it was more cost-effective and had comparable clinical efficacy and safety.[170]

The safety outcomes of tofacitinib and tocilizumab in RA patients were compared using data from the Taiwan National Health Insurance Research Database. The results showed that death proportions and other safety concerns were similar in both groups, even though the tocilizumab group had fewer herpes zoster incidents.[86] According to a real-world cohort research with 7580 individuals, RA patients treated with tofacitinib had a greater incidence of dyslipidemia than RA patients treated with adalimumab; nevertheless, MACE and all-cause mortality did not vary.[32]

One RA patient using tofacitinib was reported to have a significant lung nodule.[171] A RA patient on tofacitinib had disseminated cryptococcosis that manifested as a widespread cutaneous manifestation.[172] After receiving tofacitinib therapy, a 70-year-old female with RA who had bilateral hip replacements later experienced a prosthetic joint infection caused by Listeria monocytogenes.[173] On the sixth day after starting tofacitinib, a 58-year-old Tunisian

female with a 4-year history of RA developed severe pancreatitis.[174] Tofacitinib-treated RA patients frequently develop herpes zoster, and recent usage of bDMARDs (TNFi, tocilizumab, or abatacept) increased the likelihood of developing herpes zoster.[175]

Baricitinib

JAK1/JAK2 is selectively inhibited by baricitinib. Its effectiveness in RA has been revealed in a number of phase III studies.[176,177] In the Mahmoud et al. trial, 334 RA patients were divided into three groups[178]: the first group received baricitinib (4 mg daily), the second group received TNFi (golimumab at 50 mg/month, etanercept at 50 mg/week, and adalimumab at 40 mg/2 weeks), and the third group received cDMARDs. According to the findings, at weeks 12 and 24, patients in the baricitinib group showed a substantial improvement in all end measures, including TJC, SJC, VAS, DAS28, CDAI, HAQ-DI, ACR20, ACR50, and ACR70. Baricitinib performed noticeably better than cDMARDs and on par with TNF inhibitors. Infection, GIT, and CVS problems were the most frequent adverse outcomes in the baricitinib group. However, this study was a single-center experiment; thus, multicenter studies are recommended to support the results. According to the composite measures of disease activity 28-joint count and CDAI, after roughly 6–12 months of treatment, 40.7–93.8% and 55.6–88.0% of patients achieved remission and LDA, respectively, according to real-world data analyzed by Edwards et al.[179] This suggests that baricitinib monotherapy can be a suitable treatment option in routine clinical practice for patients with RA. However, several limitations were there in this study. First, the conclusions were limited by the inconsistent categories of data provided by each registry and the different trends observed across registries. Second, the number of patients with post-baseline data available for composite measures was low in each registry and the number of patients with missing data was not available. Third, the patients included in the registries reviewed may not be representative of patients currently eligible for baricitinib monotherapy, limiting the generalizability of findings. Fourth, it was unable to consider the safety of baricitinib monotherapy, as only the Erlangen baricitinib cohort data included safety information.

Results of a long-term study to assess the effectiveness of baricitinib in patients with moderate-to-severe RA up to 6.5 years of treatment showed that treatment with 4 mg or 2 mg of baricitinib was effective for up to 6.5 years, with maintained LDA/remission results across SDAI, CDAI, and DAS28-hsCRP consistent with previously published data.[180] However, the included patients were fully LTE-compliant, which was one of the limitations of this descriptive study. Besides, the fact that a large proportion of patients were discontinued before the final study visit when the sponsor ended LTE because of the fulfillment of objectives, also limited this study. A retrospective cohort research comprising 78 patients, 33 of whom had D2TRA and 45 without D2TRA, discovered that baricitinib shared similar safety and efficacy profiles between these two groups despite the non-D2TRA group exhibiting higher proportions at 24 months.[181] However, a limited number of patients with the retrospective analysis was the flaw of this study.

After 241 patients received baricitinib treatment, their CDAI scores at 4, 12, 24, and 52 weeks were considerably lower than their baseline scores. Furthermore, at 4, 12, and 24 weeks, baricitinib's impact on CDAI scores was noticeably less than that of the abatacept group.[132] However, this was a non-randomized observational study, and there may occur the selection bias related to different treatment periods. In addition, the registry did not include radiographic data and the relatively short follow-up period may limit the generalizability of results.

