CENTER OF EXCELLENCE FOR OPEN SCIENCE

Open Access

Email: COR@ceospublishers.com

CEOS Orthopedics and Rheumatology

Research Article

Received Date: December 09, 2023

Accepted Date: January 09, 2024

Published Date: January 11, 2024

*Corresponding Author

Xiaofeng Rong, Department of Combination of Chinese and Western Medicine, The First Affiliated Hospital of Chongqing Medical University, Chongqing 400016, China, E-mail: rongxiaofeng2022@163.com, ORCID: 0000-0001-9549-8099

Citation

Lianying Cheng and Xiaofeng Rong (2024) Application of Biological Agents in Rheumatoid Arthritis. CEOS Orthop Rheumatol 2(1): 101

Application of Biological Agents in Rheumatoid Arthritis

Lianying Cheng and Xiaofeng Rong*

Department of Combination of Chinese and Western Medicine, The First Affiliated Hospital of Chongqing Medical University, Chongqing 400016, China

Abstract

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune disease with synovial inflammation as the main pathological characteristic. Joint destruction and loss of function seriously affect patient quality of life. Currently, disease-modifying antirheumatic drugs (DMARDs) and glucocorticoids are the main strategies to treat RA.

Long-term use of this medicine can cause drug resistance and poor treatment effects, even leading to organ damage. Therefore, there is an urgent need to find novel targeted drugs for RA treatment. Recently, biologic agents for the treatment of RA have received increasing attention due to their few side effects, low drug dependence and direct action on target cells for precise therapy. This review discusses in detail the pathogenesis of RA and the development of biologics that target and inhibit inflammatory cytokine (TNF-α, IL-6, and IL-1β) receptors, B lymphocyte receptors and JAK inhibitors in RA, providing new insights and directions for the treatment of RA.

Keywords: Rheumatoid Arthritis; Targeted Therapy; Receptor Inhibitors

Introduction

Rheumatoid arthritis (RA) is a chronic, systemic, autoimmune disease characterized by pathological changes such as intra-articular synovial inflammation, bone erosion and bone destruction, as well as extra-articular pannus formation, with a worldwide incidence of 0.5-1% [1-3].

RA can cause damage not only to the joints, but also to other tissues and organs, including the heart, kidneys, lungs, digestive system, eyes, skin, and nervous system. These complications are closely related to the prognosis of patients with RA [4,5]. RA can also be associated with Sjogren's syndrome. Primary Sjogren's syndrome (pSS) is distinguished from secondary Sjögren's syndrome (sSS) which occurs as a part of other autoimmune diseases. sSS is commonly diagnosed with systemic lupus erythematosus (15-36%), rheumatoid arthritis (20-32%) and limited and progressive systemic sclerosis (11-24%) and, is less frequently found with multiple sclerosis and autoimmune hepatitis and thyroiditis [5]. Bone destruction in the later stage of the disease leads to loss of joint function, which seriously affects patient quality of life. Moreover, the long-term treatment process results in a major financial and psychological burden on patients [6]. The currently used disease-modifying antirheumatic drugs (DMARDs) and glucocorticoid therapies are insufficient in the treatment of RA and have many side effects. Therefore, finding an economical, safe and efficient drug is crucial for the treatment of RA. However, the pathogenesis of RA is still unclear, and several studies have shown that it is related to abnormal immune responses and inflammation mediated by antigens (foreign or self), antigen-presenting cells, lymphocytes, and cytokines [1,7,8].

In RA, B-cell reduction and immunodeficiency lead to the formation of autoantibodies and trigger a cascade of inflammatory responses [9]. As the disease progresses, citrulline-specific B cells (plasmablasts or plasma cells) express autoantibodies to citrullinated antigens (ACPAs), and these ACPA-positive plasmablasts circulate in the peripheral bloodstream [10]. Citrullinated fibrinogen directly leads to bone destruction and loss of osteoprotective effects. The development of ACPA is thought to be related to certain genetic background factors such as HLA-DR. ACPA and RF form immune complexes with citrullinated proteins and activate macrophages, triggering the release of inflammatory cytokines such as tumor necrosis factor TNF-α and interleukin IL-6 [11]. Moreover, ACPAs can stimulate macrophages and synovial fibroblasts (FLSs) to release inflammatory cytokines, promoting the development and progression of inflammation [12]. Therefore, ACPAs are important inflammatory markers in the synovial fluid of RA patients, and the detection rate of ACPA-IgG-Fab glycosylation is 100% [13]. Additionally, inflammatory cytokines including proinflammatory cytokines and anti-inflammatory cytokines, directly influence inflammation and play an important role in the disease progression of RA. Proinflammatory cytokines (TNF-α, IL-6, IL-1, IL-1β, IL-17, IL-9, M-CSF, etc.) can regulate the proliferation and apoptosis of FLSs through the nuclear factor kappa-B (NF-KB) and Janus kinase-signal transducers activators (JAK-STAT) signaling pathways and promote macrophage polarization of transcription. When proinflammatory substances are released, they gradually amplify the inflammatory response, which in turn aggravates the progression of the disease [14,15]. Inflammatory cytokines function mainly through the JAK-STAT signaling pathway [16]. Members of the JAK family [JAK 1, JAK 2, JAK 3, and tyrosine kinase 2 (tyk2)] activate STAT via phosphorylation and mediate intracellular communication between cytokine receptors and cell membranes [17]. By activating the transcription of proinflammatory protein genes in the nucleus, the JAK/STAT signaling pathway enhances T-cell recruitment and differentiation. Therefore, this pathway plays an important role in initiating immune activation and inflammation and interfering with important cellular functions, including signal transmission, growth, and survival.

Thus, methods to inhibit the production of proinflammatory cytokines, the antigen-antibody response and JAK/STAT signaling pathway activation in RA have become the current focus of research on RA treatment. Recent medical research with innovative bioengineering technology has led to, an increasing number of targeted drugs being used for the treatment of rheumatic disease [18]. This review focuses on the current targeted drugs used for RA treatment.

Pathogenesis of RA

Environmental and Genetic Factors

Various environmental and genetic factors contribute to the pathogenesis of RA and, which mainly include the following. (1) Inherited susceptibility genes, the most strongly associated factor with RA, are the human leucocyte antigen (HLA) gene cluster, located on the short arm of chromosome 6, such as HLA-I (HLA-A, B, C), HLA-II (HLA-DR, DQ, DP) and HLA-III(C2,C4,Bf). The relationship between HLA-II genes and RA has attracted attention [19]. This relationship can affect the costimulatory pathway, cytokine signaling, lymphocyte receptor activation and innate immunity activation [20,21]. (2) Epigenetic modifications may also play a role in RA by integrating environmental and genetic effects. A recent epigenomic association study identified ten differential methylation locations that may increase the genetic risks of RA [22]. (3) Posttranslational modifications, alterations in histone acetylation, and DNA methylation can modulate the biological functions of FLSs and leukocytes. (4) Environmental factors, such as periodontitis, smoking, and low socioeconomic status or educational attainment, can contribute to the occurrence of RA. Periodontitis and smoking can promote the endogenous expression of recombinant human arginine deiminase 4 (PADI4), thereby inducing abnormal citrulline levels, promoting the conversion of arginine to citrulline, and ultimately reducing tissue tolerance to citrulline peptides [23-25].

Immune Activation and Inflammation

The immune activation and inflammatory response in RA occur mainly through the following 5 steps: (1) activation of complement: ACPAs form immune complexes with antigens containing citrulline that subsequently bind to rheumatoid factor autoantibodies (RFs), resulting in substantial complement activation and enhanced immune signaling cascades. (2) The immune response: the common epitopes of high-risk RA patients are positively correlated with ACPA and IgG autoantibody seropositivity [26]. ACPAs activate macrophages by binding to antigens to form complexes and binding to Toll-like receptors or crystallizable fragment (Fc) receptors, enhancing the inflammatory response [27]. (3) Inflammatory response: in the active phase of RA, the infiltration of immune cells, including innate immune cells (such as monocytes, dendritic cells, mast cells, and innate lymphocytes) and acquired immune cells (such as Th-1 and Th-17 cells, B cells, plasmablasts, and plasma cells),is promoted. (4) Cytokine release: the inflammatory environment of RA is regulated by a complex cytokine network, in which tumor necrosis factor (TNF), interleukin-6 (IL-6), and GM-CSF may play an important regulatory role, while other components (IL-1 and various lymphokines) may have less of an impact [28,29]. (5) Bone remodeling: the release of inflammatory cytokines induces or exacerbates the inflammatory response by activating endothelial cells and attracting immune cells to accumulate between the synovial membranes of the joint. Activated fibroblasts, together with activated T cells, B cells, monocytes and macrophages infiltrating the joint cavity, ultimately trigger osteoclast production by interacting with receptor activator of NF-κB (RANK) expressed in T cells, B cells, and fibroblasts with RANK receptors in precursor cells of macrophages, dendritic cells, and osteoclasts. Moreover, cartilage is stimulated by inflammatory cytokines, and the metabolism of chondrocytes is affected, which triggers changes in bone structure. Additionally, cytokines can trigger various intracellular signaling pathways by binding to homologous receptors, and many intermediates that transduce intracellular signals and extracellular events further cause or aggravate inflammatory damage [30,31].

In summary, in the occurrence and development of RA, the inflammatory response plays a central role, and inhibiting inflammatory cytokine receptors and cytokine signaling pathways and modulating immune cells are important ways to control the inflammatory response (Figure1).

