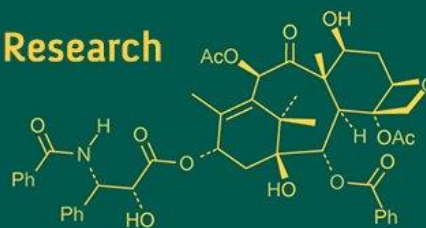


International Journal of Advanced Biochemistry Research



ISSN Print: 2617-4693

ISSN Online: 2617-4707

NAAS Rating (2026): 5.29

IJABR 2026; 10(6): 67-75

www.biochemjournal.com

Received: 24-03-2026

Accepted: 27-04-2026

Alamani Sachin

Researcher, Department of
Veterinary Pathology,
Veterinary College Hassan,
KVAFSU, Bidar, Karnataka,
India

Hanamantappa Kalasapur

Researcher, Department of
Veterinary Pathology,
Veterinary College Hassan,
KVAFSU, Bidar, Karnataka,
India

Abhilash NS

Big Data Engineer, Walmart
Global Tech India, Bengaluru,
Karnataka, India

Shilpa VT

Assistant Professor,
Department of Veterinary
Pathology, Veterinary College
Hassan, Karnataka, India

Ravikumar C

Associate Professor and Head,
Department of Veterinary
Pharmacology and toxicology,
Veterinary College Hassan,
Karnataka, India

Girish BC

Associate Professor and Head,
Department of Veterinary
Pathology, Veterinary College
Hassan, Karnataka, India

Corresponding Author:**Alamani Sachin**

Researcher, Department of
Veterinary Pathology,
Veterinary College Hassan,
KVAFSU, Bidar, Karnataka,
India

Cytokine-mediated mechanisms in rheumatoid arthritis: pathogenesis and emerging therapeutic target: Review article

Alamani Sachin, Hanamantappa Kalasapur, Abhilash NS, Shilpa VT, Ravikumar C and Girish BC

DOI: <https://www.doi.org/10.33545/26174693.2026.v10.i6a.8557>

Abstract

Rheumatoid arthritis (RA) is a complex systemic autoimmune disorder for which current therapies are palliative, characterized by persistent inflammation, synovial hyperplasia, and progressive joint destruction if untreated or not managed properly it can affect many tissues and organs, such as skin, blood vessels, heart, lungs, and muscles, but it primarily affects the joints, causing a nonsuppurative proliferative and inflammatory synovitis that often progresses to articular cartilage destruction and joint ankylosis consequently one's life quality. Cytokines play a pivotal role in disease initiation and progression by orchestrating immune responses and inflammatory cascades. Key mediators such as TNF- α , IL-1, and IL-6 contribute to synovial inflammation and cartilage degradation. Advances in molecular biology have highlighted intracellular signaling pathways, particularly the JAK-STAT Signaling Pathway, as critical regulators of cytokine activity. Targeted therapies including biologics and small-molecule inhibitors have significantly improved clinical outcomes. This review summarizes recent advances in cytokine biology in RA and discusses translational insights from experimental models.

Keywords: Rheumatoid arthritis, cytokines, TNF- α , IL-6, JAK-STAT, biologics, inflammation

1. Introduction

Rheumatoid arthritis (RA) is a chronic multisystemic autoimmune disorder characterized by persistent inflammation, primarily affecting the synovial joints. The term "rheumatoid arthritis" originates from the Greek words describing inflamed and watery joints. The disease was first systematically described by French physician Augustin Jacob Landré-Beauvais in 1800 as "asthenic gout," highlighting its prevalence in women. Later, British rheumatologist Alfred Baring Garrod formally coined the term "rheumatoid arthritis" in 1859. Globally, RA affects approximately more than 1% of the population, with incidence increasing with age and peaking above 40 years. Women are affected three to five times more frequently than men [Ding *et al.*, 2023]^[1].

Clinically, RA is hallmarked by recurrent, symmetrical polyarthritis, predominantly involving the small joints of the hands and feet, as well as larger joints such as the knees and shoulders. Early disease manifestations include redness, swelling, warmth, pain, and functional impairment, which may progress to joint deformity, rigidity, and erosive changes in bones and cartilage. Disease progression is often associated with synovial hyperplasia, cartilage degradation, subchondral bone erosion, ligamentous injury, and muscle atrophy, collectively resulting in significant disability and reduced quality of life [Weber *et al.*, 2023]^[3].

The American College of Rheumatology (ACR) and the European League against Rheumatism (EULAR) have developed updated classification criteria for RA, integrating joint involvement, serologic markers (rheumatoid factor [RF] and anti-citrullinated protein antibodies [ACPA]), symptom duration, and acute phase reactants into a structured scoring system. Early identification of high-risk patients has enabled more targeted therapeutic strategies, including methotrexate and biologic therapies, to prevent progressive joint damage [Yang *et al.*, 2023]^[5]. RA is multisystemic, and extra-articular manifestations may involve

the eyes, skin, lungs, heart, kidneys, and nervous system. Chronic systemic inflammation contributes to comorbidities such as cardiovascular disease, renal amyloidosis, interstitial Lung disease, and peripheral neuropathies, highlighting the complexity of disease management [Bilski *et al.*, 2023] [8]. Although the precise etiology of rheumatoid arthritis (RA) remains unclear, the disease has attracted increasing research attention over the past few decades. Aberrant signaling pathways in RA have emerged as a central area of investigation, providing crucial insights into the underlying mechanisms and serving as a basis for the development of innovative therapeutic strategies. Further, it is widely accepted that disease development is driven by an interplay of genetic susceptibility, environmental triggers, and epigenetic modifications. Dysregulated immune responses lead to autoimmune-mediated joint attack, synovial inflammation, and cartilage and bone destruction. Laboratory assessments, imaging studies, and clinical evaluation facilitate accurate diagnosis and differentiation from related autoimmune disorders, such as systemic lupus erythematosus, psoriatic arthritis, and fibromyalgia [Magoni & Zinellu *et al.*, 2024] [45].

RA imposes a substantial personal and socioeconomic burden, including reduced functional capacity, decreased quality of life, work productivity loss, and increased healthcare costs. Recent research has focused on the molecular mechanisms driving RA pathogenesis, particularly the roles of cytokines and intracellular signaling pathways. Advancements in understanding the interactions among genetic susceptibility, epigenetic modifications, and environmental factors have facilitated the development of targeted therapies aimed at modulating specific pathogenic pathways. This review provides an overview of the risk factors, signaling pathways, and molecular mechanisms involved in rheumatoid arthritis (RA). It also discusses existing treatment approaches, emerging preclinical and clinical therapeutic candidates, and innovative precision medicine strategies aimed at improving RA management.