In patients with RA who were not responding to csDMARDs, the PERFECTRA (a pragmatic, multicentre, real-life) study indicated that starting with baricitinib was better than starting with TNFi in terms of response at 12 weeks and improved outcomes across all clinical measures and Patient-Reported Outcome Measures (PROMs) during the study period.[182] The limited number of patients and study duration, however, were the limitations of this study.

In a Swiss cohort study of RA patients, a comparison of the efficacy of baricitinib and other bDMARDs revealed differences in clinical outcomes, with baricitinib exhibiting a considerably higher medication maintenance proportion than TNFi.[183] However, this was a non-randomized study, and the average length of follow-up was short, which were the limitations of this study.

A 3-year post-marketing monitoring analysis of baricitinib was conducted on Japanese RA patients. The results showed that the 3-year persistence proportion of patients in the safety population, who received baricitinib, was 45.4% based on Kaplan–Meier analysis; 10.42% patients had SAEs, and there were 0.43% deaths. AEs included herpes zoster, serious infection, malignancy, major adverse CV events, and VTE.[184] In a long-term study for the drug's real-world effectiveness, persistence, adherence, and safety in RA conducted by Calvo-Garcia et al.,[185] baricitinib exhibited efficacy, significant persistence, high adherence to treatment, and a tolerable safety profile. Therein, 15.2% patients had AEs, and 3.5% had SAEs. AEs included anemia, infection, hypercholesterolemia, abnormal liver enzymes, nausea and vomiting, alopecia, skin disorders, asthenia, weight gain, VTE, hypertriglyceridemia, rhabdomyolysis and increase in platelets. SAEs included bacterial pneumonia with intravenous treatment, cancer, abnormal liver enzymes, VTE, hypertriglyceridemia, skin disorders (urticaria), and increase in platelets. Also, baricitinib was linked to a slightly increased risk of infection and a higher risk of herpes zoster, specifically in RA patients, relative to bDMARDs.[167] In a rare instance, a patient with RA receiving baricitinib was shown to have elevated creatine kinase.[186]

Upadacitinib

A new-generation JAKi called upadacitinib is thought to be more specific for JAK1 because it is 74 times more selective for JAK1 than for JAK2. Patients with moderate-to-severe RA who are not improving with methotrexate or anti-TNF medications have been the subjects of two multicenter randomized, double-blind, placebo-controlled phase II trials. Both studies demonstrated that upadacitinib quickly improved the DAS28 with CRP and ACR 20/50/70 response criteria, compared to a placebo. RA, SpA, and PsA patients are currently treated with upadacitinib.[187,188] Overall length and size were the limitations of these two studies.

Upadacitinib-treated RA patients experienced a noteworthy proportion of disease remission or LDA, according to a multicenter observational research on the medication's effectiveness in RA.[189]

Barešić et al.,[190] after a thorough work-up, reported a Caucasian patient from South-Eastern Europe who had developed extended eosinophilia while receiving upadacitinib for RA. Despite living in a nonendemic part of the world, the patient was diagnosed with strongyloidiasis. According to a prospective, non-randomized pilot trial that included 20 adult patients with active RA, both upadacitinib and csDMARDs lessened RA disease activity. However, those who took upadacitinib demonstrated a differential regression of erosion on high-resolution peripheral quantitative computed tomography (HR-pQCT).[191] Lack of randomization and blinding, small sample size, and lack of the longer-term effect were the limitations of this study.

The 5-year benefit-risk profile for upadacitinib in RA remained good, according to a research on the medication's efficacy and safety as well as insufficient response to csDMARDs.[192] Lack of a placebo control group beyond week 12 and the possible effect of background medication during LTE are the main limitations of this study. According to the prospective observational CLOSE-UP study's interim results, upadacitinib treatment lessened disease activity and improved patient-reported outcomes in the real world. These results were consistent with clinical trial data of Canadian patients who had previously been exposed to therapy and who were receiving upadacitinib monotherapy. Overall, the benefit-risk profile was favorable.[193] However, this is an interim analysis of an ongoing trial, and long-term benefit–risk profile is still needed in the future.

