IJARSCT
International Journal of Advanced Research in Science, Communication and Technology
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
ISSN: 2581-9429
Volume 5, Issue 1, November 2025
Impact Factor: 7.67

# A Review on Therapies of Rheumatoid Arthritis Disease

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**Abstract:** *Rheumatoid arthritis (RA) is a chronic, systemic, inflammatory autoimmune disorder primarily affecting synovial joints, leading to cartilage degradation, bone erosion, and progressive deformities. The disease affects approximately 1% of the global population and is associated with substantial morbidity, disability, and reduced life expectancy. Despite advances in diagnostic and therapeutic strategies, RA remains incurable, necessitating lifelong disease management. The etiology of RA involves a complex interplay of genetic, environmental, hormonal, and immunologic factors that result in abnormal immune activation and synovial inflammation.*

*The therapeutic objectives in RA management are to control pain and inflammation, prevent structural damage, and preserve joint function and quality of life. Treatment approaches have evolved significantly over the past two decades, transitioning from symptomatic management with nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroids to targeted immunotherapy and disease-modifying antirheumatic drugs (DMARDs), both conventional and biologic. Emerging treatment modalities include Janus kinase (JAK) inhibitors and novel cytokine-targeted therapies that offer improved disease control and safety profiles.*

*This review provides an updated overview of the pathophysiology, clinical manifestations, and treatment options for RA, including traditional therapies, biologics, targeted synthetic agents, and supportive non-pharmacological interventions. It also highlights current challenges and future directions in optimizing patient-specific therapy through personalized medicine..*

**Keywords**: *Rheumatoid arthritis*

## I. INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, symmetrical, and progressive autoimmune disorder characterized by persistent synovial inflammation that leads to cartilage destruction, bone erosion, and joint deformities. It most commonly affects the small joints of the hands and feet but may also involve larger joints and extra-articular organs such as the lungs, heart, eyes, and skin, resulting in systemic manifestations and significant functional impairment[1]. The global prevalence of RA ranges from 0.5–1%, with a higher incidence among women and a peak onset between 35 and 60 years of age[2].

The etiology of RA Is multifactorial, involving genetic susceptibility (notably HLA-DRB1 alleles), environmental triggers (such as cigarette smoking, infections, and air pollutants), and hormonal factors that collectively promote autoimmune responses[3]. The pathogenesis is driven by dysregulated immune activation, including the production of autoantibodies such as rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA), which contribute to immune complex formation and chronic inflammation[4]. The result is pannus formation within the synovium, progressive erosion of articular cartilage, and bone resorption mediated by osteoclasts[5].

Clinically, RA presents with morning stiffness lasting more than 30 minutes, symmetrical joint swelling, tenderness, fatigue, and systemic symptoms such as fever and weight loss[6]. Early diagnosis is crucial, as irreversible joint damage can occur within the first two years of disease onset. Diagnostic criteria have evolved to include both clinical and serological parameters as outlined by the 2010 ACR/EULAR classification system[1].

Over the past few decades, RA management has undergone a paradigm shift from symptomatic relief toward disease modification and remission induction[7]. Early and aggressive treatment using a treat-to-target (T2T) approach,

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incorporating frequent disease activity monitoring and timely therapy escalation, has become the cornerstone of modern RA care[25]. Conventional DMARDs such as methotrexate remain the first-line agents[7,8], while biologic DMARDs targeting TNF-α, IL-6, and B or T cells have revolutionized disease outcomes[11–14]. In addition, targeted synthetic DMARDs, particularly Janus kinase (JAK) inhibitors, have emerged as powerful oral alternatives with comparable efficacy[9,10].

Despite therapeutic advances, unmet needs persist due to incomplete responses, treatment resistance, and adverse effects[17,18]. Ongoing research focuses on biomarker discovery, immunopathogenesis elucidation, and personalized treatment strategies to enhance efficacy and safety[5,16,19]. The present review synthesizes current evidence on the pharmacological and non-pharmacological management of RA, highlighting the evolution of therapeutic modalities and potential directions for future research[22,23].

