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REVIEW ARTICLE

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 leucocytes 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

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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.

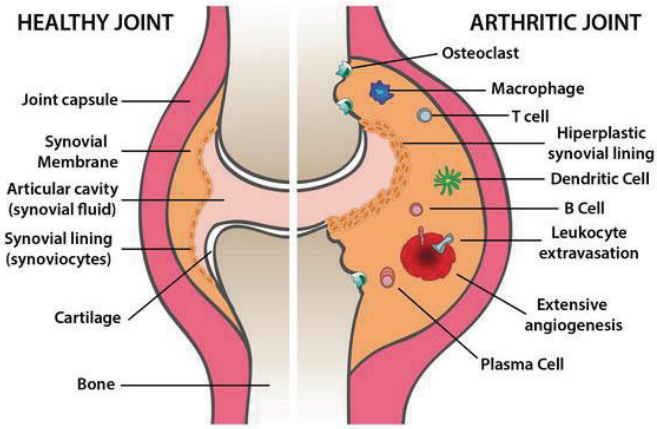

Figure 1: Comparison between healthy (left side) and RA (right side) infected joints.[19] The right side emphasizes the most critical clinical alterations and inflamed synovial membrane, and leukocytes infiltrate the synovial membrane, licensed under CC BY 3.0.

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 Fcy receptors on macrophages also occurs in ACAP-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-gamma, 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-kB 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]

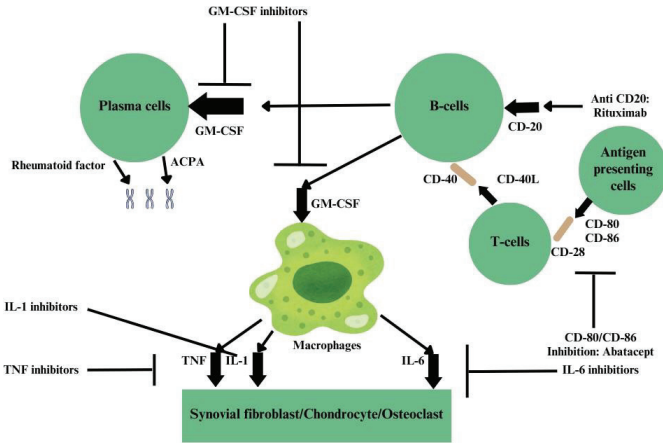

Figure 2: Pathophysiology of rheumatoid arthritis (RA). Activated CD-T cells play an essential role in inflammatory responses in the synovial membrane, including inflammatory cytokine secretion (TNF, IL-1) by macrophages, autoantibody production by plasma cells, and highlighting key immune cell types 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,

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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 administration[74], 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 ^{0}C ± 2 ^{0}C for up to 1 Month[89]	2 ^{0}C ± 8 ^{0}C for 36 months and 25 ^{0}C for 14 days[90]	Can be stored at 4 ^{0}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-6Rα 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.

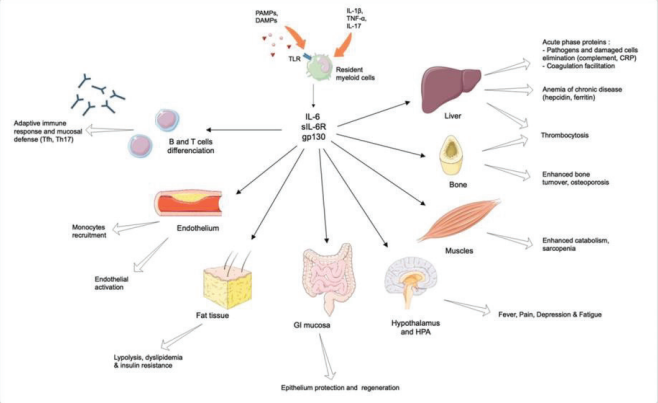

Figure 3: The pleiotropic impact of IL-6 on different body parts. The complexes formed by IL-6, by glycoprotein (gp) 130, and its soluble receptor (sIL-6R) can induce various systemic effects distant from the inflammation's initial site,107 under Creative Commons CC BY-NC-ND 4.0 license. Mainly, there 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 MOBILITY[122] and MONARCH[123] 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 0C or room temperature and should be protected from light	2 -8 0C, 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]

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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, adalimumab 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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References