Regardless of previous TNFi experience, line of therapy, or concurrent use of conventional medications, upadacitinib commencement was linked with improvements in clinical and patient-reported outcomes, according to a study from the CorEvitas registry.[194] However, the generalizability of the findings, sample size, follow-up time and descriptive data were the limitations of this study. A prospective longitudinal multicentric study's real-world experience validated upadacitinib's effectiveness in improving clinical and ultrasonographic outcomes while exhibiting a favorable safety profile.[195] Study limitations included relatively small sample size and lack of a control group for comparative analysis. It was discovered that upadacitinib effectively treats seronegative RA that is anti-PTX3 positive.[196]

Upadacitinib may increase CV risk, especially when taken at a dose of 30 mg, according to a systematic review and meta-analysis that included six studies with a total of 4202 respondents.[197] In a study conducted by Charles-Schoeman et al.,[198] discontinuation of study treatment due to AEs were rare, occurring in ≤ 2.5% patients across all treatment groups. AEs included increase in alanine aminotransferase (ALT) and aspartate aminotransferase (AST), anemia, lymphopenia, neutropenia, and elevation in creatinine and total serum creatinine phosphokinase (CPK) levels. Overall, 15-mg upadacitinib once a day for moderate-to-severe RA was shown to have a satisfactory safety profile based on integrated data spanning 6.5 years about the drug's effects on laboratory parameters and associated AEs in RA patients. The SELECT-BEYOND study's results over a 5-year period demonstrated that 15/30-mg upadacitinib remained effective in treating clinical and functional outcomes in RA patients, and the safety profile over that period was in line with previous study-specific and integrated evaluations of upadacitinib treatment. In all, 93% of all AEs were mild-to-moderate in severity and included infections, herpes zoster, malignancy, hepatic disorder, anemia, neutropenia, lymphopenia, CPK elevation, VTE, and COVID-19.[199]

The phase 3 randomized SELECT-COMPARE study's 5-year data demonstrated that there were no new safety hazards and upadacitinib's safety profile remained consistent with its established safety profile. The most common TEAEs were serious infection, opportunistic infection, herpes zoster, active tuberculosis, malignancy, adjudicated MACE, adjudicated VTE, adjudicated gastrointestinal perforation, renal dysfunction, anemia, lymphopenia, neutropenia, CPK elevation and hepatic disorder. At 5 years, upadacitinib produced quantitatively greater clinical responses than adalimumab. According to these findings, upadacitinib had a favorable benefit–risk profile for the long-term management of RA.[200] According to the SELECT-COMPARE 5-year data, RA patients who did not respond or responded partially to the first dose of upadacitinib or adalimumab were moved to the alternative treatment by week 26. Through 228 weeks after the transition, clinically significant improvements were observed in all effectiveness measures. These benefits were largely comparable across groups, with minor numerical variations primarily supporting the switch to upadacitinib. Additionally, while the proportions of TEAEs were comparable between groups, switching to upadacitinib increased the incidence of herpes zoster, lymphopenia, and creatine phosphokinase elevation.[201]

Compared to patients who cycled TNFi or transitioned to an advanced medication with a different mechanism of action, RA patients who switched from TNFi to upadacitinib saw noticeably improved clinical outcomes of remission, no discomfort, and full adherence.[202] According to the SELECT-EARLY randomized controlled study, upadacitinib had higher incidences of AEs, particularly in the 30-mg group, than methotrexate, but it also showed stronger clinical responses in patients with RA over the course of the 5-year trial. TEAEs in patients receiving upadacitinib included hepatic disorder, neutropenia, CPK elevation, serious infections, herpes zoster, and nonmelanoma skin cancer.[203] A SELECT-BEYOND phase 3 trial evaluated the long-term sustainability of response to upadacitinib among patients with active RA refractory to biological treatments. The results showed that more than three-quarters of patients with bDMARD intolerance or inadequate response were able to attain CDAI-LDA with upadacitinib, and over half of those patients were able to maintain LDA for 240 weeks of follow-up, according to SELECT-BEYOND results of up to 5 years.[204] Compared to the primary analyses at week 24, the results of the SELECT-CHOICE study for the safety and effectiveness of upadacitinib in patients with RA, who were refractory to bDMARDs, showed that efficacy responses were maintained or improved further with 15-mg upadacitinib through week 216. AEs included infection, herpes zoster, COVID-19, adjudicated gastrointestinal perforation, hepatic disorder, anemia, neutropenia, lymphopenia, CPK elevation, malignancy, lymphoma, adjudicated MACE, and adjudicated VTE.[205]