2. Pathogenesis of rheumatoid arthritis

Rheumatoid arthritis (RA) begins as a state of persistent cellular activation that ultimately leads to autoimmunity in the joints and, in some cases, other organs. Clinically, disease manifestations typically follow synovial inflammation and joint injury, with fibroblast-like synoviocytes (FLS) playing a central role in disease progression. RA development is commonly described in three stages: an initial nonspecific inflammatory phase amplified by T-cell activation in the synovium, a chronic inflammatory phase, and a tissue-damage stage mediated by pro-inflammatory cytokines such as IL-1, IL-6, and TNF- α . The autoimmune response is characterized by the production of autoantibodies, which have been associated with more severe joint damage and increased mortality. Notably, autoantibodies against citrullinated proteins (ACPAs) form immune complexes with rheumatoid factors (RF), triggering complement activation and subsequent tissue injury. Detection of these autoimmune responses to citrullinated self-proteins represents a major advance in early RA diagnosis, as ACPAs can appear up to a decade before clinical disease onset. Importantly, ACPA-positive and ACPA-negative RA may represent genetically distinct subtypes, differing in HLA associations and non-HLA susceptibility genes. Environmental triggers can lead to citrullination of proteins via peptidylarginine deiminases

(PADs), including PAD4, which is also recognized as a non-MHC genetic risk factor linked to bone damage in Asian RA populations. Other post-translational modification autoantibodies, such as anti-carbamylated protein (CarP) and acetylated protein antibodies, have been identified, indicating a broad spectrum of autoimmune responses in RA. Synovial inflammation underlies joint swelling in RA, characterized by infiltration of innate and adaptive immune cells. Innate immune cells—dendritic cells (DCs), monocytes, mast cells, and innate lymphoid cells—initiate inflammatory responses that activate T cells, which in turn stimulate B cells, macrophages, synoviocytes, chondrocytes, and osteoclasts. These cells secrete pro-inflammatory and bone-destructive mediators, including IL-1 β , IL-6, TNF- α , and matrix metalloproteinases (MMPs). The interaction of innate and adaptive pathways within the synovium and adjacent bone marrow drives tissue injury and chronic inflammation, attracting circulating leukocytes to the inflamed joints and promoting angiogenesis to sustain the hypertrophic synovium. FLS undergo profound phenotypic changes in RA, transforming from normal mesenchymal cells into aggressive, tumor-like cells with reduced apoptosis sensitivity, overexpression of adhesion molecules, and abnormal cytokine, chemokine, and MMP production. These cells contribute significantly to synovial invasion and cartilage destruction. Cytokines and chemokines regulate the inflammatory environment by activating endothelial cells, attracting immune cells, and stimulating fibroblasts. Activated B cells, supported by antigen-presenting cells and T-helper cells, differentiate into plasma cells that produce pathogenic immunoglobulins. Meanwhile, T-helper cell subsets, including Th1, Th2, Th17, Treg, and follicular helper T (Tfh) cells, orchestrate immune responses within the synovium. In RA, Th1 and Th17 cells drive IL-17 production and inflammatory infiltration, while Tfh cells enhance germinal center activity, promoting high-affinity autoantibody production and disease perpetuation. Bone destruction in RA is mediated by osteoclast activation through RANK-RANKL interactions, facilitated by monocytes, macrophages, and fibroblasts. Erosions typically occur at the cartilage-bone interface, also known as the bare area. Cytokine signaling through their respective receptors triggers cascades of intracellular events that amplify inflammation, induce tissue remodeling, and perpetuate joint damage. Collectively, RA pathogenesis reflects a complex interplay between autoimmunity, innate and adaptive immune activation, stromal cell dysfunction, and dysregulated cytokine networks, establishing a self-sustaining inflammatory milieu that drives chronic joint and systemic damage (Fig. 3–4). Chemokines play a central role in orchestrating immune cell trafficking in rheumatoid arthritis, contributing to the chronic inflammation and joint destruction characteristic of the disease. By binding to their specific G protein-coupled receptors, chemokines create gradients that guide the migration of leukocytes, including T cells, B cells, macrophages, dendritic cells, and neutrophils, into inflamed synovial tissue. For instance, chemokines such as CCL2, CCL5, and CXCL10 promote the recruitment of monocytes and T cells, amplifying local inflammation and autoantibody production. Th17 cell migration, mediated by chemokine receptors like CCR4 and CCR6, is particularly important in sustaining synovial inflammation and cartilage damage. Additionally, chemokines like CXCL8 and CXCL5 attract neutrophils, which release proteolytic enzymes and reactive oxygen species, further aggravating tissue injury.

The dysregulated chemokine network not only drives immune cell infiltration but also facilitates the formation of ectopic lymphoid structures in the synovium, perpetuating autoimmunity and disease progression. Targeting these chemokine-mediated pathways has shown promise in preclinical models, highlighting their critical role in immune cell recruitment and the potential for therapeutic intervention in RA.

3. Role of cytokines in RA

Cytokines play a central and decisive role in the pathogenesis of rheumatoid arthritis (RA), acting as key mediators that regulate synovial inflammation, immune cell activation, cartilage degradation, and bone destruction. Current evidence indicates that RA is driven by a complex cytokine network rather than a single dominant mediator, with tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1β (IL-1β) serving as major pro-inflammatory cytokines that sustain chronic synovitis and systemic inflammation. TNF-α amplifies inflammatory cascades by activating NF-κB and MAPK signaling pathways, leading to increased production of additional cytokines and recruitment of immune cells into the synovial tissue (McInnes & Schett 2007) [10, 19, 32]. IL-6 contributes to both local and systemic disease manifestations through activation of the JAK-STAT pathway, promoting B-cell differentiation, acute-phase protein synthesis, and autoantibody production, while IL-1β enhances cartilage breakdown and osteoclast-mediated bone resorption through Induction of matrix metalloproteinases (MMPs) (Smolen *et*