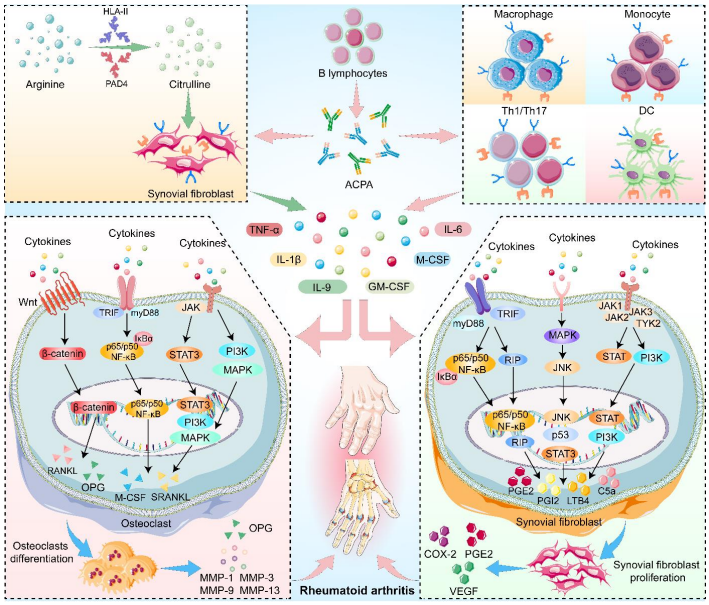

Figure 1: The pathogenesis of rheumatoid arthritis has environmental, genetic immune activation and inflammation factors.

PAD = Protein Arginine Deiminase. TNF = tumor necrosis factor. IL = Interleukin. DC = Dendritic cells. Th = helper T cell. GM-CSF = granulocyte macrophage colony-stimulating factor. M-CSF = macrophage colony-stimulating factor. OPG = osteoclastogenesis inhibitory actor. COX = Cyclooxygenase. PGE = prostaglandin E.VEGF = vascular endothelial growth factor. MMP = Matrix Metalloproteinase

Inflammatory Cytokine Receptor Inhibitors

Inflammation is a crucial factor leading to the occurrence and development of RA, and controlling inflammation inhibits the progression of RA. Inflammatory cytokines are an important part of inflammation, and targeting and inhibiting inflammatory cytokine receptors can reduce inflammatory cytokine activity, thereby regulating inflammation. This targeted mechanism is important in the treatment of RA.

TNF Receptor Inhibitors

TNF is a small protein secreted primarily by macrophages. In 1985, Shalaby named TNF produced by macrophages TNF-α (also called cachexidin) and lymphotoxin (LT) produced by T lymphocytes TNF-β [30]. TNF has two receptors, TNFR1 (also known as 55 kDa) and TNFR2 (also known as 75 kDa) [31,33]. TNFR1 is widely expressed in various cells, while TNFR2 is only expressed in immune cells, endothelial cells and synovial cells. TNF binding to these two receptors can induce the activation of multiple downstream signaling pathways.

In bone metabolism, TNF stimulates osteoblasts, fibroblasts and T lymphocytes to produce the NF-κB ligand RANKL to enhance osteoclast proliferation and can also stimulate FLSs to produce Dickkopf-associated protein 1 (DKK-1) and inhibit the Wnt/β-catenin signaling pathway, thereby inhibiting osteoblast proliferation [34,35]. In contrast, TNF-α induces DKK-1 expression to stimulate osteocytes to produce negative regulators of bone formation (scleroprotein and sclerostin), blocking osteoblast differentiation [36,37]. Moreover, TNF binding to TNFR1 can activate the NF-κB signaling pathway to produce and regulate matrix metalloproteinase 1 (MMP-1) and MMP-3 in osteoclasts, thereby affecting bone metabolism [38].

Inflammatory Response

TNF-α activates inflammatory responses by inducing macrophages and natural killer cells. TNF induces apoptosis by recruiting caspase-8 to Fas-associated death domain protein (FADD). Moreover,TNF binds to tumor TNF correlation factor 2 (TRAF2) through c-Jun N-terminal kinase (JNK), which can activate the stress-activated protein kinase (SAPK) and mitogen-activated protein kinase cascade (MAPK), and finally binds to receptor interacting protein (RIP) to activate the NF-κB signaling pathway and induce the production of in-

flammatory cytokines (IL-1β, IL-6, etc.), thereby mediating the inflammatory response [39]. TNFR2 can also recruit TRAF2 and activate the NF-κB signaling pathway to promote gene transcription for tissue regeneration, host defense against pathogens, and cell survival [40]. In addition, TNFR1 can induce cell apoptosis and necrosis through recruitment of the cohesion protein TRADD, leading to plasma membrane rupture and the entry of cell contents into the extracellular space, triggering local inflammation and further promoting bone damage [41].

Targeted Therapy for TNF in RA

As a proinflammatory cytokine, TNF-α can induce the proliferation of synovial cells in RA by activating the NF-κB signaling pathway, inhibiting synovial cell apoptosis [42], producing metalloproteinases that activate B lymphocytes, and then producing RFs, thus damaging joint bones and cartilage. TNFR1 expression also increases the population of FLSs. In RA-related inflammation, TNF-α-induced protein 3 (A20/TNFAIP3) is a key regulator, and a lack of A20/TNFAIP3 promotes NOD-like receptor protein 3 (NLRP3)-induced spontaneous arthritis, while an increase in A20/TNFAIP3 expression reduces IL-1β secretion [43]. Therefore, TNF occupies a central position among the proinflammatory cytokines that cause RA-related inflammation; thus, TNF-targeted treatment of RA, based mainly on biological agents that bind or block TNF receptors (TNFR1 and TNFR2), including etanercept, adalimumab, infliximab, certolizumab and golimumab, has become a popular research topic.

Etanercept is a soluble fusion protein synthesized in Chinese hamster ovarian cells by recombinant DNA technology. This protein is composed of the extracellular domain of human TNFR2 and the Fc of human IgG1, which can bind TNF-α and TNF-β, thereby inhibiting their activity. Etanercept was first marketed in 1998 [44]. Adalimumab, launched in 2002, is a TNF-α-specific recombinant IgG1 monoclonal antibody with a high affinity for TNF-α in vivo. This molecule binds to TNF-α and blocks its interaction with TNFR1 and TNFR2, thereby effectively inhibiting the inflammatory activity of TNF-α and exerting clinical efficacy [45]. Infliximab is a purified recombinant DNA-derived chimeric human-mouse IgG monoclonal antibody containing murine heavy (H) and light (L) chain variable regions linked to conserved chain regions of the human genome that can rapidly form stable complexes with human soluble or membrane forms of TNF and terminate the biological activity and downstream signaling of TNF. Infliximab was marketed in 1998 [46]. Certolizumab pegol (CZP), first marketed in 2008, is the humanized polyethylene glycol (PEG)-modified Fab fragment of an anti-TNF-α monoclonal antibody, which does not contain the Fc fragment and is the only protein and PEGylated inhibitor of TNF-α. PEGylation prolongs the half-life of CZP, thereby reducing the frequency of administration, immunogenicity, drug tolerance and drug resistance. In addition, because it lacks Fc fragments, CZP does not exert antibody-dependent cell-mediated cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC) in vitro, and does not induce apoptosis in human peripheral blood mononuclear cells or lymphocytes [47]. Golimumab is a fully humanized anti-TNF-α monoclonal antibody drug that targets and neutralizes soluble and transmembrane active forms of TNF-α, preventing it from binding to TNFR1 and TNFR2 and inhibiting the biological activity of TNF. Golimumab has 99.1% similarity with the human sequence, which is generally higher than that of other marketed TNF-α monoclonal antibodies. This molecule is known as the "anti-TNF-α monoclonal antibody terminator". Because it is fully humanized, golimumab has high binding potency and pharmacological advantages such as low immunogenicity and a long half-life. Golimumab was marketed in 2009 [48] (Figure 2).

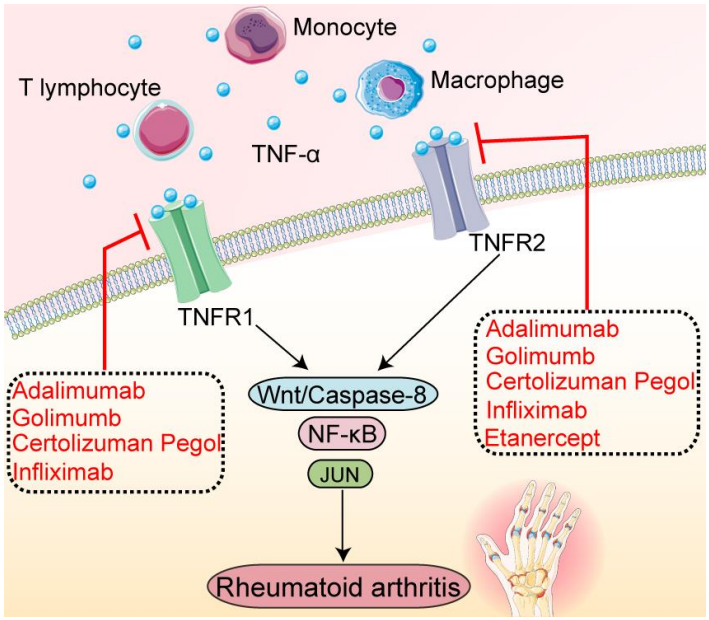

Figure 2: TNF-targeted treatment of RA, based mainly on biological agents that bind or block TNF receptors (TNFR1 and TNFR2), including Adalimumab, Infliximab, Certolizumab pegol and Etanercept. TNF= tumor necrosis fact.