After 12 and 24 weeks of upadacitinib treatment, 40% and 63.6% of patients, respectively, achieved ultrasonography plus clinical remission, according to the UPAdacitinib Rheumatoid Arthritis REmission UltraSonography (UPARAREMUS) real-life study on the clinical and ultrasonographic remission in RA patients who were bio-naïve and bio-failure.[206]

Filgotinib

Filgotinib inhibits JAK1 and JAK2 simultaneously; however, for JAK1, it is 30 times more selective. Filgotinib was discovered to be more effective than a placebo if used alone in patients with active RA who did not respond well to methotrexate. Two phase IIb trials, DARWIN1 and DARWIN2, supported this conclusion.[207,208]

In FINCH 1–3 studies, which were phase 3 RCTs, filgotinib was evaluated in patients who had not reacted well to either bDMARDs (FINCH 2) or methotrexate (FINCH 3).[209,210] Each study's primary goal was met by demonstrating that a substantially larger proportion of filgotinib-treated patients achieved the ACR20 response at week 12 (FINCH 1 and FINCH 2) or methotrexate at week 24 (FINCH 3) than those treated with either placebo.[209,210] Furthermore, filgotinib treatment improved several endpoints linked to RA manifestations and indicators.[209,210] Filgotinib was typically well tolerated in the clinical trial program for RA.[211] Filgotinib 200 mg or 100 mg is administered *de novo* to patients enrolled in the ongoing long-term extension of FINCH 4 study, or they continue to receive filgotinib 200 mg or 100 mg from FINCH 1, 2, or 3 studies. At week 156, 60.2% and 54.6% of patients who received *de novo* filgotinib 200 mg and 100 mg, and 67.3% and 59.5% of those who continued to receive filgotinib 200 mg and 100 mg, respectively, had an ACR20. Boolean remission 1.0 was observed in 18.8% and 15.4% of patients treated with *de novo* filgotinib 200 mg and 100 mg at week 156, respectively, and in 21.1% and 18.5% of patients treated with Boolean 2.0 criteria. Data on effectiveness were similar for patients in FINCH 2 and FINCH 3 studies. The safety information matched the known safety profile of filgotinib. These results indicated that filgotinib 200 mg and 100 mg (continuous or *de novo*) in FINCH 4 demonstrated maintained efficacy up to week 156 for participants enrolled from FINCH 1, 2, or 3, with no unanticipated negative effects.[212]

Filgotinib 200 mg or 100 mg once daily, adalimumab 40 mg every 2 weeks, or a placebo were given to patients with active moderate-to-severe RA in FINCH 1 who did not respond well to methotrexate (n = 1755). Comparing the two filgotinib doses to a placebo at weeks 12 and 24, a greater proportion of patients achieved DAS28-CRP < 2.6, CDAI remission (≤2.8), LDA (DAS28-CRP ≤3.2 or CDAI ≤10), and ACR20/50/70 responses. Through week 52, filgotinib's effectiveness remained on par with that of adalimumab's effectivity. The frequency of adalimumab and filgotinib AEs was comparable. With an incidence rate of 40–53% in groups receiving active treatment, infections observed were the most frequent AEs.[213]

According to FINCH 4's week 156 interim findings, Japanese patients generally tolerated well filgotinib 200 mg or 100 mg, with no new or unexpected AEs reported.[214] With the exception of herpes zoster in the general population, TEAEs of interest were stable over time and comparable between filgotinib 100-mg and 200-mg dose groups, according to an integrated safety analysis of the drug in patients with moderate-to-severe RA over a treatment duration of up to 8.3 years. Additionally, a dose-dependent relationship between malignancies and all-cause mortality was suggested in patients aged ≥65 years.[215]