1. Radu, A.-F.; Bungau, S. G. Management of Rheumatoid Arthritis: An Overview. Cells 2021, 10 (11), 2857. DOI: 10.3390/cells10112857
2. Wu, D.; Luo, Y.; Li, T.; Zhao, X.; Lv, T.; Fang, G.; Ou, P.; Li, H.; Luo, X.; Huang, A.; et al. Systemic complications of rheumatoid arthritis: Focus on pathogenesis and treatment. Frintr Immunol 2022, 13, Review. DOI: 10.3389/fimmu.2022.1051082
3. Herrero-Cervera, A.; Soehnlein, O.; Kenne, E. Neutrophils in chronic inflammatory diseases. Cell Mol Immunol 2022, 19 (2), 177-191. DOI: 10.1038/s41423-021-00832-3
4. Elgazzar, A. H.; Elmonayeri, M. Inflammation. In The Pathophysiologic Basis of Nuclear Medicine, Elgazzar, A. H. Ed.; Springer International Publishing, 2015; pp 69-98.
5. Prame, K., Kathryn; Nicholls, A. J.; Wong, C. H. Y. Partners in crime: neutrophils and monocytes/macrophages in inflammation and disease. Cell Tissue Res 2018, 371 (3), 551-565. DOI: 10.1007/s00441-017-2753-2
6. Soliman, A. M.; Barreda, D. R. Acute Inflammation in Tissue Healing. Int J Mol Sci 2023, 24 (1), 641. DOI: 10.3390/ijms24010641
7. Soares, C. L. R.; Wilairatana, P.; Silva, L. R.; Moreira, P. S.; Vilar Barbosa, N. M. M.; da Silva, P. R.; Coutinho, H. D. M.; de Menezes, I. R. A.; Felipe, C. F. B. Biochemical aspects of the inflammatory process: A narrative review. Biomed Pharmacother 2023, 168, 115764. DOI: 10.1016/j.biopha.2023.115764
8. Li, R.; Yuan, X.; Ou, Y. Global burden of rheumatoid arthritis among adolescents and young adults aged 10–24 years: A trend analysis study from 1990 to 2019. Plos One 2024, 19 (4), e0302140. DOI: 10.1371/journal.pone.0302140
9. Baerwald, C.; Kneitz, C.; Bach, M.; Licht, M. [Extra-articular manifestations of rheumatoid arthritis]. Z Rheumatol 2012, 71 (10), 841-849. DOI: 10.1007/s00393-011-0928-x
10. Cai, Y.; Zhang, J.; Liang, J.; Xiao, M.; Zhang, G.; Jing, Z.; Lv, L.; Nan, K.; Dang, X. The Burden of Rheumatoid Arthritis: Findings from the 2019 Global Burden of Diseases Study and Forecasts for 2030 by Bayesian Age-Period-Cohort Analysis. J Clin Med 2023, 12 (4). DOI: 10.3390/jcm12041291
11. GBD. Global, regional, and national burden of rheumatoid arthritis, 1990-2020, and projections to 2050: a systematic analysis of the Global Burden of Disease Study 2021. Lancet Rheumatol 2023, 5 (10), e594-e610. DOI: 10.1016/s2665-9913(23)00211-4
12. Lin, Y.-J.; Anzaghe, M.; Schülke, S. Update on the Pathomechanism, Diagnosis, and Treatment Options for Rheumatoid Arthritis. Cells 2020, 9 (4), 880. DOI: 10.3390/cells9040880
13. Tanaka, T.; Hishitani, Y.; Ogata, A. Monoclonal antibodies in rheumatoid arthritis: comparative effectiveness of tocilizumab with tumor necrosis factor inhibitors. Biologics 2014, 8, 141-153. DOI: 10.2147/btt.S37509
14. Lim, S. H.; Kim, K.; Choi, C.-I. Pharmacogenomics of Monoclonal Antibodies for the Treatment of Rheumatoid Arthritis. J Pers Med 2022, 12 (8), 1265. DOI: 10.3390/jpm12081265
15. Abbasi, M.; Mousavi, M. J.; Jamalzehi, S.; Alimohammadi, R.; Bezvan, M. H.; Mohammadi, H.; Aslani, S. Strategies toward rheumatoid arthritis therapy; the old and the new. J Cell Physiol 2019, 234 (7), 10018-10031. DOI: 10.1002/jcp.27860
16. Weyand, C. M.; Goronzy, J. J. The immunology of rheumatoid arthritis. Nat Immunol 2021, 22 (1), 10-18. DOI: 10.1038/s41590-020-00816-x
17. Deane, K. D.; Norris, J. M.; Holers, V. M. Preclinical rheumatoid arthritis: identification, evaluation, and future directions for investigation. Rheum Dis Clin North Am 2010, 36 (2), 213-241. DOI: 10.1016/j.rdc.2010.02.001
18. Greenblatt, H. K.; Kim, H. A.; Bettner, L. F.; Deane, K. D. Preclinical rheumatoid arthritis and rheumatoid arthritis prevention. Curr Opin Rheumatol 2020, 32 (3), 289-296. DOI: 10.1097/bor.0000000000000708
19. Castro-Sánchez, P.; Roda-Navarro, P. Physiology and Pathology of Autoimmune Diseases: Role of CD4+ T cells in Rheumatoid Arthritis [Internet]; InTech, 2017. DOI: 10.5772/intechopen.70239.
20. van Drongelen, V.; Holoshitz, J. Human Leukocyte Antigen-Disease Associations in Rheumatoid Arthritis. Rheum Dis Clin North Am 2017, 43 (3), 363-376. DOI: 10.1016/j.rdc.2017.04.003
21. Balsa, A.; Cabezón, A.; Orozco, G.; Cobo, T.; Miranda-Carus, E.; López-Nevot, M. A.; Vicario, J. L.; Martín-Mola, E.; Martín, J.; Pascual-Salcedo, D. Influence of HLA DRB1 alleles in the susceptibility of rheumatoid arthritis and the regulation of antibodies against citrullinated proteins and rheumatoid factor. Arthritis Res Ther 2010, 12 (2), R62. DOI: 10.1186/ar2975
22. Wysocki, T.; Olesińska, M.; Paradowska-Gorycka, A. Current Understanding of an Emerging Role of HLA-DRB1 Gene in Rheumatoid Arthritis–From Research to Clinical Practice. Cells 2020, 9 (5), 1127. DOI: 10.3390/cells9051127
23. Laurent, L.; Clavel, C.; Lemaire, O.; Anquetil, F.; Cornillet, M.; Zabraniecki, L.; Nogueira, L.; Fournié, B.; Serre, G.; Sebbag, M. Fcγ receptor profile of monocytes and macrophages from rheumatoid arthritis patients and their response to immune complexes formed with autoantibodies to citrullinated proteins. Ann Rheumatic Dis 2011, 70 (6), 1052-1059. DOI: 10.1136/ard.2010.142091
24. Gregersen, P. K.; Silver, J.; Winchester, R. J. The shared epitope hypothesis. An approach to understanding the molecular genetics of susceptibility to rheumatoid arthritis. Arthritis Rheum 1987, 30 (11), 1205-1213. DOI: 10.1002/art.1780301102
25. Weyand, C. M.; Hicok, K. C.; Conn, D. L.; Goronzy, J. J. The influence of HLA-DRB1 genes on disease severity in rheumatoid arthritis. Ann Intern Med 1992, 117 (10), 801-806. DOI: 10.7326/0003- 4819-117-10-801
26. MacGregor, A.; Ollier, W.; Thomson, W.; Jawaheer, D.; Silman, A. HLA-DRB1*0401/0404 genotype and rheumatoid arthritis: increased association in men, young age at onset, and disease severity. J Rheumatol 1995, 22 (6), 1032-1036.
27. Ting, Y. T.; Petersen, J.; Ramarathinam, S. H.; Scally, S. W.; Loh, K. L.; Thomas, R.; Suri, A.; Baker, D. G.; Purcell, A. W.; Reid, H. H.; et al. The interplay between citrullination and HLA-DRB1 polymorphism in shaping peptide binding hierarchies in rheumatoid

