

Reviewing: Monoclonal Antibody Therapies Targeting IL-6 & TNF-Alpha against Rheumatoid Arthritis

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ABSTRACT: Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by progressive joint damage with inflammation, significantly affecting the overall quality of life. Monoclonal antibody (mAbs) therapies have updated the management of RA by targeting key inflammatory pathways like tumor necrosis factor (TNF)- α and interleukin-6 (IL-6) due to their efficacy and safety profile compared to synthetic drugs. Thus, this review comprehensively investigates the mechanism of action, efficacy, and safety profile of various mAbs (TNF- α and IL-6 inhibitors). This review found significant therapeutic outcomes, like symptom alleviation, disease progression, remission rate, and safety profiles of TNF inhibitors (etanercept, adalimumab, and infliximab), and IL-6 inhibitors (tocilizumab and sarilumab). Furthermore, this review also explores adverse events and economic considerations associated with these mAbs, which can influence clinical decision-making. By synthesizing this evidence, clinicians can enhance RA management and tailor the treatment plan to individual needs.

KEYWORDS: Rheumatoid Arthritis, Monoclonal Antibody Therapy, TNF- α Inhibitors, IL-6 Inhibitors.

■ Introduction

Rheumatoid arthritis (RA), a multisystemic and multifactorial genetic autoimmune disorder, is primarily responsible for the damage to joints and later causes extra-articular manifestations.¹ RA not only causes damage to joints, but it also significantly damages other vital organs like the kidneys, heart, gastrointestinal tract, lungs, skin, eyes, and sense organs, and even causes mortality.² There are two main types of inflammation. First, acute inflammation is characterized by the infiltration of neutrophilic cells and then the monocytes. While in chronic inflammation, the presence of macrophages and lymphocytes at the inflammation site can be observed.³⁻⁵ Although inflammation serves as the first line of the human body's defense by eliminating harmful stimuli, the repair of damaged tissues or organs requires the migration of leukocytes to the affected site, subsequently.⁶ However, persistent acute inflammation leads to chronic inflammation, and this condition causes or escalates tissue damage.⁷ The RA prevalence increased from 1990 to 2019 among adolescents and young adults from 34.11 to 36.34/100000 persons. The most significant increase and decrease in the number of cases were observed in 2000 and 2014, respectively,⁸ and extra-articular manifestation also increased from 17.8% to 40.9%.⁹ Similarly, an increase from 207.46 to 224.25 in disability-adjusted life years was also observed from 1990 to 2019.¹⁰ Globally, it is estimated that by 2050, 31.7 million people will live with RA.¹¹ Therefore, its management is necessary as now monoclonal antibodies (mAb) are available for treating RA, particularly targeting tumor necrosis factor (TNF)- α and interleukin (IL) pathways, which are required to be targeted by the inhibitors.¹²

Indeed, clinical trials of TNF inhibitors and IL-6 receptor antibodies have shown significant improvement in clinical outcomes, resulting in global approval for the treatment of moderate to severe RA, particularly in patients with inadequate

response to other synthetic drugs.¹³ Furthermore, nucleotide polymorphisms are associated with the therapeutic response of mAbs, which target TNF, IL-6, and CD20 of B-cells. Similarly, numerous studies also reported the association between clinical responses of mAbs having various mechanisms, like IL-1, 7, 23, the receptor activator of nuclear factor-kappa B inhibition, and granulocyte-macrophage colony-stimulating factor.¹⁴ These mAbs are generally designed to target inflammatory cells, molecules, and pathways that cause damage to the tissues in patients with RA.¹

This literature review is a detailed analysis that aims to compare and contrast the mechanism of action, efficacy, and safety of the existing types of mAbs against RA. The first section of the paper explores the pathophysiology of RA, expands upon the mechanism and types of mAb therapies, and then delves into the detailed analysis of the varied TNF- α antagonists and IL-1, IL-6 inhibitors, as the main biological disease-modifying anti-rheumatic drugs (bDMARDs) of focus in this review. In the second section, this review draws a comparison among the mAb therapies to understand the relative advantages and disadvantages in terms of rate of remission, frequency of dosage, extent of potential side effects, financial accessibility, and overall drug efficacy.