IL-6

IL-6 is secreted by monocytes and macrophages after binding to lipopolysaccharide (LPS) and Toll-like receptors following stimulation by infection, inflammation and cancer [49]. Its biological effects can be exerted by the IL-6 receptor (IL-6R), which consists of a type I cytokine α receptor subunit (IL-6R, also known as CD126) and a common signal transduction β receptor subunit (gp130, also known as CD130) [50]. GGP130 is expressed in various cells, but IL-6R is expressed only in hepatocytes, epithelial cells, and leukocytes [51]. IL-6R exists in two forms: a membrane-bound form (mIL-6R) and a soluble form that lacks a membrane binding site (sIL-6R). sIL-6R forms a receptor complex with gp130 and transducessignals in response to IL-6 in the same way as mIL-6R [52]. Moreover, IL-6 acts on B lymphocytes and T lymphocytes through the NF-κB and STAT3 signaling pathways, regulating innate and adaptive immune responses [53].

IL-6 in Bone Destruction

During bone destruction, Wnt1 and Wnt5a are highly expressed in the synovial membrane via activation of the Wnt/β-catenin signaling pathway and induce proMMP-3, IL-6 and IL-8 production [54,55]. IL-6 induces the activation of receptors in osteoblasts expressing NF-κB ligand RANKL and promotes the differentiation of osteoclasts. Osteoblasts can also secrete IL-6 for osteoclastic trans-signaling [56,57]. Mice overexpressing IL-6 exhibit osteopenia due to disruption of the osteoclast-osteoblast balance, a decreased number of osteoblasts, and an increased number of osteoclasts, suggesting that IL-6 blockade delays fracture healing [58,59]. In a study of LPS injection into the periosteum of the mouse skull to induce inflammatory bone destruction, mature osteoclasts converted bone resorptive osteoclasts into nonabsorbing cells after treatment with anti-IL-6R antibodies, indicating that IL-6 regulates the resorptive activity of osteoblasts [60].

IL-6 in Inflammation

IL-6 is a multifunctional cytokine that can regulate the acute phase response of inflammation and hematopoietic function, and plays an important role in the body's anti-infection immune response. Dysregulation of IL-6 expression contributes to the occurrence and development of various autoimmune and chronic inflammatory diseases. IL-6 can activate B cells to stimulate an immune response and can regulate CD4+ T--cell-specific differentiation by inhibiting transforming growth factor (TGF)-β while promoting Th17 cell differentiation, and altering the Th17/Treg ratio to regulate chronic inflam-

mation. Moreover, IL-6 can promote T follicular helper cell differentiation and IL-21 production. IL-6 can also induce excessive production of vascular endothelial growth factor (VEGF), resulting in enhanced angiogenesis and increased vascular permeability. The IL-6/sIL-6R complex activates vascular endothelial cells to produce IL-6, IL-8, and MCP-1 and increases the expression of intercellular adhesion molecule (I-CAM)-1, leading to leukocyte recruitment [50,60,61].

Targeting IL-6 in RA Therapy

In 1986, Kishimoto and Hirano first identified and characterized IL-6 as a cytokine that regulates B-cell differentiation [61]. In the 1990s, early clinical studies used IL-6-targeted therapy to neutralize IL-6 antibodies in patients with multiple myeloma based on the role of IL-6 as a tumor growth factor [62]. IL-6 also regulates immune cells and acts on the inflammatory response. In RA, IL-6 levels are high in serum and synovial tissues, initiating the inflammatory response and inducing phosphorylation of STAT3 primarily through the JAK-STAT signaling pathway [63]. For the control of inflammation and bone protection, inhibition of IL-6 production and release has good therapeutic value.Recent studies have shown that IL-6 receptor inhibitors have a significant therapeutic effect in RA, and 3 kinds of pharmacological IL-6 receptor inhibitors have been developed. (1) Tocilizumab, an IL-6 receptor inhibitor developed from a humanized monoclonal antibody targeting IL-6R, was reported in 2010 [64]. (2) Sarilumab (Kevzara) is the first fully humanized monoclonal antibody that directly targets the IL-6 receptor complex α subunit (IL-6Rα), can block the binding of IL-6 to its receptor and interrupt the cytokine-mediated inflammatory signaling cascade, and is in phase III clinical trials [65]. (3) Olokizumab is an exploratory humanized monoclonal antibody specific for IL -6 developed by Alder Biopharmaceuticals and is currently in phase III clinical trials for the treatment of chronic active antibody-mediated rejection/reaction (AMR) [66] (Figure 3).

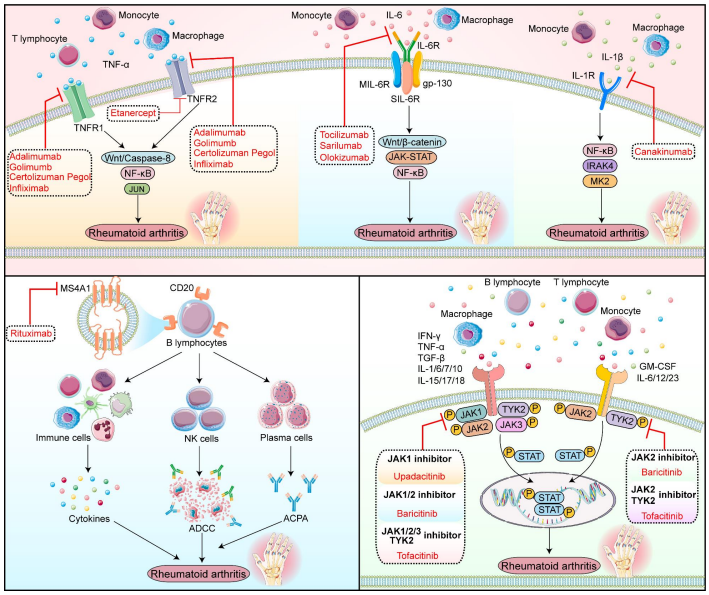

Figure 3: Targeting IL-6 treatment of RA, based mainly on biological agents that bind or block IL-6R, including Tocilizumab, Sarilumab and Olokizumab. IL = Interleukin

IL-1 Receptor Inhibitors

Produced by activated monocytes and macrophages, IL-1 is a key proinflammatory cytokine that affects numerous target immune, endothelial, and hepatic cells and is a major causative factor of autoinflammation, autoimmunity, and infection [67,68]. The IL-1 family of cytokines is divided into three subgroups: secreted molecules with agonist activity (IL-1α, IL-1b, IL-18, IL-33, IL-36a, IL-36b, and IL-36g), receptor antagonists (IL-1Ra, IL-36Ra, and IL-38), and anti-inflammatory cytokines (IL-37) [69]. IL-1β is expressed mainly in a highly controlled manner in immune cells such as monocytes,

macrophages, and neutrophils and is involved in various regulatory mechanisms [70,71]. IL-1β binds to IL-1R1 to exert proinflammatory effects, activating the intracellular IRAK4, MK2 and NF-κB signaling pathways and further expressing inflammatory cytokines and inflammasome proteins [72]. In patients with osteoarthritis, IL-1 stimulates chondrocytes to produce MMPs, MMP-1, MMP-3, and MMP-13, resulting in cartilage matrix degradation [73]. Moreover, IL-1 can also increase the production of reactive oxygen species peroxide and hydroxyl free radicals, which directly damage joint cartilage [74]. High levels of IL-1 (IL-1α and IL-1β) in the synovial membrane and synovial fluid of RA patients promote the expression of PGE2 and MMP in FLSs [75,76].

The current biologic agent for IL-1 inhibition in the treatment of RA is Anakinra. anakinra is used to treat rheumatoid arthritis to block the biological activity of IL-1 by competitively inhibiting the binding of IL-1 to the interleukin type I receptor (IL-1RI), which is expressed in a variety of tissues and organs. Anakinra has been recommended for the treatment of RA, but its clinical use is limited due to its short half-life and moderate clinical efficacy compared with anti-TNF drugs [77]. canakinumab is a selective, fully humanized, anti-IL-1β monoclonal antibody that inhibits interleukin-1β (IL-1β). Canakinumab was approved for the treatment of cyclic fever syndrome [cold pyrine-associated periodic syndrome (CAPS)] and systemic juvenile idiopathic arthritis (sJIA), another autoinflammatory disorder. Moreover, this drug it has been approved for the treatment of refractory acute gouty arthritis and adult-onset Still's disease (AOSD)[78,79] (Figure 4).