DOI: 10.36838/IJHSR85.29

arthritis. J Biol Chem 2018, 293 (9), 3236-3251. DOI: 10.1074/jbc.RA117.001013
28. Guo, Q.; Wang, Y.; Xu, D.; Nossent, J.; Pavlos, N. J.; Xu, J. Rheumatoid arthritis: pathological mechanisms and modern pharmacologic therapies. Bone Res 2018, 6, 15. DOI: 10.1038/s41413-018- 0016-9
29. Wehr, P.; Purvis, H.; Law, S. C.; Thomas, R. Dendritic cells, T cells and their interaction in rheumatoid arthritis. Clin Exp Immunol 2019, 196 (1), 12-27. DOI: 10.1111/cei.13256
30. Chen, Y.; Teng, Y.; Xu, P.; Wang, S. The Role of Citrullination Modification in CD4+ T Cells in the Pathogenesis of Immune-Related Diseases. Biomol 2024, 14 (4), 400. DOI: 10.3390/biom14040400
31. de Gruijter, N. M.; Jebson, B.; Rosser, E. C. Cytokine production by human B cells: role in health and autoimmune disease. Clin Exp Immunol 2022, 210 (3), 253-262. DOI: 10.1093/cei/uxac090
32. Ukai, T.; Yumoto, H.; Gibson, F. C., 3rd; Genco, C. A. Macrophage-elicited osteoclastogenesis in response to bacterial stimulation requires Toll-like receptor 2-dependent tumor necrosis factor-alpha production. Infect Immun 2008, 76 (2), 812-819. DOI: 10.1128/iai.01241-07
33. Niu, Q.; Gao, J.; Wang, L.; Liu, J.; Zhang, L. Regulation of differentiation and generation of osteoclasts in rheumatoid arthritis. Front Immunol 2022, 13, 1034050. DOI: 10.3389/fimmu.2022.1034050
34. Ding, Q.; Hu, W.; Wang, R.; Yang, Q.; Zhu, M.; Li, M.; Cai, J.; Rose, P.; Mao, J.; Zhu, Y. Z. Signaling pathways in rheumatoid arthritis: implications for targeted therapy. Sig Transduct Target Ther 2023, 8 (1), 68. DOI: 10.1038/s41392-023-01331-9
35. Liu, S.; Ma, H.; Zhang, H.; Deng, C.; Xin, P. Recent advances on signaling pathways and their inhibitors in rheumatoid arthritis. Clin Immunol 2021, 230, 108793. DOI: 10.1016/j.clim.2021.108793
36. El Masri, H.; Hollingworth, S. A.; van Driel, M.; Benham, H.; McGuire, T. M. Real-world questions and concerns about disease-modifying antirheumatic drugs (DMARDs): a retrospective analysis of questions to a medicine call center. BMC Rheumatol 2020, 4 (1), 27. DOI: 10.1186/s41927- 020-00126-7
37. Peasah, S. K.; Swart, E. C. S.; Huang, Y.; Kane-Gill, S. L.; Seybert, A. L.; Patel, U.; Manolis, C.; Good, C. B. Disease-Modifying Medications in Patients with Rheumatoid Arthritis in the USA: Trends from 2016 to 2021. Drugs - Real World Outcomes 2024, 11 (2), 241-249. DOI: 10.1007/s40801-024-00416-3
38. Crofford, L. J. Use of NSAIDs in treating patients with arthritis. Arthritis Res Ther 2013, 15 Suppl 3 (Suppl 3), S2. DOI: 10.1186/ar4174
39. Bobek, D.; Banić Stipetić, A.; Franić, M.; Lucijanić, M.; Lucijanić, J.; Gudelj Gračanin, A.; Mijačika, L.; Perić, P. Use of non-steroidal anti-inflammatory drugs in patients with advanced active Rheumatoid Arthritis. Acta Clin Croat 2022, 61 (4), 588-598. DOI: 10.20471/acc.2022.61.04.04
40. Iwami, R. S.; Moura, M. D.; Sorrilha, F. B.; Bergamaschi, C. C. Effectiveness and safety of oral corticosteroids in the treatment of rheumatoid arthritis: a systematic review. Revista Brasileira de Farmácia Hospitalar e Serviços de Saúde 2022, 13 (1), 749. DOI: 10.30968/rbfhss.2022.131.0749 (accessed 2025/01/25)
41. Dixit, T.; Vaidya, A.; Ravindran, S. Therapeutic potential of antibody-drug conjugates possessing bifunctional anti-inflammatory action in the pathogenies of rheumatoid arthritis. Arthritis Res Ther 2024, 26 (1), 216. DOI: 10.1186/s13075-024-03452-0
42. Shepard, H. M.; Phillips, G. L.; C, D. T.; Feldmann, M. Developments in therapy with monoclonal antibodies and related proteins. Clin Med (Lond) 2017, 17 (3), 220-232. DOI: 10.7861/clinmedicine17-3-220