■ Pathophysiology and cellular pathways of rheumatoid arthritis

Rheumatoid arthritis cannot be traced back to an individual factor, in fact. Initiation of the multisystemic autoimmune disease has been concluded as an interplay of multiple epigenetic and environmental triggers. Pathophysiology follows a complex trail of chain reactions concentrated in the synovium at a molecular level. In the first checkpoint, RA immunopathogenesis usually begins with autoantibody production (a process

in which the body's immune system mistakenly produces antibodies against its cells and tissues) against post-translationally modified proteins, in a process called citrullination. In the second checkpoint, tissue tolerance erodes, asymptomatic autoimmunity and progressive immune system remodeling take place, and failure occurs in protective joint-resident macrophages.¹⁶

In the third checkpoint, irreversible mechanisms occur with the transition of synovial stromal cells into auto-aggressive effector cells, which transfers the acute form of synovitis into destructive chronic synovitis.¹⁶ Furthermore, before the clinical phase (pre-symptomatic or preclinical RA), despite not having overt disease, many people acquire autoantibodies, like anti-cyclic citrullinated protein/peptide antibody (ACPA) and rheumatoid factor (RF), which cause chronic joint destruction and systemic inflammation^{17,18} as described in Figure 1.

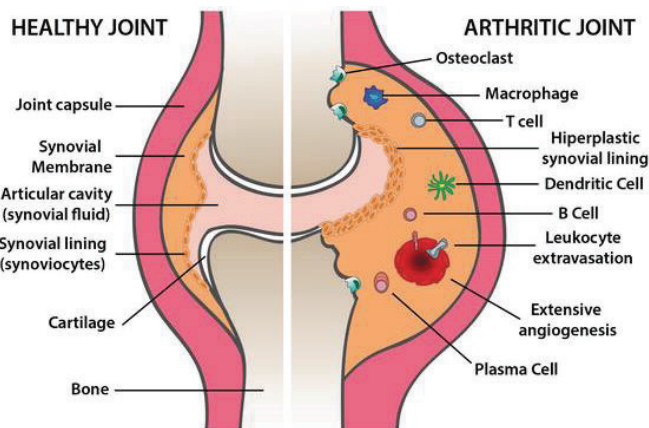


Figure 1: Comparison between healthy (left side) and RA (right side) infected joints.¹⁹ The right side emphasizes the most critical clinical alterations and inflamed synovial membrane, and leukocytes infiltrate the synovial membrane, licensed under CC BY 3.0.

Meanwhile, RA susceptibility is strongly associated with genetic factors, like differences in human leukocyte antigen (HLA)-DRB1 alleles, particularly in RF and ACPA-positive RA patients.^{20,21} The ACPA pathogenetic significance in RA patients is the outcome of their multidirectional biological activities, and two-thirds of positive patients have shown complexes that consist of ACPA and citrullinated fibrinogen. Stimulation of Fcγ receptors on macrophages also occurs in ACPA-positive RA patients.^{22,23} In addition, alleles of HLA-DRB1 associated with RA encode a common sequence at 70-75 (QKRAA) amino acids in the β-chain third hypervariable section, which is known as the shared epitope.²⁴⁻²⁶ The shared epitope in the HLA-DRB1 alleles generates citrullinated peptides, consequently leading to ACPA development.²⁷ Mainly, ACPA is categorized into two subtypes, such as ACPA-positive and ACPA-negative. Meanwhile, the citrullination process is catalyzed by the peptidyl-arginine deiminase (PAD) enzyme, which is helpful in the process of post-translational modification by changing a positively charged arginine to a polar but neutral citrulline.²⁸

Furthermore, in the synovium, the antigen-presenting cells attract the modified or citrullinated foreign antigen, which is then transported to the lymph nodes for the activation of

CD4+ T helper cells, which further cause the co-stimulation of B cells.^{29,30} As the first line of defense, these B cells propagate and differentiate into plasma cells by the expression of costimulatory cells and generate pro-inflammatory and anti-inflammatory cytokines like IL-17 and interferon-γ, which are responsible for the drawing of macrophages into the joint spaces.³¹ These activated macrophages further generate inflammatory cells, such as IL-1, 6, and TNF-α, which in turn activate FLS, which is required in the receptor activator for nuclear factor-κB ligand (RANKL) expression, leading to bone damage by activation of osteoclasts^{32,33} and detailed pathophysiology is explained in Figure 2. Moreover, the abnormal signaling pathways in RA, which are essential for the diagnosis and treatment of RA, attracted the attention of researchers. The understanding of these pathways can explain complex diseases and be helpful in the development of RA-linked intervention targets and new advanced medication.^{34,35}