al., 2018) [11, 28]. In addition, IL-17 produced by Th17 cells and GM-CSF derived from T cells and synovial macrophages further intensify inflammatory responses by sustaining neutrophil recruitment and macrophage activation, respectively (Firestein, 2017) [12, 24, 27, 31]. Recent studies also highlight upstream cytokines such as IL-23, IL-21, and BAFF, which regulate T follicular helper cell differentiation and autoantibody production, thereby linking innate and adaptive immune responses in RA pathogenesis (Weyand & Goronzy, 2021) [13, 25, 33]. Importantly, dysregulation of intracellular signaling pathways including NF-κB, MAPK, and JAK-STAT perpetuates cytokine-driven inflammation, while failure of regulatory cytokines such as IL-10 and TGF-β to suppress immune activation contributes to chronic disease persistence. The clinical importance of cytokine pathways is strongly validated by the success of targeted biologic therapies, including TNF inhibitors, IL-6 receptor blockers, and JAK inhibitors, which have significantly improved disease outcomes and represent current standard-of-care treatments (Brennan FM & McInnes IB) [14, 19, 32]. However, a subset of patients remains refractory to these agents, reflecting redundancy within cytokine networks and ongoing inflammation despite single-pathway inhibition. Recent advances therefore focus on broader cytokine modulation, biomarker-guided precision therapy, and novel strategies such as bispecific antibodies, CAR-T cell therapy, and immune reprogramming approaches aimed at achieving durable remission or functional cure (Mori *et al.*, 2025; Fujimoto *et al.*, 2025) [15,16, 18].

Table 1: Key Molecules and Signaling Mediators in Rheumatoid Arthritis (RA) — Group-wise Table (with Current Status & References)

Group	Molecule / Pathway	Role in RA	Current Status	Key Reference
Cytokines (Pro-inflammatory)	TNF-α	Central driver of synovial inflammation and joint destruction	Multiple approved biologics (e.g., infliximab, adalimumab)	McInnes, Schett, Nat Rev Immunol, 2007 [10, 19, 32]
	IL-6	Acute phase response, B-cell activation, systemic inflammation	FDA-approved IL-6 inhibitors	Smolen <i>et al.</i> Nat Rev Dis Primers, 2018 [11, 28]
	IL-1β	Cartilage degradation, osteoclast activation	Limited use; approved IL-1 blocker in select cases	Firestein. Immunity, 2017 [12, 24, 31]
	IL-17	Th17-mediated inflammation, neutrophil recruitment	Mixed efficacy; clinical trials ongoing	Alunno <i>et al.</i> BMC Rheumatology, 2017 [26]
	GM-CSF	Macrophage activation, synovial inflammation	Phase II/III clinical trials	Life (MDPI), 2025
Intracellular Signaling Pathways	JAK-STAT	Cytokine signal transduction	JAK inhibitors approved	O’Shea <i>et al.</i> Nat Rev Rheumatol, 2022 [23, 29]
	NF-κB	Master regulator of inflammatory genes	Major therapeutic target (preclinical)	Firestein. Immunity, 2017 [12, 24, 31]
	MAPK	Cytokine production and synovial activation	Experimental inhibitors	McInnes <i>et al.</i> Nat Rev Immunol, 2007 [10, 19, 32]
	PI3K/Akt	Synoviocyte survival, angiogenesis	Early-stage research	Frontiers in Medicine, 2025
Immune Cells	Macrophages	Major source of TNF-α, IL-1, IL-6	Therapeutic targeting ongoing	Weyand, Goronzy. Nat Immunol, 2021 [13, 25, 33]
	Fibroblast-like synoviocytes (FLS)	Synovial hyperplasia, cartilage invasion	Emerging drug target	Smolen <i>et al.</i> Nat Rev Dis Primers, 2018 [11, 28]
	Th17 cells	IL-17 production, inflammation amplification	Targeted in immunotherapy trials	Alunno <i>et al.</i> BMC Rheumatology, 2017 [26]
	B cells	Autoantibody production (RF, ACPA)	B-cell depletion therapy approved	Smolen JS <i>et al.</i> Ann Rheum Dis, 2020
Autoantibodies	ACPA	Early disease marker, pathogenic role	Diagnostic & prognostic biomarker	Smolen <i>et al.</i> Nat Rev Dis Primers, 2018 [11, 28]
	Rheumatoid factor (RF)	Immune complex formation	Clinical diagnostic marker	Firestein. Immunity, 2017 [12, 24, 31]
Bone Destruction Pathways	RANKL	Osteoclast differentiation and bone erosion	Denosumab approved	McInnes <i>et al.</i> Nat Rev Immunol, 2007 [10,19, 32]
	MMPs	Cartilage matrix degradation	Experimental inhibitors	Firestein. Immunity, 2017 [12, 24, 31]
Angiogenesis & Chemotaxis	VEGF	Synovial angiogenesis	Anti-angiogenic therapies under study	Smolen <i>et al.</i> Nat Rev Dis Primers, 2018 [11,28]
	Chemokines (CCL2, CXCL8)	Leukocyte recruitment	Investigational targets	Weyand <i>et al.</i> Nat Immunol, 2021 [13, 25, 33]
Inflammasome Pathway	NLRP3	Activates IL-1β and IL-18	Preclinical drug development	Firestein. Immunity, 2017 [12, 24, 31]
Emerging Targets	BTK	B-cell receptor signaling	Clinical trials ongoing	J Clin Med, 2025
	CAR-T therapy	Immune system reprogramming	Early clinical trials	Nature Medicine, 2025
	MSC therapy	Immunomodulation and tissue repair	Clinical trials ongoing	Wang <i>et al.</i> Stem Cell Res Ther

3.1 Emerging cytokines and mediators

Emerging cytokines and soluble mediators have gained increasing attention in the pathogenesis of rheumatoid arthritis (RA), expanding the traditional cytokine paradigm beyond TNF- α , IL-6, and IL-1 β to include chemokines, adipokines, and organ-derived inflammatory mediators. Among chemokines, molecules such as CCL3 (MIP-1 α), CCL2, CXCL8, and CXCL10 play a crucial role in directing leukocyte trafficking into the synovial microenvironment, thereby sustaining chronic synovial inflammation and pannus formation. Recent evidence highlights that chemokine networks not only regulate immune cell recruitment but also influence fibroblast-like synoviocyte activation and osteoclastogenesis, making them attractive therapeutic targets, although several chemokine receptor antagonists have shown limited success in clinical translation due to redundancy in signaling pathways and overlapping ligand–receptor interactions (Murayama *et al.*, 2023) [4, 17]. Concurrently, adipokines such as leptin, adiponectin, resistin, and visfatin have emerged as novel immunometabolic mediators linking metabolic dysfunction with inflammation in RA. These adipose-derived cytokines contribute to disease pathogenesis by promoting Th1/Th17 polarization, enhancing production of pro-inflammatory cytokines, and stimulating matrix metalloproteinases, thereby accelerating cartilage degradation and joint damage. Recent studies further suggest that adipokines may serve as potential biomarkers of disease activity and therapeutic response, particularly in obese RA patients where metabolic inflammation exacerbates disease severity (Fujimoto *et al.*, 2025) [16, 18]. Current trends in RA research emphasize the concept of “immunometabolism,” where adipokines and chemokines are integrated into broader cytokine networks that regulate both local joint inflammation and systemic disease manifestations (Smolen *et al.*, 2018) [11, 28]. However, despite strong preclinical evidence, translation into targeted therapies remains challenging, and ongoing research is focused on multi-target inhibition strategies, biomarker-guided patient stratification, and systems biology approaches to overcome redundancy in inflammatory signaling (McInnes & Schett, 2007) [10, 19, 32]. Collectively, emerging mediators such as chemokines and adipokines represent a rapidly evolving frontier in RA research, offering promising but still clinically underdeveloped avenues for next-generation therapeutic interventions.