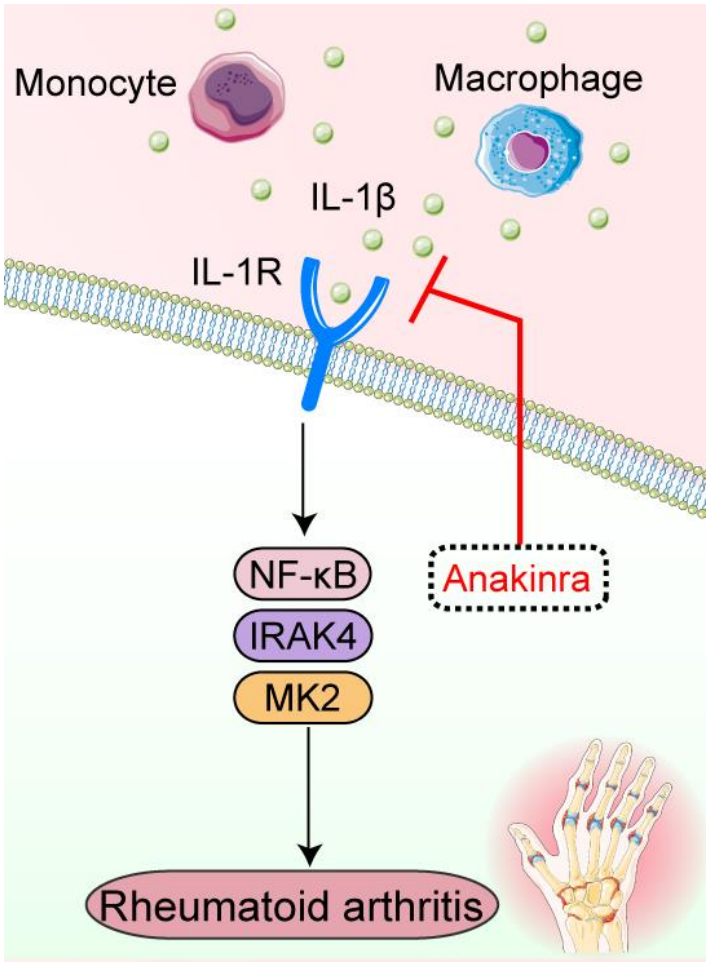

Figure 4: The current biologic agent for IL-1 inhibition in the treatment of arthritic diseases is canakinumab, and the inhibits interleukin-1β (IL-1β). IL=Interleukin

B Lymphocyte Antagonists

B lymphocytes are derived from pluripotent bone marrow stem cells and differentiate into plasma cells when stimulated by antigens. Plasma cells synthesize and secrete antibodies (immunoglobulins), which are primarily responsible for humoral immunity. CD20 is expressed on the surface of B cells at various stages of development and differentiation, and directly regulates the proliferation and differentiation of B cells into plasma cells (mature B cells that secrete immunoglobulins) by mediating transmembrane calcium ion flux. The role of lymphocytes in RA is crucial, and in-depth investigations of RFs, the discovery of RA-related autoantibodies such as ACPAs, and the study of lymphocyte follicle formation and large plasma cell infiltration in the synovium are important in elucidating the pathogenesis of RA. Approximately 50% of RA patients show low levels or the absence of $CD20^{+}$ B cells in diseased synovial joint tissue [80]. Studies have shown that ACPAs themselves can cause disease potentially through macrophage activation by binding to antigens to form complexes; binding to Toll-like receptors or Fc receptors, thereby promoting the inflammatory response; or forming immune complexes and binding to Fc receptors, thereby activating osteoclasts. Moreover, ACPAs promote bone loss by binding to citrulline wave proteins. However, RFs are more directly involved in the activation of macrophages and cytokines than ACPAs [81]. In addition, ACPAs may promote the inflammatory response through interaction with RFs [82].

Application of CD20 in RA

In experimental studies in mice, a 3-day treatment course with anti-CD20 antibodies resulted in complete dissociation of the follicular structure of B cells and a significant decrease in IL-1β and IFN-γ levels, suggesting that B cells can influence inflammatory cytokine production [83]. RF is a specific antibody against the epitope of human or animal Fc receptor antigen on IgM, IgG, and IgA antibodies, which can form immune complexes with autologous, allogeneic or xenomorphic IgG and activate the complement system to induce inflammatory responses [84]. B lymphocytes activate T lymphocytes by recruiting the chemokines CCL21 and CXCL13 [85]. T lymphocytes attract the chemokines CCL2, CCL5 and CCL8, and then efficiently attach to the required cell adhesion molecules. In RA, B cells control inflammation by secreting antibodies, recruiting chemokines, and regulating immune cells [86].

Rituximab is a chimeric mouse/human monoclonal antibody that specifically binds to CD20 on B lymphocytes and triggers an immune response via B lymphocyte lysis. Possible mechanisms of cytolysis include CDC and ADCC [87,86] (Figure 5).

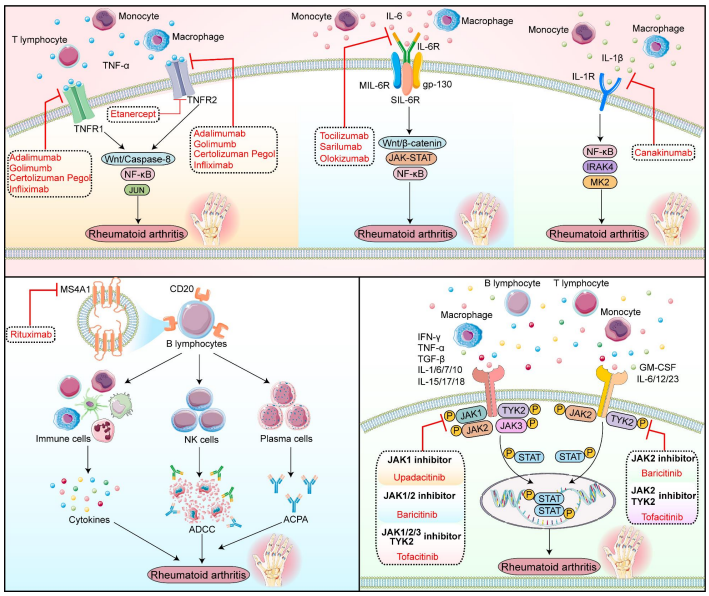

Figure 5: The Rituximab is the targeting CD20 treatment of RA, based mainly on biological agents that block MS4A1 gene. ADCC = Anti-

body dependent cell-mediated cytotoxicity. ACPA = Anti-cyclic citrullinated peptide antibody

JAK Inhibitors

JAK is a nonreceptor tyrosine protein kinase, and the JAK family includes JAK1, JAK2, JAK3, and tyk 2. JAK1, JAK2 and tyk 2 are widely expressed in various tissues and cells, while JAK3 is found only in the bone marrow and lymphatic system. In these locations, JAK family members play an indispensable role in the intracellular signaling of inflammatory factors [88-90]. JAK1 and JAK2 are ubiquitous and regulate the expression of many inflammatory and noninflammatory genes in response to IL-6, IL-23, granulocyte colony-stimulating factor, interferon, erythropoietin, and other ligands, whereas JAK3 is expressed in hematopoietic cells and participates in the signaling cascade activated by IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21. Therefore, JAK1 has become a target for inflammation, cancer, immunity and other diseases, JAK2 has become a target for blood system-related diseases, and JAK3 has become a popular target for autoimmune diseases [91]. Moreover, STAT is a signal transducer and transcriptional activator. This molecule plays a key role in signal transduction and transcriptional activation. Six members of the STAT family, namely, STAT1-STAT6, have been identified [92].

The JAK-STAT signaling pathway is a newly discovered intracellular signaling pathway closely related to cytokines and is involved in many important biological processes, such as cell proliferation, differentiation, apoptosis, and immune regulation. Compared with that of other signaling pathways, signal transduction through this pathway is relatively simple and involves mainly tyrosine kinase-related receptors, the tyrosine kinase JAK, and the transcription factor STAT [93].

The Role of JAK in RA

Clinically, JAK inhibitors (JAKis) are mainly used as therapeutic drugs for hematologic diseases, tumors, rheumatoid arthritis and psoriasis. The first-generation JAKis are baricitinib, which inhibits JAK1 and JAK2, and tofacitinib, which inhibits JAK1, JAK2, JAK3 and, to a lesser extent, TYK2 [94]. The second generation of JAKis includes upadacitinib, decernotinib, peficitinib, and itacitinib, most of which are still in development. Second-generation JAKis appear to have faster and dose-dependent efficacy,are more attractive than first-generation JAKis when used as monotherapy, and are currently in the experimental phase [95].

Tofacitinib is a novel oral JAKi developed by Pfizer. Unlike most other current RA therapeutics, which act mainly on extracellular targets, tofacitinib targets intracellular signal transduction pathways and acts on the upstream regulators of the cytokine network. The inhibitory potency of tofacitinib toward JAK3 is 5-100 times that toward JAK1 and JAK2. This is the first drug developed for the treatment of RA and is thus considered a first-in-class drug. Tofacitinib was approved by the FDA for use in RA in 2012 [96]. Baricitinib, developed by changing the structure of tofacitinib, is another first-generation ATP-competitive JAKi. Both tofacitinib and baricitinib target the JH1 tyrosine kinase domain by interacting with the active site of the ATP-binding pocket [97]. Baricitinib is selective for JAK1 and JAK2 and is currently approved only for the treatment of moderately to severely active RA in adults who do not adequately respond to or tolerate one or more DMARDs. This drug has a pyrrolopyrimidine chemical structure, which is insoluble in water and slightly soluble in hydrochloric acid. Baricitinib was approved in Europe in 2017 for the treatment of RA [98]. Finally, upadacitinib, a highly potent, selective JAK1 inhibitor, was marketed in 2019 for the treatment of adult patients with moderately to severely active RA who have an inadequate response or intolerance to methotrexate (MTX-IR) [99]. Filgotinib selectively inhibits JAK1-mediated signaling pathways. However,filgotinib has weaker inhibitory effect on JAK2 and JAK3-related pathways, which provides a theoretical basis for its different efficacy/safety. Currently, filgotinib has been approved by the European Medicines Agency (EMA) for the treatment of adult RA patients. Filgotinib is also approved by the EMA for the treatment of ulcerative colitis (UC). In addition, several studies have explored the potential of filgotinib to treat other diseases, such as axial spondyloarthritis, psoriatic arthritis, noninfectious uveitis, lupus cutaneous and Sjogren's syndrome, which have entered phase 2 studies, and Crohn's disease, which has entered phase 3 studies [100] (Figure 6).