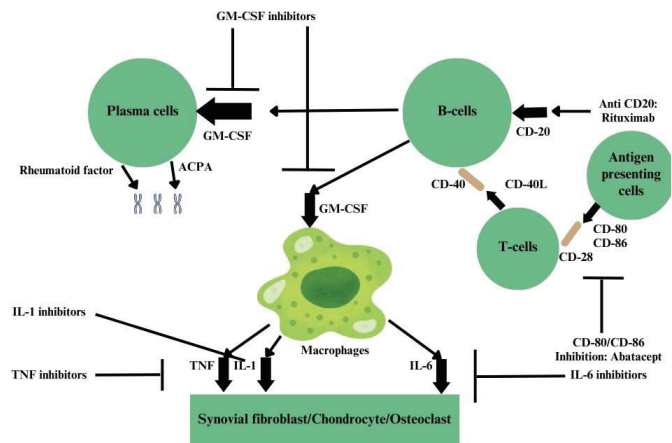


Figure 2: Pathophysiology of rheumatoid arthritis (RA). Activated CD-T cells play an essential role in inflammatory responses in the synovial membrane, including inflammatory cytokine secretion (TNF, IL-1) by macrophages, autoantibody production by plasma cells, and highlighting key immune cell types and therapeutic interventions. This figure is created with the assistance of Canva (www.canva.com).

Different treatment modalities:

Different treatment modalities have shown promising outcomes, such as DMARDs, which particularly target inflammation and inhibit joint damage.^{12,36} The three most important DMARDs are conventional synthetic DMARDs (sulfadiazine, hydrochloroquine, and methotrexate), biological DMARDs (inhibitors for TNF receptor, TNF-α inhibitors, IL-6, IL-6R, and B-cell depleting antibodies), and targeted synthetic DMARDs, like JAK ½ and pan-JAK inhibitors.^{12,37} These DMARDs have the potential for the management of RA; however, they have significant side effects and high economic costs.¹² Likewise, non-steroidal anti-inflammatory drugs (NSAIDs) are also used for treating RA and have the ability to inhibit the biosynthesis of prostaglandins at the level of the cyclooxygenase enzyme.³⁸ However, their prolonged usage can lead to functional impairment.³⁹ Moreover, corticosteroids like prednisone, budesonide, and prednisolone also showed promising outcomes; however, corticosteroids showed serious adverse events.⁴⁰

Monoclonal antibody therapy:

Over the last three decades, due to advancements, the understanding of RA pathophysiology has transformed therapeutic approaches, with mAb therapies emerging as one of the most promising modalities and having encouraging outcomes in RA management.⁴¹ The mAbs proved to be less toxic due to their target selectivity and binding to other targets and were specifically designed to target the TNF- α and IL-17 or more targets.⁴² In addition, mAbs like adalimumab, rituximab, infliximab, and tocilizumab have a connection between the clinical response of these mAbs, having different mechanisms (IL-1, 17, and 23), the receptor activator of nuclear factor-kappa B inhibition, and granulocyte-macrophage colony-stimulating factor.¹⁴ There is still no single established immunomodulator or any pharmacological preventive that is fully effective against RA.⁴³ However, certain drugs are approved and often used for RA treatment (see Table 1).

Table 1: Approved monoclonal antibody agents used for the RA.

mAbs	Dose	Structure	Target	FDA approval year
Actemra (Tocilizumab)	Every other week (132 mg sc) and then qw (wt<100) or 162 qw (wt >100)	Humanized mAb	IL-6R	2010
Cimzia (Certolizumab)	At weeks 0, 2, and 4 (400 mg sc) and then 200 mg/every other week	Humanized PEGylated fragment	TNF	2009
Enbrel (Etanercept)	Once a week (50 mg injection)	IgG fusion protein with TNF receptor	TNF	1998
Humira (Adalimumab)	Every other week (40 mg sc)	Humanized mAb	TNF	2002
Kevzara (Sarilumab)	Every other week (200 mg sc)	Humanized mAb	IL-6R	2017
Remicade (Infliximab)	At weeks 0, 2, and 6 weeks (3 mg/kg)	Chimeric mAb	TNF	1999
Rituxan (Rituximab)	2 weeks apart (1000 mg IV)	Chimeric mAb	B-cells (CD20)	2006
Simponi (Golimumab)	Once a month (50 mg sc)	Humanized mAb	TNF	2009

Abbreviations: mAb: Monoclonal Antibody therapy, TNF: Tumor Necrosis Factor, IL: Interleukin, IV: Intravenous, SC: Subcutaneous