4. Cytokine signaling pathways

Cytokine signaling pathways are central to the immunopathogenesis of rheumatoid arthritis (RA), functioning as key molecular networks that regulate inflammation, immune-cell activation, synovial proliferation, and joint destruction. Among these, the Janus kinase–signal transducer and activator of transcription (JAK–STAT) pathway is one of the most extensively studied and clinically relevant signaling cascades. In RA, pro-inflammatory cytokines such as interleukin-6 (IL-6), interferons, interleukin-2, and granulocyte-macrophage colony-stimulating factor (GM-CSF) [27] bind to their respective cell-surface receptors and activate associated Janus kinases (JAK1, JAK2, JAK3, and TYK2). This leads to phosphorylation of STAT proteins, which dimerize and translocate to the nucleus, where they regulate transcription of genes involved in inflammation, cell survival, and immune activation (McInnes & Schett, 2007) [10, 19, 32].

Recent evidence highlights that dysregulated JAK–STAT signaling not only sustains chronic synovial inflammation but also contributes to pain sensitization by enhancing neuroimmune interactions and increasing peripheral nociceptor responsiveness, linking cytokine signaling directly with RA-associated pain mechanisms (Simon *et al.*, 2021) [21]. In addition, the JAK–STAT pathway does not function in isolation but interacts with other major inflammatory cascades such as NF- κ B, MAPK, and PI3K–Akt signaling, forming an integrated and redundant signaling network that amplifies inflammatory responses within the synovial microenvironment. This crosstalk promotes fibroblast-like synoviocyte (FLS) activation, pannus formation, angiogenesis, and osteoclast differentiation, ultimately leading to cartilage degradation and bone erosion (Firestein, 2017) [12, 24, 31]. The clinical relevance of cytokine signaling pathways has been strongly validated by the successful development of targeted synthetic disease-modifying antirheumatic drugs (tsDMARDs), particularly JAK inhibitors such as tofacitinib, baricitinib, and upadacitinib. These agents block intracellular cytokine signaling and have demonstrated significant efficacy in reducing disease activity, improving physical function, and alleviating pain in patients with moderate to severe RA, including those who fail conventional biologic therapies (O’Shea *et al.*, 2022) [23, 29]. Recent clinical and translational studies further suggest that JAK inhibition may exert broader effects by modulating both peripheral inflammation and central pain processing, thereby improving patient-reported outcomes beyond traditional measures of inflammation (Smolen *et al.*, 2018) [11]. However, despite these advances, therapeutic challenges remain due to pathway redundancy, incomplete response in a subset of patients, and potential safety concerns associated with long-term immunosuppression. Consequently, current research trends are focused on developing more selective JAK inhibitors, dual-pathway inhibitors, and combination therapeutic strategies aimed at achieving greater efficacy with improved safety profiles. Beyond JAK–STAT, emerging evidence also emphasizes the importance of multiple interconnected signaling pathways in RA pathogenesis. NF- κ B signaling acts as a master regulator of inflammatory gene transcription, controlling the expression of TNF- α , IL-1 β , and IL-6, while MAPK pathways regulate cellular proliferation and production of inflammatory mediators. PI3K–Akt signaling contributes to synoviocyte survival and resistance to apoptosis, thereby sustaining pannus formation. Recent systems biology approaches and transcriptomic studies published in high-impact journals such as *Nature Reviews Rheumatology* and *Nature Immunology* have highlighted that RA should be viewed as a network disease rather than a single-pathway disorder, where multiple signaling axes interact dynamically to maintain chronic inflammation (Fujimoto *et al.*, 2025) [16, 18]. This conceptual shift has important therapeutic implications, supporting the development of multi-target drugs, pathway-specific inhibitors, and precision medicine approaches guided by molecular profiling. Overall, cytokine signaling pathways, particularly JAK–STAT and its associated networks, represent a central hub in RA pathogenesis. Their involvement in both inflammation and pain mechanisms, combined with successful clinical translation of pathway inhibitors, underscores their importance as both mechanistic drivers and therapeutic targets. Ongoing research continues

to refine our understanding of signaling crosstalk, disease heterogeneity, and biomarker-guided therapy, aiming to improve long-term disease control and move toward personalized treatment strategies in rheumatoid arthritis.

5. Therapeutic targeting of cytokines

Therapeutic targeting of cytokines represents the cornerstone of modern rheumatoid arthritis (RA) management, fundamentally transforming disease outcomes by directly interrupting key inflammatory signaling networks responsible for synovial inflammation, joint destruction, and systemic complications. Biologic disease-modifying antirheumatic drugs (bDMARDs), particularly tumor necrosis factor-alpha (TNF-α) inhibitors such as adalimumab, infliximab, and etanercept, were the first major breakthrough in cytokine-targeted therapy and remain highly effective in reducing synovial inflammation, inhibiting osteoclast activation, and slowing radiographic progression of joint damage (Jain *et al.*, 2025) [22, 40, 44]. Subsequently, interleukin-6 (IL-6) receptor blockers, including tocilizumab and sarilumab, have further expanded therapeutic options by suppressing JAK–STAT-mediated inflammatory signaling, thereby improving systemic manifestations such as fatigue, anemia, and elevated acute-phase responses. Recent studies confirm that IL-6 inhibition is particularly beneficial in patients who are non-responsive to TNF inhibitors, highlighting the importance of cytokine heterogeneity in RA pathogenesis and treatment response (Avci *et al.*, 2023). In parallel, targeted synthetic DMARDs (tsDMARDs), especially Janus kinase (JAK) inhibitors such as tofacitinib, baricitinib, and upadacitinib, have introduced an oral therapeutic strategy that blocks intracellular signaling pathways shared by multiple cytokines, thereby