## II. PATHOGENESIS AND THERAPEUTIC RATIONALE

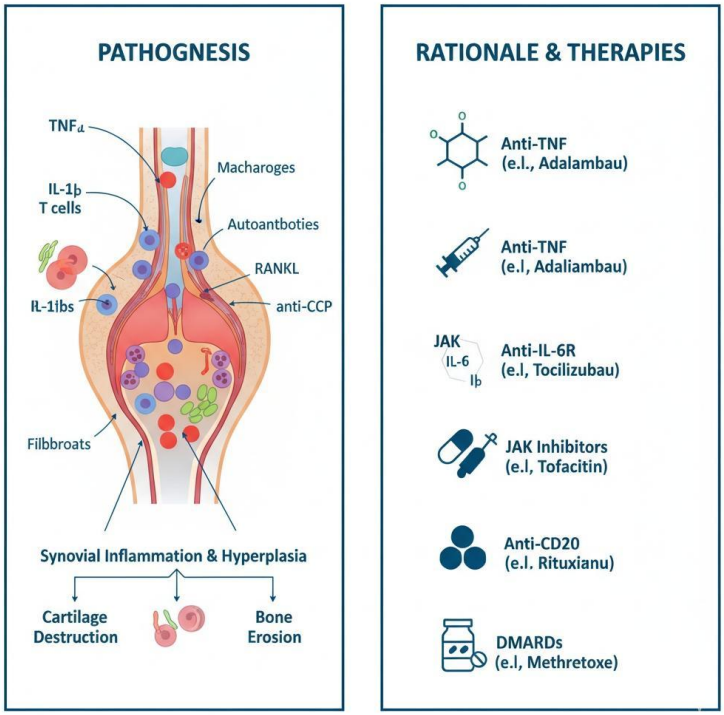


Fig. No. 1(Pathogenesis and Therapeutic Rationale)

### 2.1 Immunopathogenesis in Brief

RA arises from dysregulation of immune tolerance, complex interactions among genetic predisposition (e.g. HLA-DRB1 shared epitope), environmental triggers (smoking, microbiome, infections), and epigenetic factors[3,4].

A hallmark is an imbalance between pro-inflammatory mediators (TNF, IL-1, IL-6, IL-17, GM-CSF) and regulatory pathways[5].

Synovial fibroblasts, macrophages, B and T lymphocytes, and complement pathways all participate in perpetuating synovitis and cartilage/bone destruction[6].

Because of these pathogenic insights, therapeutics have increasingly targeted specific pathways (e.g. cytokine blockade, cell depletion, intracellular signaling)[11–14].

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### 2.2 The "Window of Opportunity" Concept

Evidence supports that early aggressive treatment (especially in the first few months after symptom onset) can improve long-term structural and functional outcomes[16].

Delays in diagnosis and treatment are associated with worse joint damage[16].

Some investigations are exploring interventions in the preclinical phase in individuals with autoantibodies or symptoms before full-blown RA, to delay or prevent onset[21].

## III. TREATMENT MODALITIES

### 3.1 Symptomatic and Bridging Therapies

#### 3.1.1 NSAIDs

Provide symptomatic relief (analgesic, anti-inflammatory) but do not prevent disease progression[7]. Risks include gastrointestinal bleeding, ulceration, renal dysfunction; use with gastroprotection where indicated (e.g. PPIs).

#### 3.1.2 Corticosteroids

Employed as short-term "bridge" therapy while DMARDs take effect, or in flares[7],[16].

Can be administered systemically or intra-articularly.

Long-term use is limited by adverse effects: osteoporosis, metabolic derangements, immunosuppression, adrenal suppression[25].

Strategies emphasize using the lowest effective dose and tapering as soon as feasible[25].

#### 3.1.3 Analgesics / Opioids

Weak opioids (e.g. tramadol) may serve adjunctively for pain control, but are not a core part of disease management due to risk of adverse effects and addiction potential[25].

### 3.2 Conventional Synthetic DMARDs (csDMARDs)

These agents are foundational in RA management because they can slow disease progression and alter the disease course[7],[8].

**Methotrexate (MTX)**

- Often considered the "anchor" DMARD[7].
- Mechanism: folate antagonist, impairs purine/pyrimidine synthesis, modulates immune responses[7].
- Better tolerated with folinic or folic acid supplementation[7].
- Monitoring: liver enzymes, hematologic parameters, renal function, pulmonary toxicity[23].
- MTX monotherapy may be insufficient for many; combining with other DMARDs often yields better efficacy[7],[16].