■ TNF- α inhibitors

A pro-inflammatory cytokine, TNF- α , is produced by activated macrophages, natural killer cells, and T lymphocytes.⁴⁶ Meanwhile, TNF- α abnormal production triggers synovial hyperplasia and generates matrix metalloproteinase and prostaglandin.⁴⁷ In addition, it stimulates bone cells to secrete the RANKL, which results in osteoclast formation.⁴⁸ The TNF- α inhibitors form a complex with the binding of the interface of the TNF- α dimer, which ultimately hinders the TNF- α receptors' binding, which stops inflammation and other signaling pathways in the TNFR1 and TNFR2 due to the activation of downstream signaling complexes.^{49,50} These TNF- α inhibitors

have a chondroprotective impact on cartilage turnover, which helps in improving the type II collagen formation/resorption (C2C/PIICP) ratios in the assessment of the response of anti-TNF- α therapeutic effect in RA patients.⁵¹

Therefore, certain inhibitors such as etanercept, adalimumab, and infliximab have been approved for the treatment of RA, as these inhibitors help eliminate the TNF- α at the site of inflammation.⁵² These inhibitors have been solidified as bDMARDs directed towards the control of TNF- α to instigate initiation and maintenance of remission in patients with RA. These bDMARDs may be registered subcutaneously (injection administered under the skin) or intravenously (drug administered through a needle or tube inserted into the vein).

Etanercept:

Etanercept is the first biological TNF- α inhibitor that is authorized by the Food and Drug Administration (FDA) to treat RA. It showed its efficacy and safety when used as a monotherapy or combined with other drugs like methotrexate.⁴⁵ Structurally, it is a dimeric human TNF receptor p75-Fc fusion protein made of 75 kD (p75) TNFR attached with human immunoglobulin (IgG)-1 constant Fc portion,^{45,53} and it contains 150 kDa of molecular weight and consists of 934 amino acids.⁵⁴ This dimeric structure of etanercept has the potential to improve the binding affinity with a short half-life mean time of 70 hours and comparatively has more inhibitory potential than monomeric soluble receptors.⁵⁵ Etanercept not only acts as a TNF inhibitor, but it also has effector activity against Fc, which triggers the production of complement-dependent cytotoxicity via triggering the complement pathway and also induces antibody-dependent cell-mediated cytotoxicity and target immune cell apoptosis.⁵⁶ It achieves this by having the TNF receptor bind to TNF- α and TNF- β since etanercept prevents the binding of both TNF- α and TNF- β to cell surface TNF receptors, which renders the TNF biologically inactive.⁵⁷ Due to its inhibitory effects, it disrupts this inflammatory cascade, resulting in the reduction of inflammation in the joints, bone erosion, and cartilage degradation. Meanwhile, clinically, it proves its efficacy. For instance, in a German research study, 824 RA individuals were treated with etanercept, and the patient's proportion achieving low disease activity or remission was 39% at 12 weeks and increased to 45% at week 24, and it further increased to week 52.⁵⁸ Similar outcomes were observed in another cohort study, which observed significantly lower disease activity after half a year of treatment. However, a higher rate of adverse events, including other serious infections and other central nervous system-associated events, was also recorded without a high rate of hospitalization.⁵⁹ Furthermore, when etanercept is combined with a gold standard DMARD methotrexate, its efficacy increases due to synergistic effects, leading to superior clinical response, a greater reduction in radiographic damage, and improved remission rates.⁶⁰

Adalimumab:

Adalimumab is a fully human recombinant immunoglobulin G1 (IgG1) with high affinity.⁶¹ It binds with the cytokine TNF- α , inhibiting its interaction with TNFR1 and TNFR2,

and FDA-approved inhibitory mAb for the treatment of RA.^{62,63} It consists of 1330 amino acids with a 148kDa molecular weight.⁶⁴ Adalimumab disrupts downstream signaling pathways, which are required for inflammation, joint destruction, and synovial hyperplasia.⁶⁵ It is also helpful in reducing the production of IL-1 and IL-6, inhibiting leukocyte recruitment and decreasing the FLS activation and osteoclasts.^{65,66} Moreover, it is helpful in downregulating serum matrix metalloproteinases (MMP) 1 and 3, and this inclusive impact causes the TNF inhibitor effectiveness in RA.⁶⁷

When adalimumab is used as monotherapy, it has demonstrated significant efficacy in treating RA, and patients showed significant, sustained, and rapid progress in their disease activity and physical function.⁶⁸