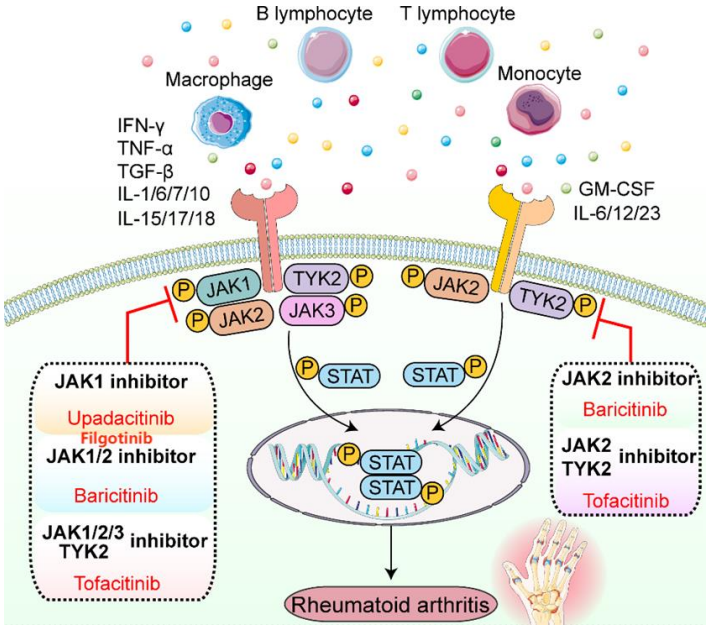

Figure 6: JAK is a nonreceptor tyrosine protein kinase, and the JAK family includes JAK1, JAK2, JAK3 and Tyk2, the act the important role in treatment RA, The JAK1 inhibitor is Upadacitinib, JAK1/2 inhibitor is Baricitinib, JAK1/2/3 and Tyk2 inhibitors are Tofacitinib. JAK = Janus kinase. TYK2 = Tyrosine kinase

The Real-world Effectiveness of these Inhibitors

In a pooled analysis of European prospective observational studies, we found golimumab to be effective in the treatment of patients with active rheumatoid arthritis, psoriatic arthritis, or axial spondyloarthritis who failed initial TNF-α inhibitor therapy. We observed the highest persistence rates with upadacitinib, followed by baricitinib and then TNF inhibitor therapy [101]. Co-therapy further improved these rates. All agents appeared to reduce the need for corticosteroids.Systemic inflammation, indicated by increased disease activity, may lead to increased RANKL levels, causing systemic bone loss in rituximab-treated patients with RA. While rituximab can control inflammation, it does not seem to modify systemic bone metabolism in RA [102]. The main objective of this multicentre study involving nine Italian hospital pharmacies was to assess the adherence, persistence, and costs of bDMARDs [103]. The drugs under investigation included Abatacept, Adalimumab, Certolizumab, Etanercept, Golimumab, and Tocilizumab. This retrospective observational study on the use of bDMARDs in the treatment of RA showed that, for all drugs studied, treatment adherence was not an issue; rather, difficulty was encountered in maintaining treatment with the same drug over time [104].

Other Targeted Medicines

Abatacept is a fusion protein consisting of the CTLA-4 extracellular domain and the Fc region of immunoglobulin IgG1. This protein can bind to CD80 and CD86 on the surface of antigen-presenting cells, and prevent the interaction between CD86 and CD28 on the surface of T cells, thereby inhibiting T-cell activation, reducing the secretion of cytokines (such as: IFN-γ, TNF-α, IL-1, IL-2, IL-4, IL-5, and IL-6), reducing their downstream inflammatory response, and then controlling joint inflammation and inhibiting joint damage. In January 2020, the world's first and only approved T-cell selective costimulatory immunomodulator in the field of RA opened a new path for biobased DMARD therapy for patients [105].

Secukinumab is a fully humanized IgG1 monoclonal antibody that selectively neutralizes the proinflammatory cytokine IL-17A.It regulates the activity of NF-κB and mitogen-activated protein kinases, which can stimulate the expression of IL6 and cyclooxygenase 2 (PTGS2/COX-2) and enhance nitric oxide (NO) production. In 2015, the US FDA approved secukinumab for the treatment of adult patients with moderate to severe plaque psoriasis. In addition to psoriasis, psoriatic arthritis, and ankylosing spondylitis, clinical trials

are ongoing or planned for other conditions, including skin conditions such as atopic dermatitis, discoid lupus, pyoderma gangrenosum, and hidradenitis suppurativa, as well as systemic diseases such as giant cell arteritis, lupus nephritis, non-alcoholic fatty liver disease, type 1 diabetes, and more recently, COVID-19 [106].

In summary, we separately discussed the targets and efficacy of biologics. In the clinic, appropriate biologics can be selected according to different disease periods of RA (Table 1).

Table 1: Biological agents for the treatment of rheumatoid arthritis

Name	Medicine	Targets	Disease	Marketed	Reference
TNF-α	Etanercept	Humanized TNF is affected by p75Fc fusion protein	RA,AS,JIA,PsA,PsO,Paed PsO,nr-AxSPA,	1998	[44]
	Adalimumab	Fully humanized anti-TNF-α Monoclonal antibodies	RA,Psoriasis,CD,UC,PsA,AS,JIA	2002	[45]
	Infliximab	Human-mouse chimeric monoclonal antibodies	RA,Psoriasis,UC,PsA,AS	1998	[46]
	Certolizumab pegol	Polyethylene glycol humanized Fab fragments	RA,CD,PsA,AS	2008	[47]
	Golimumab	Fully humanized anti-TNF-αMonoclonal antibodies	RA,PsA,AS,UC	2009	[48]
IL-1	Canakinumab	Humanized IL-1β monoclonal antibody	JIA	2009	[78,79]
	Anakinra	IL-1R	RA	2001	[77]
IL-6	Tocilizumab	IL-6 receptor monoclonal antibody	RA	2010	[64]
	Sarilumab	Fully human IgG1κ monoclonal antibody	RA	2017	[65]
	Olokizumab	Humanized monoclonal antibodies	RA	Phase III clinical trial	[66]
JAK	Tofacitinib	JAK3、JAK1、JAK2	RA	2012	[96]
	Baricitinib	JAK1 、JAK2	RA	2017	[97,98]
	Upadacitinib	JAK1	RA	2019	[99]
	Filgotinib	JAK1	RA	2019	[100]
CD20	Rituximab	MS4A1 ,CDC,ADCC	NHL,RA	2018	[87]
T Cell	Abatacept	CD28,CD80,CD86	RA	2005	[104]
IL-17	Secukinumab	IL-17A	Psoriasis,AS	2015	[106]

Conclusion

Approximately 40% of patients do not respond to the use of a single drug in the treatment of RA [100]. Moreover, refractory RA is resistant to multiple DMARDs, the prognosis of patients is poor, and the risk of complications such as cardiovascular disease is higher [107]. Therefore, choosing the right drug is crucial for the treatment of RA. Based on this review, for patients with severe clinical inflammation, we can suggest JAKis, which act on the JAK-STAT signaling pathway to reduce cytokine signaling, cytokine-induced gene expression and cell activation, thereby reducing various chronic inflammatory responses. Cardiovascular events and thrombotic events should be considered while taking medication, and regular follow-up and analysis of inflammatory indicators and pain levels of patients should be performed. For patients with RA with severe bone erosion and bone destruction on imaging, TNF-α inhibitors such as infliximab are recommended to prevent further bone loss and loss of bone mineral density (BMD) in patients with confirmed or early RA and spondyloarthropathy (SpA). Etanercept has improved BMD and bone mineralization in multiple RA, SpA, and JIA studies, and continued treatment with adalimumab has also slowed systemic bone loss in RA. Otherwise, TNF-α inhibitors in combination with MTX can slow the radiological progression of bone loss and erosion in the hand. For patients with RA combined with other rheumatic immune diseases, we consider CD-20 inhibitors, IL-6 receptor inhibitors, and abatacept, which can inhibit immune cells, reduce the release of inflammatory cytokines, and modulate the immune internal environment.