43. Falahee, M.; Raza, K. Rheumatoid arthritis prevention: any takers? RMD Open 2021, 7 (1). DOI: 10.1136/rmdopen-2021-001633
44. Sharma, S.; Basu, S.; Goyal, R. K.; Sahoo, P. K.; Mathur, R. Rituximab, a Safer Option for Rheumatoid Arthritis: A Comparison of the Reported Adverse Events of Approved Monoclonal Antibodies. J Pharmacol Pharmacotherap 2022, 13 (4), 330-340. DOI: 10.1177/0976500x231154743
45. Haraoui, B.; Bykerk, V. Etanercept in the treatment of rheumatoid arthritis. Ther Clin Risk Manag 2007, 3 (1), 99-105. DOI: 10.2147/tcrm.2007.3.1.99
46. Jang, D. I.; Lee, A. H.; Shin, H. Y.; Song, H. R.; Park, J. H.; Kang, T. B.; Lee, S. R.; Yang, S. H. The Role of Tumor Necrosis Factor Alpha (TNF-α) in Autoimmune Disease and Current TNF-α Inhibitors in Therapeutics. Int J Mol Sci 2021, 22 (5). DOI: 10.3390/ijms22052719
47. Zhao, S.; Mysler, E.; Moots, R. J. Etanercept for the treatment of rheumatoid arthritis. Immunotherapy 2018, 10 (6), 433-445. DOI: 10.2217/imt-2017-0155
48. Marahleh, A.; Kitaura, H.; Ohori, F.; Kishikawa, A.; Ogawa, S.; Shen, W. R.; Qi, J.; Noguchi, T.; Nara, Y.; Mizoguchi, I. TNF-α Directly Enhances Osteocyte RANKL Expression and Promotes Osteoclast Formation. Front Immunol 2019, 10, 2925. DOI: 10.3389/fimmu.2019.02925
49. Kalliolias, G. D.; Ivashkiv, L. B. TNF biology, pathogenic mechanisms and emerging therapeutic strategies. Nat Rev Rheumatol 2016, 12 (1), 49-62. DOI: 10.1038/nrrheum.2015.169
50. Zia, K.; Ashraf, S.; Jabeen, A.; Saeed, M.; Nur-e-Alam, M.; Ahmed, S.; Al-Rehaily, A. J.; Ul-Haq, Z. Identification of potential TNF-α inhibitors: from silicon to vitro studies. Sci Rep 2020, 10 (1), 20974. DOI: 10.1038/s41598-020-77750-3
51. Szeremeta, A.; Jura-Półtorak, A.; Zoń-Giebel, A.; Olczyk, K.; Komosińska-Vassev, K. Effects of Etanercept and Adalimumab on Serum Levels of Cartilage Remodeling Markers in Women with Rheumatoid Arthritis. J Clin Med 2023, 12 (16). DOI: 10.3390/jcm12165185
52. Lim, H.; Lee, S. H.; Lee, H. T.; Lee, J. U.; Son, J. Y.; Shin, W.; Heo, Y. S. Structural Biology of the TNFα Antagonists Used in the Treatment of Rheumatoid Arthritis. Int J Mol Sci 2018, 19 (3). DOI: 10.3390/ijms19030768
53. Murray, K. M.; Dahl, S. L. Recombinant human tumor necrosis factor receptor (p75) Fc fusion protein (TNFR:Fc) in rheumatoid arthritis. Ann Pharmacother 1997, 31 (11), 1335-1338. DOI: 10.1177/106002809703101111
54. Molta, C. T. Etanercept. In Biologics in General Medicine, Boehncke, W.-H., Radeke, H. H. Eds.; Springer Berlin Heidelberg, 2007; pp 32-41.
55. Combe, B. Update on the use of etanercept across a spectrum of rheumatoid disorders. Biologics 2008, 2 (2), 165-173. DOI: 10.2147/btt.s1379
56. Chen, S. J.; Lin, G. J.; Chen, J. W.; Wang, K. C.; Tien, C. H.; Hu, C. F.; Chang, C. N.; Hsu, W. F.; Fan, H. C.; Sytwu, H. K. Immunopathogenic Mechanisms and Novel Immune-Modulated Therapies in Rheumatoid Arthritis. Int J Mol Sci 2019, 20 (6). DOI: 10.3390/ijms20061332
57. Mohler, K. M.; Torrance, D. S.; Smith, C. A.; Goodwin, R. G.; Stremler, K. E.; Fung, V. P.; Madani, H.; Widmer, M. B. Soluble tumor necrosis factor (TNF) receptors are effective therapeutic agents in lethal endotoxemia and function simultaneously as both TNF carriers and TNF antagonists. J Immunol 1993, 151 (3), 1548-1561. DOI: 10.4049/jimmunol.151.3.1548
58. Feist, E.; Baraliakos, X.; Behrens, F.; Thaçi, D.; Klopsch, T.; Plenske, A.; Blindzellner, L. K.; Klaus, P.; Meng, T.; Löschmann, P. A. Effectiveness of Etanercept in Rheumatoid Arthritis: Real-World