In German clinical practice, filgotinib was primarily used as monotherapy and was discovered to be both efficacious and generally well tolerated.[216] Filgotinib was discovered to be safe and to have a decent efficacy profile if used alone or in combination with glucocorticoids, according to data from the Italian Group for the Study of Early Arthritis (GISEA) registry.[217] The efficacy and safety of filgotinib in the treatment of RA, particularly in patients who have never used a bDMARD, were demonstrated by a real-world multicenter experience.[218]

Peficitinib

A pan-JAK inhibitor called peficitinib (ASP015K) is presently in late-stage development in China[219] and is approved for clinical usage in RA patients in Taiwan, South Korea, and Japan.[220] A multicenter, randomized, double-blind, placebo-controlled phase 3 study discovered that peficitinib 100 mg and 150 mg were better than placebo for lessening RA manifestations, and were well tolerated in Asian patients with RA who had an inadequate response or intolerance to methotrexate.[221] Long-term peficitinib treatment at a dose of 100 mg/day was usually well tolerated and, after induction therapy, maintained effectiveness through week 48, according to a long-term open-label extension study conducted in Japan, South Korea, and Taiwan (RAJ2).[222] Peficitinib showed persistent efficacy in clinical remission up to week 52, according to a *post hoc* analysis of patients with RA in clinical remission in two Japanese phase 3 trials of the medication (RAJ3 and RAJ4). Baseline characteristics linked to CDAI remission were largely in line with earlier research using other disease-modifying antirheumatic medications.[223]

Role of b/tsDMARDs on Juvenile Idiopathic Arthritis

Juvenile idiopathic arthritis is one of the most prevalent chronic conditions affecting children. JIA is defined as chronic joint inflammation that appears in children aged <16 years and lasts for more than 6 weeks without any other discernible cause (e.g., infections, metabolic illnesses, malignancies, etc.).[224] The International League of Associations for Rheumatology (ILAR) has classified JIA into a number of clinical types, such as: systemic (sJIA), polyarticular (pJIA, rheumatoid factor negative [RF-] or rheumatoid factor positive [RF+]), oligoarticular (oJIA, persistent or extended), psoriatic (psJIA), enthesitis-related arthritis (ERA), and undifferentiated types.[225]

Biologic drugs are used as therapeutic options in the treatment of JIA, including TNFi, IL-6 inhibitors, IL-1ß inhibitors, and biologics acting directly on cellular function and/or interaction.[226,227] There are five TNFis used in the treatment of JIA: etanercept, infliximab, adalimumab, golimumab, and certolizumab. Etanercept is indicated for the treatment of pJIA patients aged <2 years, PsJIA patients

aged >12 years, and ERA patients aged >12 years. Infliximab is off-label for the treatment of JIA-related uveitis and pJIA based on the recommendations of the European Medicines Agency (EMA). Adalimumab is indicated for the treatment of pJIA patients aged >2 years and ERA patients aged >6 years but is off-label for the treatment of uveitis. Golimumab is recommended for the treatment of pJIA only in the experimental stage.

Tocilizumab, an IL-6 inhibitor, is indicated for the treatment of sJIA and pJIA patients aged >2 years. Three IL-1ß inhibitors are used in the treatment of JIA. Among them, anakinra is off-label for the treatment of sJIA. Canakinumab is indicated for the treatment of sJIA patients aged >2 years. Two biologics acting directly on cellular function and/or interaction include abatacept and rituximab. Abatacept is indicated for the treatment of pJIA patients aged >6 years, while rituximab is off-label for the treatment of pJIA.

Conclusion

We have compiled the original research papers on b/tsDMARDs for the treatment of RA that were published within the past year, along with their recently introduced biosimilar compounds. The indications and mechanism action of biologics in the treatment of RA were listed in Table 1. The development of more b/tsDMARDs and adherence to the treat-to-target principle are essential for improving RA prognosis. Early treatment during the window of opportunity is also a key. More RA patients being able to employ biologic agents earlier in the course of their disease is made possible by the availability of b/tsDMARDs, which is equally significant for improving therapeutic response and the final prognosis. However, the fact that many patients do not respond well or experience AEs that outweigh the benefits should be addressed when intending these therapies for RA treatment. In addition, it should be noted that some questions, such as

Table 1 The indications and mechanism action of biologics in the treatment of RA.