Inflammation plays an important role during RA, and further expansion of inflammation causes an imbalance between osteoblasts and osteoclasts, which eventually leads to bone erosion and bone destruction. In the future, the main research direction of targeted therapy for RA is to control inflammation, inhibit angiogenesis and regulate osteoblasts and osteoclasts. By controlling inflammation, treatments can inhibit the binding of inflammatory cytokines in the synovial fluid of the joint to receptors, block the conduction of signaling pathways (such as NF-κB), or inhibit the production of cytokines such as COX-2, PGE2 and VEGF in FLSs. Because IL-4 and IL-13 expression is high in the synovial fluid of early RA [108,109]. IL-13 exerts its antiangiogenic function by activating protein kinase C (PKC) a/b II and ERK-1/2 while inhibiting the NF-κB/p65 pathway [110]. Therefore, for the early stage of RA, we can use IL-13 receptor inhibitors to delay the further progression of the disease. This molecule plays an important role in recruiting leukocytes and affecting angiogenesis-related chemokines. Chemokines are abnormally expressed in synovial fluid, synovial tissue, fibroblasts, and endothelial cells in patients with RA [111-113] and promote angiogenesis by causing vascular endothelial cell proliferation and capillary formation through chemotaxis of endothelial cells [114]. In bone destruction in RA, activated immune cells promote the formation, differentiation and activation of osteoclasts by directly upregulating the expression of RANKL or indirectly increasing the expression of RANKL through the secretion of proinflammatory cytokines. During bone resorption, osteoblasts secrete RANKL and M-CSF under the action of bone resorption stimulatory factors in combination with RANK and colony-stimulating factor-1 receptors (c-Fms) to induce osteoclast differentiation. The increase in osteoclasts enhances bone resorption, resulting in an imbalance in bone reconstruction. With the imbalance of osteoblasts and osteoclasts, osteoporosis occurs in the early stage of RA, and bone destruction occurs in the late stage [115]. Therefore, targeted inhibition of RANKL and M-CSF expression in RA can alleviate further bone destruction.

In addition to inhibiting inflammatory cytokines and immune cells in the treatment of RA, we can improve this condition through modulation of the RA cellular microenvironment by regulating FLSs, inhibiting osteoblast differentiation, and administering gene therapy and traditional Chinese medicine monomer therapy. In a collagen-induced arthritis model, the tumor suppressor proteins p53 and FADD of Fas regulated FLSs and promoted FLS apoptosis . A decrease in FLSs and inflammatory cell infiltration and an increase in the synthesis of a new matrix of cartilage tissue can alleviate arthritis symptoms [107,116]. Moreover, inhibition of matrix metalloproteinase production can improve RA. MMPs and their endogenous protease inhibitors (TIMPs) are both produced by macrophages and synovial cells. In mouse studies,

adenovirus-mediated overexpression of TIMP-3 significantly reduced the invasion and metastasis of RA synovial cells [117]. Next, inhibition of angiogenesis, such as delivery of THE VEGF soluble receptor gene to the body by adenovirus to increase its expression, can alleviate RA to some extent [118]. Moreover, RANKL and the adhesion molecule cadherin-1, which are involved in bone injury, have the potential to become new targets for RA gene therapy [119]. Finally, recent research has shown that extracts of traditional Chinese medicine monomers, such as *Tripterygium* polyglycosides and emodin, which have important anti-inflammatory, antitumor, and immunosuppressive effects, are useful for the treatment of RA [120,121].

Overall, future precise treatment of RA may be based on the individualized symptoms of patients and involve multiple targets in the pathogenesis of RA to ultimately obtain an optimized treatment plan. In addition, the treatment method will be more biased toward local treatment of RA lesions to modulate the immune microenvironment. Moreover, in the exploration of ideal targets, it is necessary to strongly consider the biosafety, in vivo distribution and metabolism of the biological agent. Overall, targeted and individualized therapy for RA still has broad research prospects and challenges.

References

1. McInnes IB, Schett G (2011) The pathogenesis of rheumatoid arthritis. N Engl J Med 365: 2205-19.

2. Lee DM, Weinblatt ME (2001) Rheumatoid arthritis. Lancet 358: 903-11.

3. Silman AJ, Pearson JE, Pincus T, et al. (2002) Epidemiology and genetics of rheumatoid arthritis. Arthritis Res 4: S265-72.

4. Di Wu, Yehao Luo, Tong Li (2022) Systemic complications of rheumatoid arthritis: Focus on pathogenesis and treatment. Front Immunol 13: 1051082.

5. Tomiak C, Dorner T (2006) Sjogren's syndrome. Current aspects from a rheumatological point of view. Z Rheumatol 65: 505-17.

6. Iain B McInnes, Georg Schett (2017) Pathogenetic insights from the treatment of rheumatoid arthritis. Lancet 389: 2328-37.

7. Catrina AI, Joshua V, Klareskog L, Malmstrom V (2016) Mechanisms involved in triggering rheumatoid arthritis. Immunol Rev 269: 162-74.

8. Tan EM, Smolen JS (2016) Historical observations contributing insights on etiopathogenesis of rheumatoid arthritis and role of rheumatoid factor. Journal of Experimental Medicine 213: 1937-50

9. Wang Y, Liu J, Burrows PD, Wang JY (2020) B cell development and maturation. Adv Exp Med Biol 1254: 1-22.

10. Kerkman PF, Rombouts Y, van der Voort EIH et al. (2013) Circulating plasmablasts/plasmacells as a source of anticitrullinated protein antibodies in patients with rheumatoid arthritis. Ann Rheum Dis 72: 1259-63.

11. Clavel C, Nogueira L, Laurent L, Iobagiu C, Vincent C et al. (2018) Induction of macrophage secretion of tumor necrosis factor through Fc receptor IIa engagement by rheumatoid arthritis–specific autoantibodies to citrullinated proteins complexed with fibrinogen. Arthritis Rheum 58: 678-88.

12. Kim JS, Choi M, Choi JY et al. (2020) Implication of the association of fibrinogen citrullination and osteoclastogenesis in bone destruction in rheumatoid arthritis. Cells 9: 2720.

13. Hafkenscheid L, Bondt A, Scherer HU et al. (2017) Structural analysis of variable domain glycosylation of anti-citrullinated protein antibodies in rheumatoid arthritis reveals the presence of highly sialylated glycans. Mol Cell Proteomics 16: 278-87.

14. Chen Z, Bozec A, Ramming A, et al. (2019) Anti-inflammation and Immune-regulatory cytokines in rheumatoid arthritis. Nat Rev Rheumatol 15: 9-17.

15. Kim EY, Moudgil KD (2017) Immunomodulation of autoimmune arthritis By proc-inflammation Cytokines. Cytokine 98: 87-96.

16. O'Shea JJ, Kontzias A, Yamaoka K, Tanaka Y, Laurence A (2013) Janus kinase inhibitors in autoimmune diseases.Ann Rheum Dis 72: 111-5.

17. Muller R (2019) JAK inhibitors in 2019, synthetic review in 10 points. European Journal of Internal Medicine 66: 9-17.

18. Xin P, Xu X, Deng C, Liu S, Wang Y, Zhou X, et al. (2020) The role of JAK/STAT signaling pathway and its inhibitors in diseases. International Immuno pharmacology 80: 106210.

19. Gregersen PK, Silver J, Winchester RJ (1987) The shared epitope hypothesis: an approach to understanding the molecular genetics of susceptibility to rheumatoid arthritis. Arthritis Rheum 198730: 1205-13.

20. Tan EM, Smolen JS (2016) Historical observations contributing insights on etiopathogenesis of rheumatoid arthritis and role of rheumatoid factor. J Exp Med 213: 1937-50.

21. van der Helm-van Mil AH, Wesoly JZ, Huizinga TW (2005) Understanding the genetic contribution to rheumatoid arthritis. Curr. Opin. Rheumatol 17: 299-304.

22. Catrina AI, Joshua V, Klareskog L, Malmstrom V (2016)

Mechanisms involved in triggering rheumatoid arthritis. Immunol Rev 269: 162-74

23. Källberg H, Ding B, Padyukov L, et al. (2011) Smoking is a major preventable risk factor for rheumatoid arthritis: estimations of risks after various exposures to cigarette smoke, Ann Rheum Dis 70: 508.

24. Harre U, Georgess D, Bang H, et al. (2012) Induction of osteoclastogenesis and bone loss by human autoantibodies against citrullinated vimentin. J Clin Invest 122: 1791-802.

25. Krishnamurthy A, Joshua V , Haj Hensvold A, et al. (2016) Identification of a novel chemokine-dependent molecular mechanism underlying rheumatoid arthritis-associated autoantibody-mediated bone loss. Ann Rheum Dis 75: 721-29.

26. Okada Y, Wu D, Trynka G, et al. (2014) Genetics of rheumatoid arthritis contributes to biology and drug discovery. Nature 506: 376.

27. Schett G, Elewaut D, McInnes IB, Dayer JM, Neurath MF. How cytokine networks fuel inflammation: T oward a cytokine-based disease taxonomy. Nat. Med. 19: 822-4 .

28. Cascao R, Rosario HS, Souto-Carneiro MM, Fonseca JE (2020) Neutrophils in rheumatoid arthritis: more than simple final effectors. Autoimmun 9: 531-5.

29. Hueber AJ et al. (2010) Mast cells express IL-17A in rheumatoid arthritis synovium. J. Immunol. 184: 3336-40.

30. M. Refaat Shalaby, Diane Pennica (1986) An Overview of the History and Biologic Properties of Tumor Necrosis Factors. Springer Semin Immuno pathol 19: 33-7.

31. Hideki Kitaura, Aseel Marahleh, Fumitoshi Ohori (2022) Role of the Interaction of Tumor Necrosis Factor-α and T umor Necrosis Factor Receptors 1 and 2 in Bone-Related Cells. Int. J. Mol. Sci. 23: 1481.

32. Aggarwal BB (2003) Signalling pathways of the TNF superfamily: a double- edged sword. Nat. Rev. Immunol. 3: 745-56.

33. Chen X, Baumel M, Mannel DN, Howard OM, Oppenheim JJ (2007) Interaction of TNF with TNF receptor type 2 promotes expansion and function of mouse CD4+CD25+ T regulatory cells. J. Immunol 179: 154-61.