offering broader immunomodulation compared to single-cytokine blockade. These agents are increasingly recognized as effective options for moderate-to-severe RA and are particularly useful in patients with inadequate response to biologics (O’Shea *et al.*, 2022) [23, 29]. Current therapeutic trends are shifting beyond single-cytokine inhibition toward more integrated and precision-based strategies. Emerging biologics targeting GM-CSF, [27] IL-17, and IL-23 pathways are being investigated in clinical trials, although their efficacy in RA remains variable due to redundancy in cytokine networks. Recent advances in molecular engineering have also introduced bispecific antibodies and next-generation JAK inhibitors with improved selectivity and safety profiles. Additionally, precision medicine approaches using cytokine profiling, genetic markers, and synovial tissue analysis are being explored to personalize treatment selection and improve therapeutic response rates. Contemporary reviews emphasize that RA is not driven by a single cytokine axis but rather by a complex, redundant inflammatory network involving TNF, IL-6, IL-1β, and downstream signaling pathways such as NF-κB and JAK–STAT, which explains both the success and limitations of current therapies (Smolen *et al.*, 2018) [11, 28]. Despite remarkable progress, a subset of patients remains refractory to existing treatments, driving ongoing research into combination biologic strategies, immune cell reprogramming, and novel cytokine network modulation. Overall, cytokine-targeted therapy continues to evolve rapidly, with current trends focusing on broader pathway inhibition, personalized medicine, and long-term immune modulation aimed at achieving sustained remission or potential disease modification in RA (Fujimoto *et al.*, 2025) [16, 18].

Table 2: Approved Immune-Targeted Therapies in Rheumatoid Arthritis (RA)

Class	Drug	Target / Mechanism	Route	Current Status (RA)	Clinical Role	Key Reference
TNF Inhibitors (bDMARDs)	Etanercept	TNF-α blocker (decoy receptor)	SC	Approved	First-line biologic for moderate–severe RA	(Johns Hopkins Arthritis Center)
	Infliximab	Anti-TNF-α monoclonal antibody	IV	Approved	Used with MTX for refractory RA	(Johns Hopkins Arthritis Center)
	Adalimumab	Anti-TNF-α monoclonal antibody	SC	Approved	Widely used biologic DMARD	(Johns Hopkins Arthritis Center)
	Golimumab	Anti-TNF-α monoclonal antibody	SC/IV	Approved	Long-acting TNF inhibitor	(Johns Hopkins Arthritis Center)
	Certolizumab pegol	PEGylated TNF inhibitor	SC	Approved	Pregnancy-friendly option	(Johns Hopkins Arthritis Center)
IL-6 Pathway Inhibitors	Tocilizumab	IL-6 receptor blocker	IV/SC	Approved	Reduces systemic inflammation & acute phase response	Smolen <i>et al.</i> , 2018 [11, 28]
	Sarilumab	IL-6 receptor blocker	SC	Approved	Used in MTX-resistant RA	Smolen <i>et al.</i> , 2018 [11, 28]
	Olokizumab	Direct IL-6 cytokine inhibitor	SC	Approved (selected regions)	Blocks IL-6 signaling upstream	(Wikipedia)
T-cell Costimulation Blocker	Abatacept	CTLA-4–Ig (blocks CD80/86–CD28)	IV/SC	Approved	Reduces T-cell activation	Firestein, Immunity
B-cell Targeting Therapy	Rituximab	Anti-CD20 B-cell depletion	IV	Approved	For refractory/seropositive RA	Smolen <i>et al.</i> , 2018 [11, 28]
JAK Inhibitors (tsDMARDs)	Tofacitinib	JAK1/JAK3 inhibitor	Oral	Approved	First oral targeted synthetic DMARD	(WebMD)
	Baricitinib	JAK1/JAK2 inhibitor	Oral	Approved	Strong efficacy in MTX-resistant RA	(PMC)
	Upadacitinib	Selective JAK1 inhibitor	Oral	Approved	High efficacy in active RA	(WebMD)
Emerging/Adjunct Immune Targets (Selected use/approval evolving)	GM-CSF inhibitors (e.g., mavrilimumab) [27]	Macrophage activation pathway	SC	Clinical trials / limited approval status	Promising in refractory RA	Frontiers Immunology 2025
	IL-17 inhibitors	Th17 pathway blockade	SC	Not fully effective in RA	More effective in PsA than RA	Alunno <i>et al.</i> , 2017 [26]

6. Insights from Preclinical Models

Preclinical animal models have played a crucial role in advancing the understanding of rheumatoid arthritis (RA) pathogenesis and in the development of novel therapeutic strategies. Among these, the collagen-induced arthritis (CIA) model is the most widely used and well-characterized experimental system, as it closely mimics key pathological features of human RA, including synovial hyperplasia, immune cell infiltration, autoantibody production, and progressive cartilage and bone destruction. CIA is induced by immunization with type II collagen in genetically susceptible mouse strains and is particularly valuable for studying T-cell and B-cell mediated autoimmune mechanisms and cytokine-driven inflammation (Luan *et al.*, 2021) ^[30, 35]. In addition, collagen antibody-induced arthritis (CAIA) and K/BxN serum transfer models are frequently used to investigate effector phases of disease, especially neutrophil-driven inflammation and immune complex-mediated joint damage. Recent literature highlights that these models consistently demonstrate the involvement of major inflammatory cytokines such as TNF- α , IL-6, and IL-1 β , along with activation of downstream signaling pathways including NF- κ B, MAPK, and JAK-STAT, thereby validating their translational relevance to human disease (Wei *et al.*, 2025) ^[34]. Current trends in RA research

emphasize that CIA and related models are not only used for mechanistic studies but also serve as essential platforms for preclinical drug evaluation, particularly for biologic DMARDs and targeted synthetic DMARDs such as JAK inhibitors (Chidomere *et al.*, 2023) ^[36]. However, recent studies also reveal important limitations, including variability in disease severity, strain dependency, microbiome influence, and incomplete replication of chronic and systemic aspects of human RA, which can affect reproducibility and translational success. To address these gaps, emerging approaches are integrating humanized mouse models, multi-omics technologies, and systems biology analyses to better capture disease heterogeneity and improve predictive accuracy for therapeutic responses. Furthermore, contemporary research increasingly uses these models to explore extra-articular manifestations of RA, including cardiovascular and pulmonary comorbidities, reflecting a shift toward viewing RA as a systemic inflammatory disease rather than a joint-limited disorder (Marco-Bonilla *et al.*, 2025) ^[37, 39] (Krock *et al.*, 2019) ^[38]. Overall, preclinical models remain indispensable in RA research, bridging the gap between molecular mechanisms and clinical therapy development while evolving toward more sophisticated and human-relevant experimental systems.