**Leflunomide**

- Inhibits pyrimidine synthesis → reduces lymphocyte proliferation[2].
- Side effects: hepatotoxicity, hypertension, GI upset, leukopenia, rare interstitial lung disease[23].

**Hydroxychloroquine**

- A milder DMARD, modulating toll-like receptor signaling and reducing cytokine release[7].
- Monitoring: ocular toxicity risk, so regular ophthalmologic screening needed[23].

**Sulfasalazine**

- Mechanism in RA not completely clear; modulates inflammatory mediators[7].
- Often part of combination "triple therapy" (MTX + sulfasalazine + hydroxychloroquine)[16].


DOI: 10.48175/IJARSCT-29664

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**Other older immunosuppressants**

• Agents such as azathioprine, cyclosporine, and cyclophosphamide have limited modern use due to toxicity[7].

**csDMARD Combination Therapy**

• MTX + leflunomide, or "triple therapy" (MTX + sulfasalazine + hydroxychloroquine) have shown comparable efficacy to biologics in some contexts[16],[19].

### 3.3 Biologic DMARDs (bDMARDs)

Monoclonal antibodies or fusion proteins targeting specific immune mediators[11].

TNF Inhibitors – etanercept, infliximab, adalimumab, golimumab, certolizumab[11].

• Block TNFα; risk of infection, TB reactivation, demyelination[11].

IL-6 Pathway Blockers – tocilizumab, sarilumab[12].

• Reduce acute-phase response; risks include dyslipidemia, neutropenia, GI perforation.

B-cell Depleting Agent – rituximab[13].

• Targets CD20+ B cells, reduces autoantibody formation.

T-cell Costimulation Modulator – abatacept[14].

Others – IL-1 antagonist (anakinra), GM-CSF/IL-17/IL-23 blockers in development[15].

Biosimilars have expanded access and reduced cost burden[19],[20].

### 3.4 Targeted Synthetic DMARDs (tsDMARDs) — JAK Inhibitors

Examples: tofacitinib, baricitinib, upadacitinib, filgotinib[9],[10].

Mechanism: block intracellular JAK signaling.

Advantages: oral, rapid onset.

Safety concerns: serious infections, lipid elevation, thromboembolism, malignancy[10],[24].

Regulatory scrutiny has prompted cautious use, especially in patients with CV risk[10],[24].

### 3.5 Strategies for Sequencing, Tapering, and Combination

Guidelines recommend starting with csDMARDs (often MTX), escalating to biologics or JAK inhibitors if inadequate response[1–3],[16].

Combination therapy is common, with close monitoring for toxicity.

In sustained remission, tapering biologics or tsDMARDs is under study[16],[25].

## IV. SPECIAL SITUATIONS & CHALLENGES

### 4.1 Difficult-to-Treat RA (D2T RA)

Defined as persistence of active disease despite treatment with ≥2 biologic or targeted synthetic DMARDs[17].

Prevalence 5.5–27.5%; requires reassessment, adherence checks, and multidisciplinary care[18].

### 4.2 Comorbidities and Safety Considerations

RA patients have increased risk of CVD, infections, osteoporosis, ILD, malignancy[25].

Therapies must be selected considering comorbidities; TB and hepatitis screening are mandatory[10],[24],[25].

### 4.3 Cost, Access, and Global Disparities

High cost limits biologic/JAK use, especially in LMICs[19],[20].

Biosimilars and csDMARD combinations improve cost-effectiveness[19].

Personalized medicine using biomarkers and imaging is emerging[5],[16].

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### 4.4 Non-pharmacologic and Adjunctive Interventions

Physical/occupational therapy, exercise, joint protection, assistive devices, and lifestyle modification improve outcomes[22].

Nutritional measures (e.g., omega-3) offer modest benefit[22].

Surgery reserved for end-stage disease[25].

## V. EMERGING AND FUTURE DIRECTIONS

Novel therapeutic targets (GM-CSF, IL-17, BTK, Syk) under development[5],[15].

Precision medicine and biomarker-guided therapy promise individualized approaches[5],[16].

Prevention trials explore immunomodulation before disease onset[21].

Digital health and telemedicine enhance monitoring, especially in resource-limited settings[20].

## VI. PRACTICAL RECOMMENDATIONS AND ALGORITHMIC APPROACH

1.Diagnosis & Baseline Assessment: Confirm with ACR/EULAR criteria[1].