For RA individuals who persistently used adalimumab for one year, 67% of individuals demonstrated low disease activity and showed clinically improved functions.⁶⁹ Similarly, significant improvement was noticed in week 4. After 12 weeks, 15.3% of RA individuals achieved clinical remission, and 28.9% had low disease activity.⁷⁰ Moreover, when adalimumab is combined with methotrexate, it promotes the efficacy of adalimumab by inhibiting the formation of anti-drug antibodies, and this combination demonstrated better clinical and radiological outcomes than when used alone.⁷¹ In short, studies have endorsed the benefits of adalimumab in promoting quality of life, work efficiency, and safety, and in how it is well-tolerated, and its ability to solve sleep problems.⁷²

Infliximab:

Infliximab, a chimeric mAb, has been widely used to treat TNF-α-associated diseases for a decade and binds with the human IgG1 Fc region, and a further mechanism involves the overlapping with the TNF-α receptor interface, indicating its pivotal role in the E-F loop.⁷³ It can further bind to free types, and inhibition can take place for the cytokines binding and other associated receptors, with complement-dependent cytotoxicity and antibody-dependent cell-mediated cytotoxicity effects superior to etanercept.¹⁵ In addition, it is also helpful in reducing IL-6 and CRP concentrations in the blood after its administration⁷⁴, and it provides evidence for the reduction in IL-1 and soluble TNF receptors, two main types of anti-cytokines regulated by TNF-α.⁷⁵ Moreover, it can successfully inhibit the formation of osteoclasts and activity in vitro and suppress RANKL expression by blocking TNF.⁷⁶ Another important mode of action is regulating the immune responses by restoring the altered regulatory T cell function in RA, which is an efficient method to treat RA.⁷⁷ Furthermore, CD4+ and CD25+ Treg functions regulate immune response and the suppression of auto-reactivity, which is often dysregulated in RA patients.⁷⁸ The efficacy of infliximab is evident in numerous studies. For instance, RA patients were treated with infliximab for 36 months, and patients demonstrated significant and sustained improvement in all parameters associated with the disease. Meanwhile, <2% of patients showed adverse events, like arthralgia, headache, upper respiratory tract infection, pruritus, infection, nausea, rash, fatigue, back pain, bronchitis,

dizziness, pyrexia, and dyspnea.⁷⁹ Key characteristics of these three TNF inhibitors are mentioned in Table 2.

Table 2: Summary of key characteristics of TNF-α inhibitors.

Key variables	Etanercept	Adalimumab	Infliximab
Molecule	IgG fusion protein with TNF receptor ⁸⁰	Humanized mAb ⁶⁴	Chimeric mAb ⁸¹
Mode of action	Soluble TNF receptor binding to TNF-α ⁸²	Inhibition of the TNF-α binding ⁶⁴	Blinds both soluble and membrane-bound TNF-α ⁸³
Administration route	SC and injected ⁸⁴	IV and SC ⁸⁵	SC and IV ⁸⁶
Indication	Ankylosing spondylitis, plaque psoriasis, psoriatic arthritis, RA, juvenile idiopathic Arthritis ⁸⁴	RA, psoriasis, psoriatic arthritis, juvenile idiopathic arthritis, Crohn's disease ⁶²	Ankylosing spondylitis, RA, psoriatic arthritis, Crohn's disease ^{87,88}
Dosage	50 mg once a week ⁸⁴	40-80 mg every 2 Weeks ⁶⁷	3 mg/kg ⁷⁶
Storage and stability	25 °C ± 2 °C for up to 1 Month ⁸⁹	2 °C ± 8 °C for 36 months and 25 °C for 14 days ⁹⁰	Can be stored at 4 °C over 6 weeks ⁹¹
Use	Monotherapy or in Combination ⁹²	Monotherapy and in Combination. ⁷¹	Monotherapy and in Combination. ⁷⁶
Efficacy	Effective monotherapy & in combination ⁹²	Effective ⁶⁸	Effective ⁷⁹
Safety or Adverse events	Serious infections (viral, fungal, and bacterial) are mostly in upper respiratory tract ⁹² , and injection site reactions (pain, itching, erythema, bleeding, swelling, and bruising), and central nervous system related adverse events ⁹³	Safe and well-tolerated ⁷⁰ , adverse events like reactivation of tuberculosis can be seen ⁹⁴	Adverse events were reported: lower and upper respiratory symptoms, urticarial/angioedema, ⁹⁵ bacterial pneumonia ⁹⁶
Cost-effectiveness	High acquisition cost (61,552 \$)/year ^{97,98}	Higher cost (91,695 \$/year) ⁹⁹	Lower cost (79,518 \$/year ⁹⁹