Data from the German Non-interventional Study ADEQUATE with Focus on Treat-to-Target and Patient Reported Outcomes. Rheumatol Ther 2022, 9 (2), 621-635. DOI: 10.1007/s40744-021-00418-5

59. Kotak, S.; Mardekian, J.; Horowicz-Mehler, N.; Shah, A.; Burgess, A.; Kim, J.; Gemmen, E.; Boyd, H.; Koenig, A. Impact of Etanercept Therapy on Disease Activity and Health-Related Quality of Life in Moderate Rheumatoid Arthritis Patients Population from a National British Observational Cohort. Value in Health 2015, 18 (6), 817-823. DOI: 10.1016/j.jval.2015.05.005
60. van Riel, P. L.; Taggart, A. J.; Sany, J.; Gaubitz, M.; Nab, H. W.; Pedersen, R.; Freundlich, B.; MacPeek, D. Efficacy and safety of combination etanercept and methotrexate versus etanercept alone in patients with rheumatoid arthritis with an inadequate response to methotrexate: the ADORE study. Ann Rheum Dis 2006, 65 (11), 1478-1483. DOI: 10.1136/ard.2005.043299
61. Mease, P. J. Adalimumab in the treatment of arthritis. Therap Clin Risk Manag 2007, 3 (1), 133-148. DOI: 10.2147/tcrm. s31133
62. Reimold, A. M. The role of adalimumab in rheumatic and autoimmune disorders: comparison with other biologic agents. Open Access Rheumatol 2012, 4, 33-47. DOI: 10.2147/oarrr. S14569
63. Hu, S.; Liang, S.; Guo, H.; Zhang, D.; Li, H.; Wang, X.; Yang, W.; Qian, W.; Hou, S.; Wang, H.; et al. Comparison of the inhibition mechanisms of adalimumab and infliximab in treating tumor necrosis factor α-associated diseases from a molecular view. J Biol Chem 2013, 288 (38), 27059-27067. DOI: 10.1074/jbc.M113.491530
64. Vena, G. A.; Cassano, N. Drug focus: adalimumab in the treatment of moderate to severe psoriasis. Biologics 2007, 1 (2), 93-103. DOI: 10.2147/btt.s12160280
65. Simonds, M. M.; Freer, S. T.; Al-Jaberi, L.; Brescia, A. C. Adalimumab Effectively Decreases Inflammation Downstream of TNFα Signaling in Synoviocytes from Extended Oligoarticular Juvenile Idiopathic Arthritis. Rheumatol Ther 2024, 11 (1), 143-155. DOI: 10.1007/s40744-023-00628-z
66. Shukla, V.; Tripathi, D.; Sharma, S.; Purohit, A.; Singh, P. Phytomedicine meets nanotechnology: A cellular approach to rheumatoid arthritis treatment. Nano TransMed 2024, 3, 100051. DOI: 10.1016/j.ntm.2024.100051
67. Mease, P. J. Adalimumab in the treatment of arthritis. Ther Clin Risk Manag 2007, 3 (1), 133-148. DOI: 10.2147/tcrm.2007.3.1.133
68. van de Putte, L. B. A.; Atkins, C.; Malaise, M.; Sany, J.; Russell, A. S.; van Riel, P. L. C. M.; Settas, L.; Bijlsma, J. W.; Todesco, S.; Dougados, M.; et al. Efficacy and safety of adalimumab as monotherapy in patients with rheumatoid arthritis for whom previous disease modifying antirheumatic drug treatment has failed. Ann Rheumatic Dis 2004, 63 (5), 508-516. DOI: 10.1136/ard.2003.013052
69. Pappas, D. A.; Kremer, J. M.; Griffith, J.; Reed, G.; Salim, B.; Karki, C.; Garg, V. Long-Term Effectiveness of Adalimumab in Patients with Rheumatoid Arthritis: An Observational Analysis from the Corrona Rheumatoid Arthritis Registry. Rheumatol Ther 2017, 4 (2), 375-389. DOI: 10.1007/s40744-017-0077-z
70. Haraoui, B.; Cividino, A.; Stewart, J.; Guérette, B.; Keystone, E. C. Safety and effectiveness of adalimumab in a clinical setting that reflects Canadian standard of care for the treatment of rheumatoid arthritis (RA): Results from the CanACT study. BMC Musculoskelet Disord 2011, 12 (1), 261. DOI: 10.1186/1471-2474-12-261
71. Heiberg, M. S.; Rødevand, E.; Mikkelsen, K.; Kaufmann, C.; Didriksen, A.; Mowinckel, P.; Kvien, T. K. Adalimumab and methotrexate are more effective than adalimumab alone in patients with established rheumatoid arthritis: results from a 6-month longitudinal, observational, multicentre study. Ann Rheum Dis 2006, 65 (10), 1379-1383. DOI: 10.1136/ard.2006.051540
72. Tektonidou, M. G.; Katsifis, G.; Georgountzos, A.; Theodoridou, A.; Koukli, E. M.; Kandili, A.; Giokic-Kakavouli, G.; Karatsourakis, T. D. Real-world evidence of the impact of adalimumab on work productivity and sleep measures in patients with rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis. Ther Adv Musculoskelet Dis 2020, 12, 1759720x20949088. DOI: 10.1177/1759720x20949088
73. Liang, S.; Dai, J.; Hou, S.; Su, L.; Zhang, D.; Guo, H.; Hu, S.; Wang, H.; Rao, Z.; Guo, Y.; et al. Structural basis for treating tumor necrosis factor α (TNFα)-associated diseases with the therapeutic antibody infliximab. J Biol Chem 2013, 288 (19), 13799-13807. DOI: 10.1074/jbc.M112.433961
74. Elliott, M. J.; Maini, R. N.; Feldmann, M.; Long-Fox, A.; Charles, P.; Katsikis, P.; Brennan, F. M.; Walker, J.; Bijl, H.; Ghrayeb, J.; et al. Treatment of rheumatoid arthritis with chimeric monoclonal antibodies to tumor necrosis factor alpha. Arthritis Rheum 1993, 36 (12), 1681-1690. DOI: 10.1002/art.1780361206
75. Charles, P.; Elliott, M. J.; Davis, D.; Potter, A.; Kalden, J. R.; Antoni, C.; Breedveld, F. C.; Smolen, J. S.; Eberl, G.; deWoody, K.; et al. Regulation of cytokines, cytokine inhibitors, and acute-phase proteins following anti-TNF-alpha therapy in rheumatoid arthritis. J Immunol 1999, 163 (3), 1521- 1528. DOI: 10.4049/jimmunol.163.3.1521
76. Perdriger, A. Infliximab in the treatment of rheumatoid arthritis. Biologics 2009, 3, 183-191. DOI: 10.2147/btt.2009.3099
77. Zhang, J.; Liu, H.; Chen, Y.; Liu, H.; Zhang, S.; Yin, G.; Xie, Q. Augmenting regulatory T cells: new therapeutic strategy for rheumatoid arthritis. Front Immunol 2024, 15, Review. DOI: 10.3389/fimmu.2024.1312919
78. Yu, Q.; Xu, M.; Yu, F.; Jin, Y. CD4(+) CD25(+) regulatory T cells as a therapeutic target in rheumatoid arthritis. Cent Eur J Immunol 2014, 39 (1), 100-103. DOI: 10.5114/ceji.2014.42133
79. Thorne, C.; Bensen, W. G.; Choquette, D.; Chow, A.; Khraishi, M.; Atkins, C. J.; Kelsall, J. T.; Lehman, A. J.; Shawi, M.; Khalil, H.; et al. Effectiveness and safety of infliximab in rheumatoid arthritis: analysis from a Canadian multicenter prospective observational registry. Arthritis Care Res (Hoboken) 2014, 66 (8), 1142-1151. DOI: 10.1002/acr.22290
80. Marotte, H.; Cimaz, R. Etanercept - TNF receptor and IgG1 Fc fusion protein: is it different from other TNF blockers? Expert Opin Biol Ther 2014, 14 (5), 569-572. DOI: 10.1517/14712598.2014.896334
81. Richter, J. A.; Bickston, S. J. Infliximab Use in Luminal Crohn's Disease. Gastroenterol Clin North America 2006, 35 (4), 775-793. DOI: 10.1016/j.gtc.2006.09.003
82. Reddy, S. P.; Shah, V. V.; Lin, E. J.; Wu, J. J. Chapter 8 - Etanercept. In Therapy for Severe Psoriasis, Wu, J. J., Feldman, S. R., Lebwohl, M. G. Eds.; Elsevier, 2016; pp 83-96.
83. Knight, D. M.; Trinh, H.; Le, J.; Siegel, S.; Shealy, D.; McDonough, M.; Scallon, B.; Moore, M. A.; Vilcek, J.; Daddona, P.; et al. Construction and initial characterization of a mouse-human chimeric anti-TNF antibody. Mol Immunol 1993, 30 (16), 1443-1453. DOI: 10.1016/0161-5890(93)90106-l
84. Pan, A.; Gerriets, V. Etanercept. StatPearls Publishing: 2023.
85. Ellis, C. R.; Azmat, C. E. Adalimumab. StatPearls Publishing: 2020.
86. Constantin, A.; Caporali, R.; Edwards, C. J.; Fonseca, J. E.; Iannone, F.; Keystone, E.; Schulze- Koops, H.; Kwon, T.; Kim, S.; Yoon, S.; et al. Efficacy of subcutaneous vs intravenous infliximab in rheumatoid arthritis: a post-hoc analysis of a randomized phase III trial. Rheumatol 2022, 62 (8), 2838- 2844. DOI: 10.1093/rheumatology/keac689 (accessed 1/27/2025)