Table 3: Preclinical Models in Rheumatoid Arthritis (RA)

Model Type	Induction Method	Key Features (What it mimics in RA)	Main Use	Current Insights	Key Reference
Collagen-Induced Arthritis (CIA)	Immunization with type II collagen in mice/rats	Synovitis, autoantibodies, cartilage & bone erosion	Standard model for RA pathogenesis & drug testing	Best model for studying adaptive immunity (T & B cell response, cytokines TNF- α , IL-6, IL-17)	Luan <i>et al.</i> , <i>PMC</i> , 2021 ^[30, 35]
Collagen Antibody-Induced Arthritis (CAIA)	Injection of anti-collagen antibodies	Rapid joint inflammation, neutrophil-driven damage	Study of effector phase of RA	Useful for studying innate immune mechanisms independent of adaptive immunity	Luan <i>et al.</i> , 2021 ^[30, 35]
K/BxN Serum Transfer Model	Transfer of arthritogenic serum	Severe acute arthritis, immune-complex mediated inflammation	Study of effector inflammatory pathways	Strong model for Fc receptor, complement, and neutrophil activation	Firestein, <i>Immunity</i> , 2017 ^[12, 24, 31]
Adjuvant-Induced Arthritis (AIA)	Injection of Freund's adjuvant	Systemic inflammation, polyarthritis	Drug screening and anti-inflammatory studies	Mimics chronic inflammation and cytokine storm	Smolen <i>et al.</i> , 2018 ^[11, 28]
TNF-Transgenic Mouse Model	Genetic overexpression of TNF- α	Chronic progressive arthritis	Study of TNF-driven pathology	Highly relevant for testing TNF inhibitors	McInnes & Schett, 2007 ^[10, 19, 32]
SKG Mouse Model	Mutation in ZAP-70 gene	Spontaneous autoimmune arthritis	Study of T-cell mediated autoimmunity	Useful for studying Th17/IL-17 axis	Weyand & Goronzy, 2021 ^[13, 25, 33]
Humanized Mouse Models	Engrafted human immune cells/tissues	Human-like immune response	Translational drug testing	Increasingly used for biologics and precision medicine studies	Frontiers in Medicine, 2025
Glycoprotein-Induced Arthritis (GIA)	Immunization with cartilage glycoproteins	Joint inflammation & cartilage damage	Study of autoantigen-specific immunity	Models antigen-driven RA mechanisms	Luan <i>et al.</i> , 2021 ^[30, 35]
Spontaneous Arthritis Models (e.g., SKG, IL-1RA knockout)	Genetic mutations	Chronic autoimmune arthritis	Pathogenesis studies	Useful for studying genetic susceptibility factors	Smolen <i>et al.</i> , 2018 ^[11, 28]

7. Biomarkers and clinical implications

Biomarkers play a crucial role in improving the early diagnosis, disease monitoring, and risk stratification of rheumatoid arthritis (RA), particularly in identifying patients at higher risk of systemic complications such as cardiovascular disease. Among the most promising biomarker groups are circulating cell adhesion molecules (CAMs), including intercellular adhesion molecule-1

(ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and selectins (E-, P-, and L-selectin), which reflect endothelial activation and vascular inflammation. A recent systematic review and meta-analysis by Mangoni and Zinellu demonstrated that RA patients exhibit significantly elevated circulating levels of ICAM-1, VCAM-1, E-selectin, and P-selectin compared with healthy controls, indicating persistent endothelial dysfunction and chronic systemic

inflammation in RA patients (Mangoni & Zinellu, 2024) [9, 45]. These findings are clinically important because endothelial activation is now recognized as a key link between RA and accelerated atherosclerosis, explaining the increased cardiovascular morbidity and mortality observed in these patients. Importantly, the study also highlighted that elevated adhesion molecules are present even in patients with short disease duration and low disease activity, suggesting that vascular inflammation begins early in RA and is not solely dependent on clinical disease severity. Recent meta-regression analyses further indicate that inflammatory markers such as erythrocyte sedimentation rate (ESR) correlate with VCAM-1 levels, reinforcing the close interaction between systemic inflammation and endothelial dysfunction. Moreover, differential effects of treatments, particularly glucocorticoids, appear to modulate ICAM-1 expression, suggesting that commonly used anti-inflammatory therapies may partially influence biomarker levels. From a clinical perspective, these adhesion molecules are emerging as potential tools for cardiovascular risk stratification, allowing earlier identification of RA patients who may benefit from aggressive anti-inflammatory and cardioprotective strategies. Current trends in RA research are increasingly focused on integrating such biomarkers into precision medicine frameworks, combining inflammatory profiling, genetic susceptibility markers, and imaging techniques to improve individualized disease management. However, despite strong evidence supporting their association with disease pathology, routine clinical use of adhesion molecules remains limited due to assay variability, lack of standardized thresholds, and incomplete validation in prospective studies. Therefore, ongoing research is directed toward validating these biomarkers in large longitudinal cohorts and integrating them into multi-biomarker panels for improved diagnostic and prognostic accuracy in RA.