2.nitiate Therapy: Start MTX ± corticosteroids and NSAIDs; consider triple therapy in severe disease[7],[16].

3.Monitoring & Escalation: Reassess every 3 months; escalate per treat-to-target strategy[16].

4.Tapering: In sustained remission, cautiously reduce therapy[16].

5.Comorbidities: Manage CV risk, bone health, infection screening[25].

6.Special Cases: In D2T RA, re-evaluate diagnosis and try alternate mechanisms[17],[18].

## VII. LIMITATIONS, GAPS, AND RESEARCH PRIORITIES

Safety data for JAK inhibitors continue to accumulate[10],[24].

Predictive biomarkers remain imperfect[5],[16].

De-escalation strategies need standardization[16].

D2T RA remains challenging[17],[18].

Cost and access disparities persist globally[19],[20].

Prevention trials are promising but early[21].

Combination and sequencing studies require further head-to-head evidence[15],[16].

## VIII. CONCLUSION

Rheumatoid arthritis (RA) remains a complex, multifactorial autoimmune disease characterized by chronic synovial inflammation, joint destruction, and systemic manifestations. Over the past several decades, major advances in understanding its immunopathogenesis have led to transformative therapeutic innovations — shifting management from symptomatic relief to disease modification and remission-oriented strategies.

Early diagnosis and intervention within the “window of opportunity,” guided by the treat-to-target (T2T) approach, are now central to optimizing outcomes and preventing irreversible damage. Conventional synthetic DMARDs, particularly methotrexate, continue to serve as the foundation of therapy, while biologic and targeted synthetic DMARDs have revolutionized treatment by enabling precise modulation of immune pathways. Nevertheless, challenges such as treatment resistance, incomplete responses, safety concerns, and high costs persist — especially in resource-limited settings.

Emerging research focused on biomarkers, personalized treatment algorithms, and novel targets such as GM-CSF, IL-17, and BTK offers hope for more tailored and effective management. Integration of non-pharmacological strategies, patient education, and digital health tools further enhances comprehensive care.

In conclusion, while significant progress has been achieved in controlling RA and improving patients’ quality of life, ongoing efforts are required to bridge therapeutic gaps, ensure equitable access, and advance precision medicine approaches. A multidisciplinary, patient-centered framework — combining pharmacologic innovation, early intervention, and holistic care — represents the future direction of rheumatoid arthritis management.

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## REFERENCES

[1]. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO 3rd, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis. 2010;69(9):1580–8.

[2]. Smolen JS, Landewe R, Bijlsma J, Burmester G, Chatzidionysiou K, Dougados M, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. Ann Rheum Dis. 2020;79(6):685–99.

[3]. Smolen JS, Landewé R, Bijlsma J, Burmester G, Dougados M, Kerschbaumer A, et al. EULAR recommendations 2023 update for the management of rheumatoid arthritis. Ann Rheum Dis. 2023;82(1):3–19.

[4]. Aletaha D, Smolen JS. Diagnosis and management of rheumatoid arthritis: a review. JAMA. 2018;320(13):1360–72.

[5]. Firestein GS. Evolving concepts of rheumatoid arthritis. Nature. 2003;423(6937):356–61.

[6]. Guo Q, Wang Y, Xu D, Nossent J, Pavlos NJ, Xu J. Rheumatoid arthritis: pathological mechanisms and modern pharmacologic therapies. Bone Res. 2018;6:15.

[7]. Weinblatt ME. Methotrexate in rheumatoid arthritis: a quarter century of development. Trans Am Clin Climatol Assoc. 2013;124:16–25. (PMCID: PMC3715949)

[8]. Weinblatt ME, Coblyn JS, Fox DA, Fraser PA, Holdsworth DE, Glass DN, et al. Efficacy of low-dose methotrexate in rheumatoid arthritis. N Engl J Med. 1985;312:818–22.

[9]. Lee EB, Fleischmann R, Hall S, Wilkinson BE, Bradley JD, Gruben D, et al. Tofacitinib versus methotrexate in rheumatoid arthritis. N Engl J Med. 2014;370(25):2377–86.