■ **IL-6 inhibitors**

Interleukin-6 is transiently and promptly produced in the infection or tissue injury response. However, the expression of IL-6 is managed by posttranscriptional and transcriptional mechanisms, while irregular IL-6 synthesis plays a critical role in the pathogenesis of chronic inflammation.¹⁰⁰ It is a small polypeptide of 6 kDa molecular weight.¹⁰¹ In 1986, human B cell stimulatory factor 2 was successfully cloned, and due to its multiple activities, later numerous names were used; however, now all those names are unified and are called IL-6.¹⁰² Furthermore, biological activities exerted by IL-6 are through two molecules, gp130 and IL-6R. A high functional receptor complex comprising IL-6, IL-6R, and gp130 is formed when

IL-6 binds with the membrane-bound type of IL-6R.¹⁰³ Initially, the interaction between IL-6 and IL-6R α takes place, and later, this interacting pair forms a complex with gp130. This high affinity of the complex of these three subunits is associated with a second high-affinity complex, which further forms a hexameric complex and is essential to induce signal transduction.¹⁰⁴

Furthermore, IL-6 exerts its impact via two primary signaling pathways, such as classic signaling and trans-signaling, and both pathways involve IL-6R and gp130.¹⁰⁵ Overall, IL-6 promotes joint destruction and inflammation and causes pain, morning stiffness, and fatigue.¹⁰⁶ In addition, the pleiotropic impact of mAbs (IL-6) on the other body organs is also described in Figure 3.

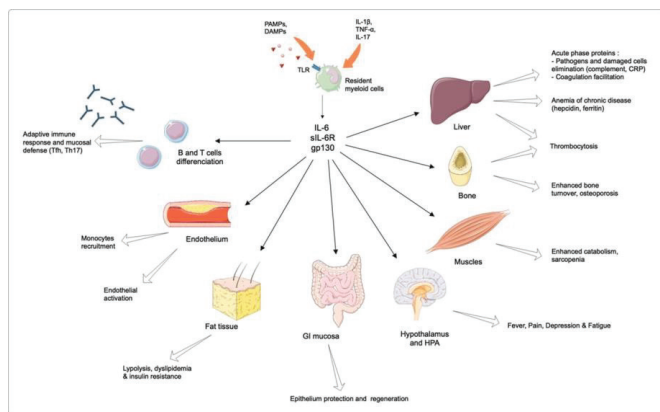


Figure 3: The pleiotropic impact of IL-6 on different body parts. The complexes formed by IL-6, by glycoprotein (gp) 130, and its soluble receptor (sIL-6R) can induce various systemic effects distant from the inflammation's initial site,¹⁰⁷ under Creative Commons CC BY-NC-ND 4.0 license. Mainly, there are two types of IL-6 inhibitors, including tocilizumab and sarilumab, which have been approved to treat RA and are discussed below.

Tocilizumab:

Tocilizumab is the first anti-IL-6R humanized mAb approved for treating RA alternative to methotrexate and helps inhibit the cis and trans signaling cascades, which involves the activator of transcription pathway and Janus kinase signal transducer.¹⁰⁸ It prevents the IL-6 interaction with the signal transducer gp130 and IL-6R by targeting both membrane-bound and soluble IL-6R.¹⁰⁹ It also decreases B-cell hyperactivity, induces expansion in regulatory B-cells, and decreases peripheral memory B-cell numbers.¹¹⁰ This action reduces inflammation, modulates the function of immune function, and is also helpful in mitigating tissue damage, making it a powerful treatment option for RA patients. Moreover, it also prevents joint destruction progression by the inhibition of bone or cartilage resorption and is also helpful in improving hematological abnormalities, like high levels of autoantibodies, hypergammaglobulinemia, and elevation of ESR and acute phase proteins.¹¹¹ Notably, it improves life quality by inhibiting symptoms like anemia, fever, fatigue, and anorexia.¹¹¹ In terms of efficacy, it is effective from as early as week 2 after its administration, and its effectiveness increases with time.¹¹¹

Two efficacy studies, SATORI and SAMURAI, were performed with adult moderate-to-severe RA patients, and tocilizumab was administered as monotherapy, and patients

receiving a dose every 4 weeks. At weeks 24 and 52, excellent ACR and remission rates were observed.^{112,113} Similarly, when used in combination with methotrexate, the efficacy was maintained with no patient demonstrating a decrease in effectiveness.¹¹⁴ Adverse events associated with tocilizumab are presented in Table 3.