DOI: 10.36838/IJHSR85.29

87. Smolen, J. S.; Emery, P. Infliximab: 12 years of experience. Arthritis Res Ther 2011, 13 (1), S2. DOI: 10.1186/1478-6354-13-S1-S2
88. Maini, R. N.; Feldmann, M. How does infliximab work in rheumatoid arthritis? Arthritis Res 2002, 4 Suppl 2 (Suppl 2), S22-28. DOI: 10.1186/ar549
89. Shannon, E.; Daffy, J.; Jones, H.; Paulson, A.; Vicik, S. M. Etanercept (Enbrel(®)) alternative storage at ambient temperature. Clin Pharmacol 2017, 9, 87-99. DOI: 10.2147/cpaa.S131832
90. Park, D.; Yun, J.; Hwang, S. J.; Park, S. J. Evaluation of Physicochemical and Biological Stability of 36-Months-Aged SB5 (Adalimumab Biosimilar) for 4 Weeks at Room Temperature. Adv Ther 2019, 36 (2), 442-450. DOI: 10.1007/s12325-018-0851-5
91. Beer, P. M.; Wong, S. J.; Schartman, J. P.; Kulas, K. E.; Hartman, C. L.; Giganti, M.; Falk, N. S. Infliximab stability after reconstitution, dilution, and storage under refrigeration. Retina 2010, 30 (1), 81-84. DOI: 10.1097/IAE.0b013e3181b48fb4
92. Kotak, S.; Mardekian, J.; Horowicz-Mehler, N.; Shah, A.; Burgess, A.; Kim, J.; Gemmen, E.; Boyd, H.; Koenig, A. Impact of Etanercept Therapy on Disease Activity and Health-Related Quality of Life in Moderate Rheumatoid Arthritis Patients Population from a National British Observational Cohort. Value Health 2015, 18 (6), 817-823. DOI: https://doi.org/10.1016/j.jval.2015.05.005
93. Davis, J. C., Jr.; Van Der Heijde, D.; Braun, J.; Dougados, M.; Cush, J.; Clegg, D. O.; Kivitz, A.; Fleischmann, R.; Inman, R.; Tsuji, W. Recombinant human tumor necrosis factor receptor (etanercept) for treating ankylosing spondylitis: a randomized, controlled trial. Arthritis Rheum 2003, 48 (11), 3230- 3236. DOI: 10.1002/art.11325
94. Scheinfeld, N. Adalimumab: a review of side effects. Expert Opin Drug Saf 2005, 4 (4), 637- 641. DOI: 10.1517/14740338.4.4.637
95. Mourad, A. A.; Boktor, M. N.; Yilmaz-Demirdag, Y.; Bahna, S. L. Adverse reactions to infliximab and the outcome of desensitization. Ann Allergy Asthma Immunol 2015, 115 (2), 143-146. DOI: 10.1016/j.anai.2015.06.004
96. Hansen, K. E.; Cush, J.; Singhal, A.; A. Cooley, D.; Cohen, S.; Patel, S. R.; Genovese, M.; Sundaramurthy, S.; Schiff, M. The safety and efficacy of leflunomide in combination with infliximab in rheumatoid arthritis. Arthritis Rheumatism 2004, 51 (2), 228-232. DOI: 10.1002/art.20228
97. Curtis, J. R.; Singh, J. A. Use of biologics in rheumatoid arthritis: current and emerging paradigms of care. Clin Therap 2011, 33 (6), 679-707. DOI: 10.1016/j.clinthera.2011.05.044
98. Putrik, P.; Ramiro, S.; Kvien, T. K.; Sokka, T.; Pavlova, M.; Uhlig, T.; Boonen, A. Inequities in access to biologic and synthetic DMARDs across 46 European countries. Ann Rheum Dis 2014, 73 (1), 198-206. DOI: 10.1136/annrheumdis-2012-202603
99. Gholami, A.; Azizpoor, J.; Aflaki, E.; Rezaee, M.; Keshavarz, K. Cost-Effectiveness Analysis of Biopharmaceuticals for Treating Rheumatoid Arthritis: Infliximab, Adalimumab, and Etanercept. BioMed Res Int 2021, 2021 (1), 4450162. DOI: 10.1155/2021/4450162
100. Tanaka, T.; Narazaki, M.; Kishimoto, T. IL-6 in inflammation, immunity, and disease. Cold Spring Harb Perspect Biol 2014, 6 (10), a016295. DOI: 10.1101/cshperspect.a016295
101. Kishimoto, T. IL-6: from its discovery to clinical applications. Int Immunol 2010, 22 (5), 347- 352. DOI: 10.1093/intimm/dxq030
102. Kishimoto, T. Interleukin-6: discovery of a pleiotropic cytokine. Arthritis Res Ther 2006, 8 Suppl 2 (Suppl 2), S2. DOI: 10.1186/ar1916
103. Mihara, M.; Hashizume, M.; Yoshida, H.; Suzuki, M.; Shiina, M. IL-6/IL-6 receptor system and its role in physiological and pathological conditions. Clin Sci (Lond) 2012, 122 (4), 143-159. DOI: 10.1042/cs20110340
104. Paonessa, G.; Graziani, R.; De Serio, A.; Savino, R.; Ciapponi, L.; Lahm, A.; Salvati, A. L.; Toniatti, C.; Ciliberto, G. Two distinct and independent sites on IL-6 trigger gp 130 dimer formation and signalling. Embo J 1995, 14 (9), 1942-1951. DOI: 10.1002/j.1460-2075.1995.tb07186.x
105. Xu, S.; Deng, K.-Q.; Lu, C.; Fu, X.; Zhu, Q.; Wan, S.; Zhang, L.; Huang, Y.; Nie, L.; Cai, H.; et al. Interleukin-6 classic and trans-signaling utilize glucose metabolism reprogramming to achieve anti- or pro-inflammatory effects. Metabolism 2024, 155, 155832. DOI: 10.1016/j.metabol.2024.155832
106. Favalli, E. G. Understanding the Role of Interleukin-6 (IL-6) in the Joint and Beyond: A Comprehensive Review of IL-6 Inhibition for the Management of Rheumatoid Arthritis. Rheumatol Ther 2020, 7 (3), 473-516. DOI: 10.1007/s40744-020-00219-2
107. Jarlborg, M.; Gabay, C. Systemic effects of IL-6 blockade in rheumatoid arthritis beyond the joints. Cytokine 2022, 149, 155742. DOI: 10.1016/j.cyto.2021.155742
108. Biggioggero, M.; Crotti, C.; Becciolini, A.; Favalli, E. G. Tocilizumab in the treatment of rheumatoid arthritis: an evidence-based review and patient selection. Drug Des Devel Ther 2019, 13, 57-70. DOI: 10.2147/dddt.S150580
109. Rose-John, S.; Winthrop, K.; Calabrese, L. The role of IL-6 in host defence against infections: immunobiology and clinical implications. Nat Rev Rheumatol 2017, 13 (7), 399-409. DOI: 10.1038/nrrheum.2017.83
110. Stubenrauch, K.; Wessels, U.; Birnboeck, H.; Ramirez, F.; Jahreis, A.; Schleypen, J. Subset analysis of patients experiencing clinical events of a potentially immunogenic nature in the pivotal clinical trials of tocilizumab for rheumatoid arthritis: Evaluation of an antidrug antibody ELISA using clinical adverse event-driven immunogenicity testing. Clin Ther 2010, 32 (9), 1597-1609. DOI: 10.1016/j.clinthera.2010.07.021
111. Mihara, M.; Ohsugi, Y.; Kishimoto, T. Tocilizumab, a humanized anti-interleukin-6 receptor antibody, for treatment of rheumatoid arthritis. Open Access Rheumatol 2011, 3, 19-29. DOI: 10.2147/oarrr.S17118
112. Nishimoto, N.; Miyasaka, N.; Yamamoto, K.; Kawai, S.; Takeuchi, T.; Azuma, J.; Kishimoto, T. Study of active controlled tocilizumab monotherapy for rheumatoid arthritis patients with an inadequate response to methotrexate (SATORI): significant reduction in disease activity and serum vascular endothelial growth factor by IL-6 receptor inhibition therapy. Mod Rheumatol 2009, 19 (1), 12-19. DOI: 10.1007/s10165-008-0125-1
113. Nishimoto, N.; Hashimoto, J.; Miyasaka, N.; Yamamoto, K.; Kawai, S.; Takeuchi, T.; Murata, N.; van der Heijde, D.; Kishimoto, T. Study of active controlled monotherapy used for rheumatoid arthritis, an IL-6 inhibitor (SAMURAI): evidence of clinical and radiographic benefit from an x ray reader-blinded randomised controlled trial of tocilizumab. Ann Rheum Dis 2007, 66 (9), 1162-1167. DOI: 10.1136/ard.2006.068064
114. Okuda, Y. Review of tocilizumab in the treatment of rheumatoid arthritis. Biologics 2008, 2 (1), 75-82. DOI: 10.2147/btt.s1828
115. Genovese, M.; Fleischmann, R.; Fiore, S.; Radin, A.; Fan, C.; Huizinga, T. SAT0117 sarilumab, a subcutaneously-administered, fully human monoclonal antibody inhibitor of the IL-6 receptor: Relationship between eular responses and change from baseline of selected clinical parameters. Ann Rheumatic Dis 2013, 72 (Suppl 3), A620-A620. DOI: 10.1136/annrheumdis-2013-eular.1843
116. Zhang, L.; Luan, B.; Adler, A.; Eichten, A.; Daly, C.; Thurston, G. Sarilumab (REGN88), a fully human anti-IL6R antibody, inhibits tumor growth in preclinical models, as a single agent and in combination with the VEGF blocker aflibercept. Cancer Res