8. Challenges and limitations

Despite remarkable advances in the management of rheumatoid arthritis (RA) through biologic and targeted synthetic disease-modifying antirheumatic drugs (DMARDs), several important challenges and limitations continue to hinder optimal disease control. One of the major issues is the variable treatment response among patients, as RA is a highly heterogeneous disease influenced by genetic, immunological, environmental, and microbiome-related factors. Recent studies emphasize that nearly 30–40% of patients show inadequate or partial response to first-line biologics or JAK inhibitors, leading to persistent disease activity and the need for multiple therapeutic switches, reflecting the complexity of cytokine redundancy and overlapping inflammatory pathways in RA pathogenesis (Jain *et al.*, 2025) [22, 40, 44]. Another significant limitation is long-term safety concerns, particularly with prolonged use of biologics and JAK inhibitors, which have been associated with increased risks of infections, malignancy, cardiovascular events, and thromboembolic complications. Although newer selective agents aim to improve safety profiles, real-world evidence continues to highlight the need for long-term pharmacovigilance and risk stratification in vulnerable populations (Tanaka *et al.*, 2025) [43]. A further major barrier is the high cost of biologic therapies, which limits accessibility in low- and middle-income countries and contributes to treatment inequity globally. Even with the

introduction of biosimilars, cost remains a significant healthcare burden, especially for lifelong therapy required in chronic RA management (Yiu *et al.*, 2025) [41]. In addition, a critical unresolved challenge is the incomplete understanding of disease heterogeneity, where RA is now recognized as a spectrum of molecularly distinct subtypes rather than a single uniform disease. This heterogeneity contributes to unpredictable treatment responses and underscores the need for biomarker-driven precision medicine approaches. Current research trends are increasingly focused on overcoming these limitations through precision medicine, multi-omics profiling, artificial intelligence-based prediction models, and synovial tissue stratification, which aim to identify patient-specific inflammatory signatures and optimize therapeutic selection. Emerging strategies such as combination biologic therapy, novel cytokine network modulation, and immune cell reprogramming are also being explored to address refractory disease and reduce treatment failure rates. Moreover, real-world data registries and machine learning approaches are being integrated to better predict treatment response and long-term outcomes, marking a shift toward individualized and adaptive RA management strategies (Skydel & Hsiao, 2026) [42]. Overall, while current therapies have transformed RA prognosis, addressing variability in response, safety concerns, cost barriers, and disease heterogeneity remains essential for achieving sustained remission and true precision medicine in RA care.

9. Future perspectives

Future perspectives in rheumatoid arthritis (RA) research are increasingly focused on transforming disease management from a standardized treatment approach to a highly individualized and mechanism-based strategy. One of the most promising directions is personalized medicine, which aims to tailor therapy based on genetic, molecular, and immunological profiling of patients. Recent advances in multi-omics technologies, including genomics, transcriptomics, proteomics, and synovial tissue analysis, are enabling researchers to identify distinct RA endotypes associated with differential cytokine signatures and treatment responses, thereby improving prediction of therapeutic outcomes and minimizing trial-and-error prescribing strategies. A growing body of literature highlights that integrating clinical data with molecular biomarkers and machine learning approaches can significantly enhance early diagnosis and optimize drug selection, particularly for biologics and JAK inhibitors, supporting a shift toward precision rheumatology models (Jain *et al.*, 2025) [22, 40, 44].

Another major emerging trend is multi-cytokine targeting strategies, which address the limitation of single-cytokine inhibition by simultaneously modulating multiple inflammatory pathways such as TNF- α , IL-6, IL-17, GM-CSF, [27] and JAK-STAT signaling. Recent studies emphasize that RA pathogenesis is driven by highly redundant and interconnected cytokine networks, which often compensate when a single pathway is inhibited, leading to incomplete therapeutic responses or drug resistance. Consequently, next-generation biologics, including bispecific antibodies and combination biologic approaches, are being developed to achieve broader and more sustained suppression of inflammation, especially in refractory RA cases (Smolen *et al.*, 2018; Weyand CM &

Goronzy, 2021) [11, 13, 25, 28, 33].

A third important advancement is the integration of clinical and preclinical data, which is reshaping drug discovery and translational research. Preclinical models such as collagen-induced arthritis are now being combined with patient-derived datasets, real-world evidence, and systems biology approaches to better simulate human disease heterogeneity and improve predictive accuracy of therapeutic responses. This integrated framework is further supported by artificial intelligence and computational modeling, which help identify optimal drug combinations and predict disease progression patterns. Recent reviews suggest that such integrative strategies bridge the gap between bench and bedside, accelerating the development of more effective and safer RA therapies while improving translational success rates in clinical trials (Firestein, 2017; Mangoni AA & Zinellu, 2024) [9, 12, 24, 31, 45].

Overall, the future of RA management is moving toward a precision-driven, multi-target, and data-integrated therapeutic paradigm, aiming not only to control inflammation but also to achieve sustained remission and potentially prevent disease onset in high-risk individuals.

10. Conclusion

Rheumatoid arthritis (RA) is now widely recognized as a network-driven cytokine disease, where complex and interconnected signaling systems rather than single mediators govern disease initiation, persistence, and progression. The concept of network-based cytokine mechanisms has reshaped traditional views of RA pathogenesis by highlighting how pro-inflammatory cytokines such as TNF- α , IL-6, IL-1 β , IL-17, and GM-CSF operate within tightly linked signaling circuits involving JAK-STAT, [27] NF- κ B, and MAPK pathways. These interconnected networks amplify synovial inflammation, promote immune cell activation, and drive irreversible structural damage to cartilage and bone, while also contributing to systemic manifestations. Importantly, recent advances in molecular immunology and systems biology demonstrate that cytokine interactions are highly redundant and dynamic, which explains both disease heterogeneity and variable therapeutic responses observed in clinical practice. From a therapeutic perspective, the success of biologic DMARDs and targeted synthetic DMARDs has validated cytokines as central drug targets and significantly improved clinical outcomes in RA patients. However, limitations such as incomplete response rates, long-term safety concerns, and treatment resistance underscore the need for more comprehensive approaches that move beyond single-cytokine inhibition. In this context, precision therapy guided by cytokine network profiling, multi-omics integration, and artificial intelligence-based prediction models represents a major advancement toward individualized treatment strategies. Emerging approaches, including multi-cytokine blockade, bispecific antibodies, and immune network modulation, further reflect a shift toward targeting the broader inflammatory network rather than isolated pathways.

Overall, understanding RA through the lens of network-based cytokine mechanisms bridges molecular immunopathology with clinical therapeutics and provides a strong foundation for next-generation precision medicine. Continued research integrating mechanistic biology, clinical data, and computational modeling will be essential to refine

therapeutic strategies, overcome disease heterogeneity, and ultimately achieve sustained remission or functional cure in rheumatoid arthritis.