Sarilumab:

Sarilumab, a humanized IL-6R mAb, binds both soluble and membrane-bound human IL-6R with a high affinity, which blocks the cis and trans inflammatory signaling cascade.¹¹⁵ Its effectiveness in inhibiting IL-6 signaling depends on the dose and is also helpful in reducing CRP levels.^{116,117} This blockage suppresses phase reactants, reduces systemic and local inflammation, and mitigates immune cell recruitment to the synovium, which is helpful in halting the progression of joint damage and promoting life quality.¹¹⁸ Furthermore, it also decreases bone resorption by inhibiting osteoclast differentiation, reducing radiographic evidence of joint erosion and narrowing.¹¹⁹ It was developed using animal models for the production of human antibodies with an affinity of 20-fold greater than tocilizumab for the human IL-6R.¹²⁰ Clinical trials using sarilumab as monotherapy or combined with other DMARDs demonstrated that it is effective either alone or in combination.¹²¹ Similarly, the MOBILITY¹²² and MON-ARCH¹²³ studies have shown functional and symptomatic improvement in RA patients with intolerance or inadequate responses to conventional DMARDs like methotrexate. The key characteristics of these two IL-6 inhibitors, including adverse events, are described in Table 3.

Table 3: Summary of key characteristics of IL-6 inhibitors.

Key variables	Tocilizumab	Sarilumab
Molecule	Humanized mAb ¹⁰⁸	Humanized mAb ¹²⁰
Mode of action	Bind with both soluble and membrane bound IL-6R ¹⁰⁹	Bind with both soluble and membrane bound IL-6R ¹¹⁵
Administration route	IV and SC ¹²⁴	SC ¹²⁰
Use	Monotherapy and in combination ¹²⁵	Monotherapy and in combination ¹²⁶
Dosage	8 mg/kg ¹¹¹	Every two weeks, 150 or 200 Mg ¹²⁶
Storage and stability	2 - 8 °C or room temperature and should be protected from light	2 - 8 °C, once removed from refrigeration, use with 14 days ^{120,127}
Indication	Systemic juvenile idiopathic arthritis, giant cell arteritis, juvenile idiopathic	Acute moderate to severe RA ^{120,127}
Efficacy	Effective ¹¹²	Effective ¹¹⁵
Safety or adverse events	Adverse events were reported (infections [cellulitis, herpes zoster, tuberculosis, pneumonia]), ¹²⁸ skin and subcutaneous tissue disorders, and eye abnormalities ¹²⁹	Serious adverse events like cardiovascular events, upper respiratory tract infections, injection site erythema, malignancies, and venous thromboembolism are rare ¹³⁰
Cost-effectiveness	More cost-effective compared to other DMARDs (ICER=1301 \$) ¹³¹	Compared to adalimumab, sarilumab is more cost-effective with total cost of 492,000 \$ ¹³²

■ Discussion

Monoclonal antibody therapies have revolutionized RA management by targeting specific molecules involved in the disease pathogenesis, offering more effective and precise alternatives to conventional therapies. Despite having small molecule therapies, mAbs offer a more targeted approach, specifically blocking key inflammatory cytokines that play an essential role in the pathogenesis of RA, leading to more precise and potent effects on the reduction of inflammation. Therefore, this comprehensive literature review aimed to compare mAbs used to manage RA.

In the present literature review, we discussed two types of mAbs, such as TNF- α and IL-6 inhibitors, and the literature highlights their efficacy when compared to other drugs used for the management of RA individuals. The efficacy of TNF- α inhibitors is well established as RA patients were treated between 2004-2014. EULAR moderate and good treatment responses (69% and 40%) were achieved at 6-month follow-up.¹³³ Likewise, the clinical response of three TNF inhibitors (etanercept, adalimumab, and infliximab) was evaluated for 6 and 12 months of treatment. The adalimumab had the highest number of patients (32 and 39) with remission rates.¹³⁴ Similar findings were observed in the SAMURAI trial, which included individuals with inadequate response towards sDMARDs, and patients were treated with IL-6 inhibitor (tocilizumab) and found superior with ACR 20 and lower disease activity 28 at 24 weeks compared to the control groups.¹¹³ Similarly, another study also observed a 55.3% remission rate in the tocilizumab group.¹³⁵ Furthermore, RA individuals treated with either TNF or IL-6 inhibitors, 10-50% of patients achieve remission in 6-12 months.^{136,137} Likewise, randomized phase 3 and 4 trials demonstrated better remission rates and superiority when RA individuals with high disease activity were treated with tocilizumab and sarilumab.^{123,138} In contrast, RA individuals were treated with baricitinib and compared with sarilumab, although sarilumab induced similar improvement in disease activity. However, at week 24, the baricitinib-treated group significantly improved the clinical disease activity index. At 52 weeks, both groups had similar outcomes.¹³⁹