2012, 72 (8_Supplement), 2723-2723. DOI: 10.1158/1538-7445.AM2012-2723
117. Radin, A.; Mellis, S.; Jasson, M.; Nadler, D.; Belomestnov, P.; Wu, R. REGN88/SAR153191, a fully-human interleukin-6 receptor monoclonal antibody, reduces acute phase reactants in patients with rheumatoid arthritis: preliminary observations from Phase 1 studies. Arthritis Rheum 2010, 62 (Suppl 10), S470.
118. Huizinga, T. W.; Fleischmann, R. M.; Jasson, M.; Radin, A. R.; van Adelsberg, J.; Fiore, S.; Huang, X.; Yancopoulos, G. D.; Stahl, N.; Genovese, M. C. Sarilumab, a fully human monoclonal antibody against IL-6Rα in patients with rheumatoid arthritis and an inadequate response to methotrexate: efficacy and safety results from the randomised SARIL-RA-MOBILITY Part A trial. Ann Rheum Dis 2014, 73 (9), 1626-1634. DOI: 10.1136/annrheumdis-2013-204405
119. Boyapati, A.; Msihid, J.; Fiore, S.; van Adelsberg, J.; Graham, N. M. H.; Hamilton, J. D. Sarilumab plus methotrexate suppresses circulating biomarkers of bone resorption and synovial damage in patients with rheumatoid arthritis and inadequate response to methotrexate: a biomarker study of MOBILITY. Arthritis Res Ther 2016, 18 (1), 225. DOI: 10.1186/s13075-016-1132-9
120. Rafique, A.; Martin, J.; Blome, M.; Huang, T.; Ouyang, A.; Papadopoulos, N. AB0037 Evaluation of the binding kinetics and functional bioassay activity of sarilumab and tocilizumab to the human IL-6 receptor (IL-6R) alpha. Ann Rheum Dis 2013, 72 (Suppl 3), A797-A797. DOI: 10.1136/annrheumdis- 2013-eular.2360
121. Burmester, G. R.; Bykerk, V. P.; Buch, M. H.; Tanaka, Y.; Kameda, H.; Praestgaard, A.; van Hoogstraten, H.; Fernandez-Nebro, A.; Huizinga, T. Sarilumab monotherapy vs sarilumab and methotrexate combination therapy in patients with rheumatoid arthritis. Rheumatology (Oxford) 2022, 61 (6), 2596-2602. DOI: 10.1093/rheumatology/keab676
122. Strand, V.; Kosinski, M.; Chen, C. I.; Joseph, G.; Rendas-Baum, R.; Graham, N. M.; van Hoogstraten, H.; Bayliss, M.; Fan, C.; Huizinga, T.; et al. Sarilumab plus methotrexate improves patient-reported outcomes in patients with active rheumatoid arthritis and inadequate responses to methotrexate: results of a phase III trial. Arthritis Res Ther 2016, 18 (1), 198. DOI: 10.1186/s13075- 016-1096-9
123. Burmester, G. R.; Lin, Y.; Patel, R.; van Adelsberg, J.; Mangan, E. K.; Graham, N. M.; van Hoogstraten, H.; Bauer, D.; Ignacio Vargas, J.; Lee, E. B. Efficacy and safety of sarilumab monotherapy versus adalimumab monotherapy for the treatment of patients with active rheumatoid arthritis (MONARCH): a randomised, double-blind, parallel-group phase III trial. Ann Rheum Dis 2017, 76 (5), 840-847. DOI: 10.1136/annrheumdis-2016-210310
124. Scott, L. J. Tocilizumab: A Review in Rheumatoid Arthritis. Drugs 2017, 77 (17), 1865-1879. DOI: 10.1007/s40265-017-0829-7
125. Jones, G.; Sebba, A.; Gu, J.; Lowenstein, M. B.; Calvo, A.; Gomez-Reino, J. J.; Siri, D. A.; Tomšič, M.; Alecock, E.; Woodworth, T. Comparison of tocilizumab monotherapy versus methotrexate monotherapy in patients with moderate to severe rheumatoid arthritis: the AMBITION study. Ann Rheumatic Dis 2010, 69 (01), 88-96. DOI: 10.1136/ard.2008.105197
126. Genovese, M. C.; Fleischmann, R.; Kivitz, A. J.; Rell-Bakalarska, M.; Martincova, R.; Fiore, S.; Rohane, P.; van Hoogstraten, H.; Garg, A.; Fan, C.; et al. Sarilumab Plus Methotrexate in Patients With Active Rheumatoid Arthritis and Inadequate Response to Methotrexate: Results of a Phase III Study. Arthritis Rheumatol 2015, 67 (6), 1424-1437. DOI: 10.1002/art.39093
127. Kivitz, A.; Baret-Cormel, L.; van Hoogstraten, H.; Wang, S.; Parrino, J.; Xu, C.; Stanislav, M. Usability and patient preference phase 3 study of the sarilumab pen in patients with active moderate to severe rheumatoid arthritis. Rheumatol Ther 2018, 5, 231-242. DOI: 10.1007/s40744-017-0090-2
128. Kaneko, A. Tocilizumab in rheumatoid arthritis: efficacy, safety and its place in therapy. Ther Adv Chronic Dis 2013, 4 (1), 15-21. DOI: 10.1177/2040622312466908
129. Saki, A.; Rajaei, E.; Rahim, F. Safety and efficacy of tocilizumab for rheumatoid arthritis: a systematic review and meta-analysis of clinical trial studies. Reumatologia 2021, 59 (3), 169-179. DOI: 10.5114/reum.2021.107026
130. Burmester, G. R.; Strand, V.; Kivitz, A. J.; Hu, C. C.; Wang, S.; van Hoogstraten, H.; Klier, G. L.; Fleischmann, R. Long-term safety and efficacy of sarilumab with or without background csDMARDs in rheumatoid arthritis. Rheumatology (Oxford) 2023, 62 (10), 3268-3279. DOI: 10.1093/rheumatology/kead062
131. Metghalchi, Y.; Yaghoubi, N.; Yousefi, N.; Ahmadi, R.; Kargar, A.; Zargaran, M.; Rezaei, S. Cost-effectiveness analysis of Tocilizumab compared to Adalimumab in the treatment of severe active rheumatoid arthritis in Iran. Cost Eff Resour Alloc 2024, 22 (1), 82. DOI: 10.1186/s12962-024-00592-7 132. Whittington, M. D.; McQueen, R. B.; Ollendorf, D. A.; Chapman, R. H.; Kumar, V. M.; Synnott, P. G.; Agboola, F.; Campbell, J. D. Assessing the Value of Sarilumab Monotherapy for Adults with Moderately to Severely Active Rheumatoid Arthritis: A Cost-Effectiveness Analysis. J Manag Care Spec Pharm 2019, 25 (1), 80-87. DOI: 10.18553/jmcp.2019.25.1.080
133. Aaltonen, K. J.; Ylikylä, S.; Tuulikki Joensuu, J.; Isomäki, P.; Pirilä, L.; Kauppi, M.; Rannio, T.; Eklund, K.; Blom, M.; Nordström, D. Efficacy and effectiveness of tumour necrosis factor inhibitors in the treatment of rheumatoid arthritis in randomized controlled trials and routine clinical practice. Rheumatol 2017, 56 (5), 725-735. DOI: 10.1093/rheumatology/kew467 (accessed 1/28/2025)
134. Ma, X.; Xu, S. TNF inhibitor therapy for rheumatoid arthritis (Review). Biomed Rep 2013, 1 (2), 177-184. DOI: 10.3892/br.2012.42
135. Nishimoto, N.; Miyasaka, N.; Yamamoto, K.; Kawai, S.; Takeuchi, T.; Azuma, J. Long-term safety and efficacy of tocilizumab, an anti-IL-6 receptor monoclonal antibody, in monotherapy, in patients with rheumatoid arthritis (the STREAM study): evidence of safety and efficacy in a 5-year extension study. Ann Rheum Dis 2009, 68 (10), 1580-1584. DOI: 10.1136/ard.2008.092866
136. Tanaka, Y.; Martin Mola, E. IL-6 targeting compared to TNF targeting in rheumatoid arthritis: studies of olokizumab, sarilumab and sirukumab. Ann Rheum Dis 2014, 73 (9), 1595-1597. DOI: 10.1136/annrheumdis-2013-205002
137. Stevenson, M.; Archer, R.; Tosh, J.; Simpson, E.; Everson-Hock, E.; Stevens, J.; Hernandez-Alava, M.; Paisley, S.; Dickinson, K.; Scott, D.; et al. Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for the treatment of rheumatoid arthritis not previously treated with disease-modifying antirheumatic drugs and after the failure of conventional disease-modifying antirheumatic drugs only: systematic review and economic evaluation. Health Technol Assess 2016, 20 (35), 1-610. DOI: 10.3310/hta20350
138. Gabay, C.; Emery, P.; van Vollenhoven, R.; Dikranian, A.; Alten, R.; Pavelka, K.; Klearman, M.; Musselman, D.; Agarwal, S.; Green, J.; et al. Tocilizumab monotherapy versus adalimumab monotherapy for treatment of rheumatoid arthritis (ADACTA): a randomised, double-blind, controlled phase 4 trial. Lancet 2013, 381 (9877), 1541-1550. DOI: 10.1016/s0140-6736(13)60250-0
139. Yukishima, T.; Nakamura, Y.; Ohmura, S.-i.; Kobayakawa, T. Effectiveness of baricitinib versus sarilumab on disease activity in patients with rheumatoid arthritis: a propensity score matching