34. Ágnes Szentpétery,Ágnes Horváth, Katalin Gulyás (2017) Effects of targeted therapies on the bone in arthritides. Autoimmun Rev 16: 313-20.

35. Dostert C, Grusdat M, Letellier E, Brenner D (2019) The TNF Family of Ligands and Receptors: Communication Modules in the Immune System and Beyond. Physiol. Rev 99: 115-60.

36. Du G, Song Y, Wei L, et al. (2015) Osthole inhibits proliferation and induces catabolism in rat chondrocytes and cartilage tissueJ..Cell Physiol.Biochem 36: 2480-93.

37. Schett G, Gravallese E (2012) Bone erosion in rheumatoid arthritis: mechanisms, diagnosis and treatment. Nat Rev Rheumatol 8: 656-64.

38. Ahn SJ, EM Rhim, JY Kim et al. (2014) Tumor necrosis factor-alpha induces matrix metalloproteinases-3, -10, and -13 in human periodontal ligament cells. J. Periodontol 85: 490-7.

39. Michal Lata, Aubryanna S, Hettinghouse, Chuan-Ju Liu (2019) Targeting tumor necrosis factor receptors in ankylosing spondylitis. Ann N Y Acad Sci 1442: 5-16.

40. liolias GD, LB Ivashkiv (2016) TNF biology, pathogenic mechanisms and emerging therapeutic strategies. Nat. Rev. Rheumatol 12: 49-62.

41. Linkermann A, DR Green (2014) Necroptosis. N. Engl. J. Med. 370: 455-65.

42. Gupta SC (2014) Down regulation of tumor necrosis factor and other pro inflammatory biomarkers by polyphenols, Archives of Biochemistry and Biophysics 599: 91-9.

43. Robert R Graham, Chris Cotsapas (2008) Genetic variants near TNFAIP3 on 6q23 are associated with systemic lupus erythematosus. Nat Genet 40: 1059-61.

44. Olivera I, Sanz-Pamplona R, Bolanos E, Rodriguez I (2022) A therapeutically actionable pro-tumoral axis of cytokines involving interleukin-8, TNFa and IL-1B. Cancer Discov 30: cd.21.1115.

45. Daniel E Furst, Janusz Jaworski (2022) Efficacy and safety of switching from reference adalimumab to CT-P17 (100 mg/ml): 52-week randomized, double-blind study in rheumatoid arthritis. Rheumatology (Oxford) 61: 1385-95.

46. J L Nam, E Villeneuve, EM A Hensor (2014) Remission induction comparing infliximab and high-dose intravenous steroid, followed by treat-to-target: a double-blind, randomised, controlled trial in new-onset, treatment-naive, rheumatoid arthritis (the IDEA study). Ann Rheum Dis 73: 75-85.

47. Janet Pope, Emmanouil Rampakakis (2020) An open-label randomized controlled trial of DMARD withdrawal in RA patients achieving therapeutic response with certolizumab pegol combined with DMARDs. Rheumatology (Oxford) 59: 1522-8.

48. M. Elaine Husni, Atul Deodhar, Sergio chwartzman (2022) Pooled safety results across phase 3 randomized trials of intravenous golimumab in rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis. Arthritis Res Ther 24: 73.

49. Heinrich PC, Castell JV, Andus T (1990) Interleukin-6 and the acute phase response. Biochem. J. 265: 621-36.

50. Rose-John S, Neurath MF (2002) IL-6 trans-signaling: the heat is on. Immunity 20: 2-4

51. Scheller J, Chalaris A, Schmidt-Arras D, Rose-John S (2011) The pro- and anti-inflammatory properties of the cytokine interleukin-6. Biochim. Biophys. Acta 1813: 878-88.

52. Rose-John S, Neurath MF (2004) IL-6 trans-signaling: the heat is on. Immunity 20: 2-4.

53. Cressman DE et al. (1996) Liver failure and defective hepatocyte regeneration in interleukin-6-deficient mice. Science 274: 1379-83.

54. Sen M, Lauterbach K, El-Gabalawy H, Firestein GS, Corr M, Carson DA (2000) Expression and function of wingless and frizzled homologs in rheumatoid arthritis. Proc Natl Acad Sci USA 97: 2791-6.

55. Sen M, Reifert J, Lauterbach K, Wolf V, Rubin JS, Corr M, et al. (2002) Regulation of fibronectin and metalloproteinase expression by Wnt signaling in rheumatoid arthritis synoviocytes. Arthritis Rheum 46: 2867-77.

56. Udagawa N et al. (1995) Interleukin (IL) 6 induction of osteoclast differentiation depends on IL 6 receptors expressed on osteoblastic cells but not on osteoclast progenitors. J. Exp. Med. 182: 1461-8.

57. Garbers C, Heink S, Korn T, Rose-John S (2018) Interleukin 6: designing specific therapeutics for a complex cytokine. Nat Rev Drug Discov 17: 395-412.

58. De Benedetti F et al. (2006) Impaired skeletal development in interleukin 6 transgenic mice: a model for the impact of chronic inflammation on the growing skeletal system. Arthritis Rheum 54: 3551-63.

59. Prystaz K et al. (2018) Distinct effects of interleukin 6 classic and trans signaling in bone fracture healing. Am. J. Pathol 188: 474-90.

60. Matsuura Y, Kikuta J, Kishi Y, Hasegawa T, Okuzaki D, Hirano T, et al. (2018) In vivo visualisation of different modes of action of biological DMARDs inhibiting osteoclastic bone resorption. Ann Rheum Dis 77: 1219-25.

61. Hirano T, Yasukawa K, Harada H, Taga T, Watanabe Y, Matsuda T, et al. (1986) Complementary DNA for a novel human interleukin (BSF-2) that induces B lymphocytes to produce immunoglobulin. Nature 324: 73-6.

62. Klein B, Lu ZY, Gaillard JP, Harousseau JL, Bataille R (1992) Inhibiting IL 6 in human multiple myeloma. Curr. T op. Microbiol. Immunol 182: 237-44.

63. Tsuyoshi Narimiya, Hiroyuki Kanzaki (2019) Nrf2 activation in osteoblasts suppresses osteoclastogenesis via inhibiting IL-6 expression. Bone Rep 11: 100228.

64. Larid G, Joffres L, Ricard E, Pereira Gillion C et al. (2022) Stable efficacy and safety after switching from intravenous to subcutaneous tocilizumab in a cohort of 200 patients in real life conditions. Joint Bone Spine. 89: 105347.

65. Lamb YN, Deeks ED (2018) Sarilumab: A Review in Moderate to Severe Rheumatoid Arthritis. Drugs 78: 929-40.

66. Nasonov E, Fatenejad S, Feist E, Ivanova M, Korneva E (2022) Olokizumab.a monoclonal antibody against interleukin 6, in combination with methotrexate in patients with rheumatoid arthritis inadequately controlled by methotrexate: efficacy and safety results of a randomised controlled phase III study. Ann Rheum Dis. 81: 469-79.

67. Stojanov S, Kastner DL (2005) Familial autoinflammatory diseases: genetics, pathogenesis and treatment. Curr Opin Rheumatol 17: 586-99.

68. Schett G, Dayer JM, Manger B (2015) Interleukin-1 function and role in rheumatic disease. Nat Rev Rheumatol 12: 14-24.

69. Dinarello CA (2018) Overview of the IL-1 family in innate inflammation and acquired immunity. Immunol. Rev 281: 8-27.

70. Shi L et al. (2020) IL-1 transcriptional responses to lipopolysaccharides are regulated by a complex of RNA binding proteins. J. Immunol 204: 1334-44 .

71. Sneezum L et al. (2020) Context- dependent IL-1 mRNA-destabilization by TTP prevents dys regulation of immune homeostasis under steady state conditions. Front. Immunol 11: 1398.

72. Li S et al. (2019) IL-1α and IL-1β promote NOD2-induced immune responses by enhancing MAPK signaling. Lab. Invest 99: 1321-34.

73. X Wang, F Li, C Fan, C Wang, H Ruan (2011) Effects and relationship of ERK1 and ERK2 in interleukin-1beta-induced alterations in MMP3, MMP13, type II collagen and aggrecan expression in human chondrocytes, International journal of molecular medicine 27: 583-9.

74. V Afonso, R Champy, D Mitrovic, P Collin A. Lomri (2007) Reactive oxygen species and superoxide dismutases: role in joint diseases, Joint, bone, spine : revue du rhumatisme 74: 324-9.

75. Dayer JM, Bresnihan B (2002) Targeting interleukin-1 in the treatment of rheumatoid arthritis. Arthritis Rheum 46: 574-8.

76. Ulfgren AK, Grondal L, Lindblad S, Khademi M, Johnell O et al. (2000) Interindividual and intraarticular variation of proinflammatory cytokines in patients with rheumatoid arthritis: potential implications for treatment. Ann Rheum Dis 59: 439-47.

77. John Tesser, Roy Fleischmann, et al. (2004) Concomitant medication use in a large, international, multicenter, placebo controlled trial of anakinra, a recombinant interleukin 1 receptor antagonist, in patients with rheumatoid arthritis. J Rheumatol 31: 649-54.

78. Tanja Hinze, Christoph Kessel, Claas H Hinze (2021) A dysregulated interleukin-18-interferon-γ-CXCL9 axis impacts treatment response to canakinumab in systemic juvenile idiopathic arthritis. Rheumatology (Oxford) 60: 5165-74.