In addition, the efficacy of these mAbs is dose-dependent. For instance, the tocilizumab standard dose is 8 mg/kg every 4 weeks (q4W) for treating RA individuals. However, for patients with high disease activity and high body weight, which resulted in high levels of IL-6, the effectiveness of tocilizumab at the current rate is inadequate, so reducing the interval between the administration of tocilizumab to once a week can be beneficial in the management of the disease.¹⁴⁰ Similarly, another randomized trial demonstrated that adequate effectiveness can be achieved when RA patients with a weight of >100 kg are treated weekly with tocilizumab SC.¹⁴¹ In contrast, TNF inhibitors did not significantly improve the efficacy with increasing doses.¹⁴² Likewise, in RA patients with low levels of IL-6, tocilizumab SC or IV prolonged dose interval can sustain remission.^{143,144}

Even though mAbs demonstrate effectiveness, they are not free from adverse events or complications. For instance, adali-

mumab is associated with 63 unique adverse events, such as vascular dementia, systemic lupus erythematosus rash, and ovarian cancer. Similarly, etanercept has 180 unique adverse events, including chondrolysis, ankle and finger deformity, and joint warmth. Meanwhile, infliximab demonstrated 60 unique adverse events, such as metastatic neoplasm and Hodgkin's disease.¹⁴⁵ In addition, meta-analysis observed an increased risk of cancer with 1.36 OR (95% CI, 1.20-1.653; $p < 0.00001$) and severe infections with 1.72 OR (95% CI, 1.56-1.90; $p < 0.00001$) in TNF TNF-treated group.¹⁴⁶ Furthermore, three (4%) patients reported neurological adverse events when treated with adalimumab, etanercept, and infliximab.¹⁴⁷ Similarly, 612 RA individuals who were treated with tocilizumab reported adverse events, and 27.5 events/100 patients were reported every year, with 5.7 serious infections/100 patients/year.¹³⁵ In another study, five cases of malignancy with an incidence rate of 1.36/100 patients per year, and an incidence rate for major adverse cardiovascular events of 0.83/100 patients per year, were reported in patients treated with IL-6 inhibitors.¹⁴⁸

Meanwhile, for every effective drug, cost-effectiveness should also be considered. TNF inhibitors and IL-6 inhibitors like IL-6 had lower costs with higher quality-adjusted life years (QALYs) than rituximab, and TNF inhibitors showed the most cost-effective treatment modality.¹⁴⁹ Similarly, tocilizumab had a lower cost with higher QALYs than rituximab.¹⁴⁹ Furthermore, when tocilizumab was compared with adalimumab, tocilizumab was found to be more cost-effective with 76% probability, with higher 4.²⁴ QALYs gained compared to adalimumab.¹³¹ In contrast, a Swedish study reported a higher cost per QALY for three different types of TNF inhibitors, and the cost ranged from €50,000-120,000.¹⁵⁰ Similarly, another pragmatic randomized trial documented that rituximab therapy was significantly more cost-effective, compared to TNF inhibitors, over a willingness to pay ranging from \$0-80,000.¹⁵¹

A primary limitation should be considered, and that is the meta-analysis was not performed due to the nature of the study, as meta-analyses are necessary for better comparison of dosing regimen, age-wise impact, and comparison of treatment groups with control. They also calculate the heterogeneity level among the studies as well as the source of heterogeneity. Future research should include meta-analyses for a statistically better comparison between treatment and control groups.

■ Conclusion

The present review aims to compare and contrast the relative advantages and disadvantages of the existing forms of mAbs for the management of RA patients. These therapies have revolutionized disease management by targeting specific immune pathways, and the scope for further innovation remains significant. Overall, these mAbs (TNF [etanercept, adalimumab, and infliximab] and IL-6 inhibitors [tocilizumab and sarilumab]) demonstrated efficacy. These mAbs have transformed clinical outcomes for many patients by offering effective, targeted strategies to mitigate progression of the disease and improve quality of life, but they have also raised uncertainty regarding cost-effectiveness and association with adverse events, in-

cluding increased susceptibility to infections. Notably, using antibody fragments can further enhance tissue penetration, tailor delivery mechanisms, and reduce immunogenicity. Overall, this review provides insights into the importance of ongoing research to refine therapeutic approaches and bring improvement in the patient's associated outcomes. Future longitudinal and multicenter studies are required to further validate the findings of the present review.

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