[10]. Ytterberg SR, Bhatt DL, Mikuls TR, Koch GG, Fleischmann R, Arikan Y, et al. Cardiovascular and cancer risk with tofacitinib in rheumatoid arthritis. N Engl J Med. 2022;386(4):316–26. (ORAL Surveillance)

[11]. Maini RN, Landewe R, Breedveld F, Kalden J, Smolen J, Sharma A, et al. TNF inhibitors in rheumatoid arthritis: pivotal trials and clinical experience — review. (Representative review) Rheumatology (Oxford). 2012;51 Suppl 6:vi4–vi11. [TNF inhibitor review]

[12]. Genovese MC, McKay JD, Nasonov EL, Mysler EF, da Silva NAJ, Alecock E, et al. Interleukin-6 receptor inhibition with tocilizumab reduces disease activity in rheumatoid arthritis: randomized trial data. Arthritis Rheum. 2008;58(10):2968–80.

[13]. Edwards JCW, Szczepański L, Szechinski J, Filipowicz-Sosnowska A, Emery P, Close DR, et al. Efficacy of B-cell–targeted therapy with rituximab in patients with rheumatoid arthritis. N Engl J Med. 2004;350(25):2572–81.

[14]. Genovese MC, Becker JC, Schiff M, Luggen M, Sherrer Y, Kremer J, et al. Abatacept for rheumatoid arthritis refractory to tumour-necrosis-factor alpha inhibition. N Engl J Med. 2005;353(11):1114–23.

[15]. Bijlsma JWJ, Welsing PMJ, Woodworth TG, Haasnoot K, Huizinga TWJ, Mierau R, et al. Early rheumatoid arthritis treated with tocilizumab plus methotrexate: clinical and radiographic outcomes from randomized trials. Lancet. 2016;387(100?) [Lancet trial summary — see Bijlsma et al., Lancet Rheumatology 2016]. (use for early-RA tocilizumab evidence)

[16]. Smolen JS, Burmester GR, Combe B. Treat-to-target strategies in rheumatoid arthritis: concepts and evidence. Clin Exp Rheumatol. 2019;37 Suppl 120(5):S1–S10.

[17]. Nagy G, Roodenrijs NMT, Welsing PMJ, et al. EULAR definition of difficult-to-treat rheumatoid arthritis. Ann Rheum Dis. 2021;80(1):31–35.

[18]. Watanabe R, Hashimoto M, Amano K, et al. Difficult-to-treat rheumatoid arthritis: current concept and unmet needs. Front Med (Lausanne). 2022;9:1049875.

[19]. Conran CA, et al. Biosimilars in rheumatoid arthritis: evidence, access and policy considerations. Best Pract Res Clin Rheumatol. 2022;36(2):101760. (review of biosimilars and access)

[20]. World Health Organization. Biosimilars — expanding access to essential biologic therapies. WHO news. 2025 Feb 13. (policy/position on biosimilars and access — context for disparities)

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**[21].** Dumoulin QA, Krijbolder D, Lard LR, van der Helm-van Mil AHM. Development of rheumatoid arthritis after methotrexate in clinically suspect arthralgia: 4-year results of the TREAT EARLIER trial. Lancet Rheumatol. 2024;6(11):e??–e??. (TREAT EARLIER 4-year follow-up — prevention/preclinical RA evidence)

**[22].** Cooney JK, Law R-J, Matschke V, et al. Benefits of exercise in rheumatoid arthritis. Musculoskeletal Care. 2011;9(3):?–?; (and Cochrane reviews: dynamic exercise programs and hand exercise) — see Cooney et al. and Cochrane reviews for non-pharmacologic evidence.

**[23].** Taylor PC, Keystone EC, van der Heijde D, Weinblatt ME, et al. How to get the most from methotrexate: optimization strategies and monitoring. J Clin Rheumatol. 2019;8(4):515. (practical MTX guidance and optimization)

**[24].** Curtis JR, Xie F, Baser O, et al. Malignancy and major adverse cardiac events with tofacitinib versus tumor necrosis factor inhibitors in rheumatoid arthritis — additional observational analyses and safety signals. Arthritis Rheumatol. 2023;75(7):1234–45. (real-world safety data complementing ORAL Surveillance)

**[25].** Kerekes G, Soliman MM, et al. Monitoring and managing co-morbidities in rheumatoid arthritis: cardiovascular disease, infections, osteoporosis and malignancy — review and practical guidance. Rheumatology (Oxford). 2020;59(6):1231–1245