DOI: 10.36838/IJHSR85.29

study. Rheumatol Adv Pract 2025. DOI: 10.1093/rap/rkaf006 (accessed 1/28/2025)
140. Ogata, A.; Atsumi, T.; Fukuda, T.; Hirabayashi, Y.; Inaba, M.; Ishiguro, N.; Kai, M.; Kawabata, D.; Kida, D.; Kohsaka, H.; et al. Sustainable Efficacy of Switching From Intravenous to Subcutaneous Tocilizumab Monotherapy in Patients With Rheumatoid Arthritis. Arthritis Care Res (Hoboken) 2015, 67 (10), 1354-1362. DOI: 10.1002/acr.22598
141. Burmester, G. R.; Rubbert-Roth, A.; Cantagrel, A.; Hall, S.; Leszczynski, P.; Feldman, D.; Rangaraj, M. J.; Roane, G.; Ludivico, C.; Lu, P.; et al. A randomised, double-blind, parallel-group study of the safety and efficacy of subcutaneous tocilizumab versus intravenous tocilizumab in combination with traditional disease-modifying antirheumatic drugs in patients with moderate to severe rheumatoid arthritis (SUMMACTA study). Ann Rheum Dis 2014, 73 (1), 69-74. DOI: 10.1136/annrheumdis-2013-203523
142. Aaltonen, K. J.; Virkki, L. M.; Malmivaara, A.; Konttinen, Y. T.; Nordström, D. C.; Blom, M. Systematic review and meta-analysis of the efficacy and safety of existing TNF blocking agents in treatment of rheumatoid arthritis. PLoS One 2012, 7 (1), e30275. DOI: 10.1371/journal.pone.0030275
143. Saiki, O.; Uda, H. Successful extension of tocilizumab infusion intervals from 4 weeks to 6 or 5 weeks in 90% of RA patients with good response to 4-week intervals. Clin Exp Rheumatol 2017, 35 (4), 666-670. DOI: 10.1136/annrheumdis-2016-eular.4501
144. Ogata, A.; Amano, K.; Dobashi, H.; Inoo, M.; Ishii, T.; Kasama, T.; Kawai, S.; Kawakami, A.; Koike, T.; Miyahara, H.; et al. Longterm Safety and Efficacy of Subcutaneous Tocilizumab Monotherapy: Results from the 2-year Open-label Extension of the MUSASHI Study. J Rheumatol 2015, 42 (5), 799- 809. DOI: 10.3899/jrheum.140665
145. Zheng, B.; Liu, M.; Dai, D.; Shang, Y.; Dou, X.; Liu, B.; Zhong, Z.; Huang, S.; Luo, D. Safety of TNF α inhibitors: A real-world study based on the US FDA Adverse Event Reporting System Database. Med 2024, 103 (29). DOI: 10.1097/MD.0000000000039012
146. Li, J.; Zhang, Z.; Wu, X.; Zhou, J.; Meng, D.; Zhu, P. Risk of Adverse Events After Anti-TNF Treatment for Inflammatory Rheumatological Disease. A Meta-Analysis. Front Pharmacol 2021, 12, 746396. DOI: 10.3389/fphar.2021.746396
147. Kaltsonoudis, E.; Zikou, A. K.; Voulgari, P. V.; Konitsiotis, S.; Argyropoulou, M. I.; Drosos, A. A. Neurological adverse events in patients receiving anti-TNF therapy: a prospective imaging and electrophysiological study. Arthritis Res Ther 2014, 16 (3), R125. DOI: 10.1186/ar4582
148. Yoshida, S.; Miyata, M.; Suzuki, E.; Kanno, T.; Sumichika, Y.; Saito, K.; Matsumoto, H.; Temmoku, J.; Fujita, Y.; Matsuoka, N.; et al. Safety of JAK and IL-6 inhibitors in patients with rheumatoid arthritis: a multicenter cohort study. Front Immunol 2023, 14, 1267749. DOI: 10.3389/fimmu.2023.1267749
149. Huoponen, S.; Aaltonen, K. J.; Viikinkoski, J.; Rutanen, J.; Relas, H.; Taimen, K.; Puolakka, K.; Nordström, D.; Blom, M. Cost-effectiveness of abatacept, tocilizumab and TNF-inhibitors compared with rituximab as second-line biologic drug in rheumatoid arthritis. PLoS One 2019, 14 (7), e0220142. DOI: 10.1371/journal.pone.0220142
150. Lekander, I.; Borgström, F.; Lysholm, J.; van Vollenhoven, R. F.; Lindblad, S.; Geborek, P.; Kobelt, G. The cost-effectiveness of TNF-inhibitors for the treatment of rheumatoid arthritis in Swedish clinical practice. Euro J Health Econ 2013, 14 (6), 863-873. DOI: 10.1007/s10198-012-0431-6
151. Manders, S. H. M.; Kievit, W.; Adang, E.; Brus, H. L.; Moens, H. J. B.; Hartkamp, A.; Hendriks, L.; Brouwer, E.; Visser, H.; Vonkeman, H. E.; et al. Cost-effectiveness of abatacept, rituximab, and TNFi treatment after previous failure with TNFi treatment in rheumatoid arthritis: a pragmatic multi-centre randomised trial. Arthritis Res Ther 2015, 17 (1), 134. DOI: 10.1186/s13075-015-0630-5

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