79. Asher Mullard (2021) Novartis's canakinumab stumbles in cancer, again. Nat Rev Drug Discov 20: 888.

80. Humby F et al. (2019) Synovial cellular and molecular signatures stratify clinical response to csDMARD therapy and predict radiographic progression in early rheumatoid arthritis patients. Ann. Rheum. Dis 78: 761-72.

81. Schett G, Elewaut D, McInnes IB, Dayer JM, Neurath MF (2019) How cytokine networks fuel inflammation: T oward a cytokine-based disease taxonomy. Nat. Med. 19: 822-4 .

82. Iain B, McInnes (2007) Georg Schett.Cytokines in the pathogenesis of rheumatoid arthritis. Nat Rev Immunol 7: 429-42.

83. Takemura S, Klimiuk PA, Braun A, Goronzy JJ, Weyand CM (2001) T cell activation in rheumatoid synovium is B cell dependent. J Immunol 167: 4710-8.

84. Van SD，Hazes JM，De BA et al. Outcome of rheumatoid arthritis in relation to age and rheumatoid factor at diagnosis. J Rheumatol 20: 45-52.

85. Takemura S, Braun A, Crowson C, Kurtin PJ, Cofield RH et al. (2001) Lymphoid neogenesis in rheumatoid synovitis. J Immunol 167: 1072-80.

86. Braun A, Takemura S, Vallejo AN, Goronzy JJ, Weyand CM (2004) Lymphotoxin beta-mediated stimulation of synoviocytes in rheumatoid arthritis. Arthritis Rheum 50: 2140-50.

87. Felice Rivellese, Anna EA, Surace, Katriona Goldmann et al. (2022) Rituximab versus tocilizumab in rheumatoid arthritis: synovial biopsy-based biomarker analysis of the phase 4 R4RA randomized trial. Nat Med 28: 1256-68.

88. Yamaoka K, Saharinen P, Pesu M, et al. (2004) The Janus kinases (Jaks) J. Genome Biol 5: 253.

89. Rane SG, Reddy EP (1994) JAK3: a novel JAK kinase associated with terminal differentiation of hematopoietic cells J. Oncogene 9: 2415-23.

90. Firmbach-Kraft I, Byers M, Shows T, et al. (1990) Tyk2, prototype of a novel class of non-receptor tyrosine kinase genes J. Oncogene 5: 1329-36.

91. Stark GR, Darnell JE (2012) The JAK-STAT pathway at twenty. Immunity, 36: 503.

92. Tozawa H, Kanki Y, Suehiro J, et al. (2011) Genome-wide approaches reveal functional interleukin-4-inducible STAT6binding to the vascular cell adhesion molecule 1 promoter J. Mole Cell Biol 31: 2196.

93. Kiu H, Nicholson SE (2012) Biology and significance of the JAK/STAT signalling pathways.Growth Factors 30: 88.

94. Hodge JA, Kawabata TT, Krishnaswami S, Clark JD, Telliez JB et al. (2016) The mechanism of action of tofacitinib—An oral Janus kinase inhibitor for the treatment of rheumatoid arthritis. Clin. Exp. Rheumatol 34: 318-28.

95. Westhovens R (2019) Clinical efficacy of new JAK inhibitors under development. Just more of the same? Rheumatology 58: 27-33.

96. Machado MA, Moura CS, Guerra SF et al. (2018) Effectiveness and safety of tofacitinib in rheumatoid arthritis: a cohort study J. Arthritis Res Ther 20: 60.

97. Babon JJ, Lucet IS, Murphy JM, Nicola NA, Varghese LN (2014) The molecular regulation of Janus kinase (JAK) activation. Biochem. J 462: 1-13.

98. Mayence A, Eynde JJV (2019) Baricitinib: A 2018 Novel FDA-Approved Small Molecule Inhibiting Janus Kinases. Pharmaceuticals 12: 37.

99. Francesco Campanaro, Alberto Batticciotto, Andrea Zaffaroni (2021) JAK inhibitors and psoriatic arthritis: A systematic review and meta-analysis. Autoimmun Rev. 20: 102902..

100. Marinella Govoni, Anastas Batalov, et al. (2023) Real--world effectiveness of golimumab in the treatment of patients with active rheumatoid arthritis, psoriatic arthritis, or axial spondyloarthritis who failed initial TNF-α inhibitor therapy: a pooled analysis of European prospective observational studie. Clin Exp Rheumatol.

101. Lieke Scheepers, Yifei Yang, et al. (2023) Persistence of Janus-kinase (JAK) inhibitors in rheumatoid arthritis: Australia wide study. Semin Arthritis Rheum 64: 152314.

102. Mie Jin Lim, Kyong-Hee Jung et al. (2023) Inflammation is responsible for systemic bone loss in patients with seropositive rheumatoid arthritis treated with rituximab. Korean J Intern Med 38: 912-22.

103. Fiorenzo Santoleri, Ruggero Lasala, et al. (2023) ADA_ETA_BIO2021: real-world evaluation of adherence, persistence, and cost-effectiveness of originator and biosimilar biologic drugs in the treatment of rheumatoid arthritis: a multicenter study in Italy. Curr Med Res Opin 39: 1729-35.

104. Florence Namour, Kacey Anderson, Cara Nelson, Chantal Tasset (2022) Filgotinib: A Clinical Pharmacology Review. Clin Pharmacokinet 61: 819-32.

105. Bonelli M, Scheinecker C (2018) How does abatacept really work in rheumatoid arthritis?J.. Current opinion in rheumatology 30: 295-300.

106. Borghaei H et al. (2015) Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. N. Engl. J. Med. 373: 1627-39.

107. Buch MH, Eyre S, McGonagle D (2021) Persistent inflammatory and non-inflammatory mechanisms in refractory rheumatoid arthritis J. Nat Rev Rheumatol 17: 17-33.

108. Raza K, Falciani F, Curnow SJ, Ross EJ, Lee C-Y, Akbar AN, et al. (2005) Early Rheumatoid Arthritis is Characterized by a Distinct and Transient Synovial Fluid Cytokine Profile of T Cell and Stromal Cell Origin. Arthritis Res Ther 7: R784.

109. Brzustewicz E, Bryl E (2015) The Role of Cytokines in the Pathogenesis of Rheumatoid Arthritis–Practical and Potential Application of Cytokines as Biomarkers and Targets of Personalized Therapy. Cytokine 76: 527-36.

110. Haas CS, Amin MA, Ruth JH, Allen BL, Ahmed S, Pakozdi A, et al. (2007) In Vivo Inhibition of Angiogenesis by Interleukin-13 Gene Therapy in a Rat Model of Rheumatoid Arthritis. Arthritis Rheum 56: 2535-48.

111. Szekanecz Z, Koch AE, Tak PP (2011) Chemokine and Chemokine Receptor Blockade in Arthritis, a Prototype of Immune-Mediated Inflammatory Diseases. Netherlands J Med 69: 356-66.

112. Vergunst CE, Tak PP (2005) Chemokines: Their Role in Rheumatoid Arthritis.Curr Rheumatol Rep 7: 382-8.

113. Kuan WP, Tam LS, Wong CK, Ko FW, Li T, Zhu T, et al. (2010) CXCL 9 and CXCL 10 as Sensitive Markers of Disease Activity in Patients With Rheumatoid Arthritis. J Rheumatol 37: 257-64.

114. WR Gammon (1979) Phagocyte chemotaxisJ Invest Dermatol 73: 515-20.

115. BF Boyce (2013) Advances in the regulation of osteoclasts and osteoclast functions. J Dent Res 92: 860-7.

116. RM (2002) Apoptosis as a therapeutic tool in rheumatoid arthritis. Nat Rev Immunol 2: 527-35.

117. Ander Laan WH, Quax P, Seemayer CA, et al. (2003) Cartilage degradation and invasion by rheumatoid synovial fibroblasts is inhibited by gene transfer of TIMP-1 and TIMP-3. Gene Ther 10: 234-42.

118. Chroeder M, Viezens L, Fuhrhop I et al. (2013) Angiogenic growth factors in rheumatoid arthritis. Rheumat Int. 33: 523-7.

119. orgensen C (2010) Apparailly F.Prospects for gene therapy in inflammatory arthritis. Best Pract & Res Clinic Rheumat 24: 541-52.

120. Yanqiong Zhang, Xia Mao, Weijie Li (2021) Tripterygium wilfordii: An inspiring resource for rheumatoid arthritis treatment. Med Res Rev 41: 1337-74.

121. Lianying Cheng, Jie Chen, Xiaofeng Rong (2022) Mechanism of Emodin in the Treatment of Rheumatoid Arthritis. Evid Based Complement Alternat Med 9482570.

CEOS CENTER OF EXCELLENCE FOR OPEN SCIENCE

CEOS is an growing Open Access Publisher with diverse peer reviewed journals supported by Aca demic Editors, Scholars, Physicians, Instructors,

CEOS Publishers follow strict ethical standards for publication to ensure high quality scientific studies, credit for the research participants. Any ethical issues will be scrutinized carefully to maintain the integrity of literature.

CEOS Publishers believes scientific integrity and intellectual honesty are essential in all scholarly work. As an upcoming publisher, our commitment is to protect the integrity of the scholarly publications, for which we take the necessary steps in all aspects of publishing ethics.

All the articles published in **CEOS Publisher** journals are licensed under Creative CommonsCC BY 4.0 license, means anyone can use, read and dow-nload the article for free. However, the authors reserve the copyright for the published manuscript.