Biologic	Indications	Mechanism action
TNFi		
Adalimumab	Rheumatoid arthritis Ankylosing spondylitis (AS) Psoriasis Psoriatic arthritis JIA Crohn's disease (including childhood Crohn's disease) Ulcerative colitis Hidradenitis suppurativa uveitis	Binds to TNF-α and prevents TNF-mediated cellular inflammation
Etanercept	Adult patients with moderately to severely active rheumatoid arthritis, when refractory to DMARDs, including methotrexate Adult patients with severe active AS, when unresponsive to conventional treatment	Binds to either soluble or transmembrane TNF-α
Golimumab	Adult patients with moderate-to-severely active rheumatoid arthritis, when refractory to DMARDs, including methotrexate Adult patients with active AS	Binds to TNF-α with high affinity
Infliximab	Rheumatoid arthritis AS Psoriatic arthritis Crohn's disease	Binds to both membrane-bound and soluble forms of TNF-α with high affinity
Certolizumab	Moderate-to-severe rheumatoid arthritis	A PEGylated, Fc-free TNFi
Ozoralizumab	Rheumatoid arthritis	Humanized antibody against TNFα
IL-6 inhibitors		
Tocilizumab	Adult patients with moderate-to-severe active rheumatoid arthritis who do not respond well to treatment with one or more TNF antagonists.	Blocking both soluble and membrane-bound IL-6 receptors
Sarilumab	Rheumatoid arthritis	Stops IL-6 from binding to membrane-bound and soluble IL-6R-α
Olokizumab	Rheumatoid arthritis	A humanized monoclonal antibody targeting IL-6
Anti-CD20		
Rituximab	Rheumatoid arthritis Chronic lymphocytic leukemia Relapsed or refractory follicular central lymphoma	Targets the CD20 protein on the surface of B lymphocytes

(*continues*)

Table 1 Continued.

Biologic	Indications	Mechanism action
CTLA-4 immunoglobulin		
Abatacept	Adult patients with moderate-to-severe active rheumatoid arthritis who had inadequate response to one or more DMARDs, such as methotrexate (MTX) and TNFi	Prevents T-cell activation by preventing co-stimulation
JAK inhibitors		
Tofacitinib	Rheumatoid arthritis Ulcerative colitis Psoriasis	Inhibiting JAK1/JAK3, with limited efficacy against JAK2
Baricitinib	Adult patients with moderate-to-severe active rheumatoid arthritis	Selectively inhibits JAK1/JAK2
Upadacitinib	Patients with refractory, moderate-to-severe atopic dermatitis in adults and adolescents, aged ≥12 years who have had a poor response to or are not suitable for other systemic therapies Adults with moderate-to-severe active rheumatoid arthritis who have had a poor response to or intolerance to one or more TNFi Adult patients with active psoriatic arthritis who have a poor response to or intolerance to one or more DMARDs Adult patients with moderate-to-severe active ulcerative colitis who have a poor response to one or more TNF inhibitors or who are intolerant or contraindicated	Blocking the activity of Janus kinases in the JAK-STAT signaling pathway

small sample size, lack of long-term follow-up, and potential biases, exist in these clinical studies. Future research with a larger cohort and refined methodological approaches is necessary to validate and expand upon these preliminary findings. Thus, it is important to highlight a balanced perspective by focusing the risks and limitations of these treatments. Besides, owing to lower cost, bioequivalence efficacy, and safety, exploration that biosimilars fit into the treatment paradigm for RA has prominent value, which may significantly alter treatment strategies.

Availability of Data and Materials

All data generated or analyzed during this study are included in this published article. The datasets used and/or analyzed in the present study are available from the corresponding author on reasonable request.

Authors Contributions

Di Liu and Guimei Yu designed the study, completed the experiment, and supervised data collection. Na Yuan analyzed and interpreted the data. Daqing Nie prepared the manuscript for publication and reviewed the draft of the manuscript. All authors had read and approved the final manuscript.

Conflicts of Interests

The authors stated that there was no conflict of interest to disclose.

Funding

The fund was provided by Natural Science Foundation of Jilin Province (Norman Bethune Special Program) (Grant No. 20200201433JC).

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