References

1. Ding Q, *et al.* Signaling pathways in rheumatoid arthritis. *Signal Transduct Target Ther.* 2023.
2. Avci AB, *et al.* Targeting IL-6 in rheumatoid arthritis. *BioDrugs.* 2024.
3. Weber BN, *et al.* Inflammatory pathways in rheumatoid arthritis. *Nat Rev Rheumatol.* 2023.
4. Murayama MA, *et al.* Chemokines in rheumatoid arthritis. *Front Immunol.* 2023.
5. Yang YL, *et al.* Role of CCL3 in rheumatoid arthritis. *Rheumatol Ther.* 2023.
6. Perera J, *et al.* Biomarkers in rheumatoid arthritis. *Cells.* 2024.
7. Xiong Y, *et al.* JAK-STAT signaling in rheumatoid arthritis. *SAGE Journals.* 2023.
8. Bilski J, *et al.* Adipokines in rheumatoid arthritis. *Biomedicines.* 2023.
9. Mangoni AA, Zinellu A. A systematic review and meta-analysis of circulating adhesion molecules in rheumatoid arthritis. *Inflamm Res.* 2024.
10. McInnes IB, Schett G. The pathogenesis of rheumatoid arthritis. *Nat Rev Immunol.* 2007;7:429-442. doi:10.1038/nri2091.
11. Smolen JS, Aletaha D, McInnes IB. Rheumatoid arthritis. *Nat Rev Dis Primers.* 2018;4:18001. doi:10.1038/nrdp.2018.1.
12. Firestein GS. Immunopathogenesis of rheumatoid arthritis. *Immunity.* 2017;46(2):183-196. doi:10.1016/j.immuni.2017.01.013.
13. Weyand CM, Goronzy JJ. The immunology of rheumatoid arthritis. *Nat Immunol.* 2021;22(1):10-18. doi:10.1038/s41590-020-00816-x.
14. Brennan FM, McInnes IB. Evidence that cytokines play a role in rheumatoid arthritis. *J Clin Invest.*
15. Mori S, *et al.* Pathogenic role of cytokines in rheumatoid arthritis. *J Clin Med.* 2025.
16. Fujimoto S, *et al.* Cytokine networks in rheumatoid arthritis pathogenesis. *J Clin Med.* 2025.
17. Murayama MA, *et al.* Chemokines and chemokine receptors as promising targets in rheumatoid arthritis. *Front Immunol.* 2023.
18. Fujimoto S, *et al.* Pathogenic role of cytokines in rheumatoid arthritis. *J Clin Med.* 2025.
19. McInnes IB, Schett G. The pathogenesis of rheumatoid arthritis. *Nat Rev Immunol.* 2007;7:429-442. doi:10.1038/nri2091.
20. The JAK-STAT pathway in rheumatoid arthritis: mechanisms and JAK inhibitors. *Egypt Rheumatol Rehabil.* 2026.
21. Simon LS, *et al.* The JAK/STAT pathway and pain in rheumatoid arthritis. *Semin Arthritis Rheum.* 2021.
22. Jain A, *et al.* Targeting rheumatoid arthritis: molecular perspective on biologic therapies. *J Biol Eng.* 2025.
23. O'Shea JJ, Gadina M, Siegel R. JAK inhibitors in autoimmune disease. *Nat Rev Rheumatol.* 2022.
24. Firestein GS. Immunopathogenesis of rheumatoid arthritis. *Immunity.* 2017;46(2):183-196.
25. Weyand CM, Goronzy JJ. The immunology of rheumatoid arthritis. *Nat Immunol.* 2021;22(1):10-18. doi:10.1038/s41590-020-00816-x.

26. Alunno A, *et al.* Cytokines in the pathogenesis of rheumatoid arthritis: new targets and therapeutic strategies. *BMC Rheumatol.* 2017.
27. GM-CSF pathway targeting in rheumatoid arthritis: emerging therapeutic strategies. *Front Immunol.* 2025.
28. Smolen JS, *et al.* IL-6 inhibition in rheumatoid arthritis therapy. *Ann Rheum Dis.* 2018.
29. O'Shea JJ, *et al.* Janus kinase inhibitors in autoimmune diseases. *Nat Rev Rheumatol.* 2022.
30. Luan J, Zhang X, Wang S, *et al.* Applicability and implementation of collagen-induced arthritis model. *PLoS One.* 2021.
31. Firestein GS. Immunopathogenesis of rheumatoid arthritis. *Immunity.* 2017;46(2):183-196.
32. McInnes IB, Schett G. The pathogenesis of rheumatoid arthritis. *Nat Rev Immunol.* 2007;7(6):429-442.
33. Weyand CM, Goronzy JJ. The immunology of rheumatoid arthritis. *Nat Immunol.* 2021;22(1):10-18.
34. Wei Z, *et al.* Rheumatoid arthritis animal model in mice. *Animals Zoonoses.* 2025.
35. Luan J, *et al.* Applicability and implementation of collagen-induced arthritis model. *PLoS One.* 2021.
36. Chidomere CI, *et al.* Bench to bedside: modelling inflammatory arthritis. *Discov Immunol.* 2023.
37. Marco-Bonilla M, *et al.* Animal models in rheumatoid arthritis and comorbidities. *Front Med (Lausanne).* 2025.
38. Krock E, *et al.* Pain mechanisms in rheumatoid arthritis animal models. *Review Article.* 2019.
39. Marco-Bonilla M, *et al.* Animal models in rheumatoid arthritis and comorbidities. *Front Med (Lausanne).* 2025.
40. Jain A, *et al.* Contemporary approaches to rheumatoid arthritis management: precision and progress. *Best Pract Res Clin Rheumatol.* 2025.
41. Yiu CH, *et al.* Comparative effectiveness and safety of biosimilars in rheumatoid arthritis. *Int J Clin Pharm.* 2025.
42. Skydel JJ, Hsiao B. Frontiers in rheumatoid arthritis pharmacologic management. *Pharmaceuticals.* 2026;19(2):218.
43. Tanaka Y, *et al.* JAK inhibitors and biologics in rheumatoid arthritis: a systematic review. *Rheumatol Ther.* 2025.
44. Jain A, *et al.* Targeting rheumatoid arthritis: molecular perspective on biologic therapies. *J Biol Eng.* 2025.
45. Mangoni AA, Zinellu A. Biomarkers and rheumatoid arthritis pathophysiology insights. *Inflammation Research.* 2024.
46. Towards personalized medicine in rheumatoid arthritis. *PubMed Central (PMC) Review.* 2024-2025.
47. Anandan M, *et al.* Role of T cells and cytokines in rheumatoid arthritis pathogenesis. *PLoS One.* 2025.
48. Muheremu A, *et al.* Innate immune response in rheumatoid arthritis. *PubMed Central.* 2025.
49. Zhou C, *et al.* Inflammatory cytokine networks in rheumatoid arthritis. *Front Immunol.* 2025.
50. Karmarkar S, *et al.* Targeted cytokine strategies in rheumatoid arthritis. *RSC Pharm.* 2025.