WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
Coden USA: WJPRAP Impact Factor 8.63
Volume 15, Issue 22, 65-85. Review Article ISSN 2277–7105

RHEUMATOID ARTHRITIS: A RIVIEW

[1*]Kamidi Sunitha, [2]Chikurumalli Baby, [2]Mortha Greshma Sri, [2]Pabbineedi Sai Kumari, [2]Pilli Durga Malleswari, [2]Varada Veera Satyavathi

[1*]Assisstant Professor, Department of Pharmaceutical Analysis, Koringa College of Pharmacy, Korangi, Kakinada, Andhra Pradesh, India.

[2]UG Scholar, Koringa College of Pharmacy, Korangi, Kakinada, Andhra Pradesh, India.

Article Received on 13 Oct. 2026,
Article Revised on 03 Nov. 2026,
Article Published on 16 Nov. 2026,

https://doi.org/10.5281/zenodo.24271522

***Corresponding Author**

Kamidi Sunitha

Assisstant Professor, Department of Pharmaceutical Analysis, Koringa College of Pharmacy, Korangi, Kakinada, Andhra Pradesh, India.

How to cite this Article: [1*]Kamidi Sunitha, [2]Chikurumalli Baby, [2]Mortha Greshma Sri, [2]Pabbineedi Sai Kumari, [2]Pilli Durga Malleswari, [2]Varada Veera Satyavathi (2026). Rheumatoid Arthritis: A Riview. World Journal of Pharmaceutical Research, 15(22), 65–85.
This work is licensed under Creative Commons Attribution 4.0 International license.

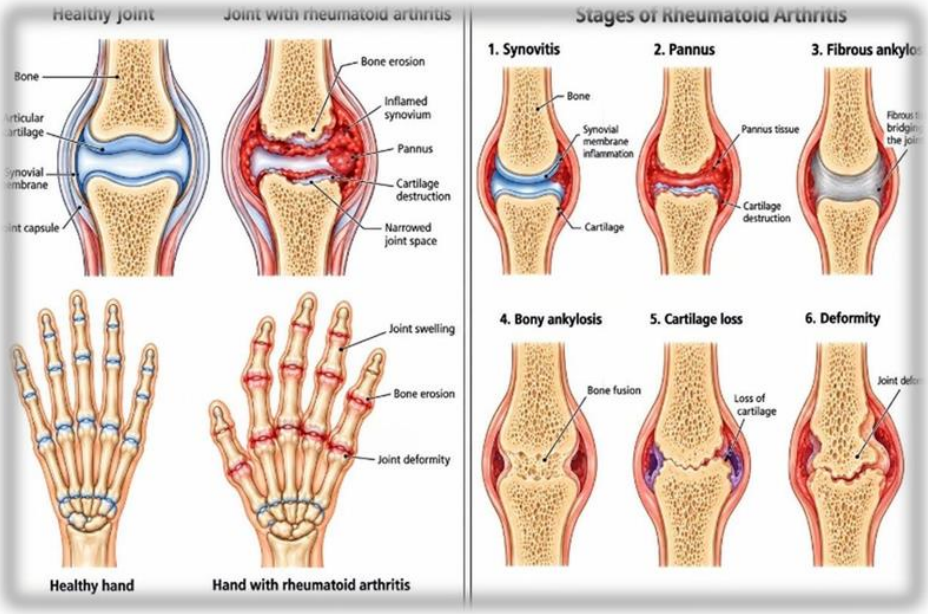
ABSTRACT

Rheumatoid arthritis (RA) is a long-standing autoimmune condition in which persistent Synovial inflammation can progressively injure cartilage and bone. Rheumatoid arthritis typically presents as inflammatory polyarthritis affecting the small joints, with a higher prevalence observed among women. Etiopathogenesis: RA does not have a single established cause. Instead, inherited Susceptibility, particularly HLA-DRB1-related risk, interacts with exposures such as tobacco smoke and disturbances of innate and adaptive immunity. Synovial expansion, pannus development, osteoclast activation, and inflammatory mediators including TNF-α, IL-1, and IL-6 are central features of the disease process. Diagnosis and Management: Assessment combines clinical examination, serological testing such as RF and ACPA, acute-phase reactants, and imaging. Timely recognition and disease-modifya ing treatment is important for limiting irreversible structural damage. Methotrexate is a key conventional synthetic DMARD, with biologic and targeted synthetic agents used when disease control remains inadequate. NSAIDs and brief glucocorticoid courses can reduce symptoms, while physiotherapy, rehabilitation, and patient education support comprehensive long-term care.

KEYWORDS: Rheumatoid arthritis, Autoimmune pathogenesis, Synovial inflammation, Joint destruction, Diagnostic biomarkers, Disease-modifying antirheumatic drugs (DMARDs), Methotrexate, Biologic therapies, Targeted therapies, Precision medicine.

INTRODUCTION

Rheumatoid arthritis: joints are the principal site of disease. Continued synovial inflammation can progressively destroy cartilage and bone, leading to deformity, loss of physical function, and disability. Manifestations outside the joints and associated comorbidities further contribute to the overall disease burden.[1,2]



(Fig 1. Comparison of healthy and rheumatoid arthritis–affected joints, highlighting synovial inflammation, pannus formation, cartilage destruction, bone erosion, joint narrowing, and deformit.)

Although RA may begin at different ages, its frequency generally increases with age and is higher among women. Susceptibility arises from the combined influence of inherited immune-related factors and environmental exposure. Genetic variants involved in antigen presentation and immune regulation contribute to risk, while cigarette smoking is one of the most consistently documented Environmental associations.[3,4]

The development of RA is influenced by interactions between genetic susceptibility, environmental exposures, immune-system abnormalities, and lifestyle-related factors.

Cigarette smoking, obesity, certain infections, and occupational exposures have been associated with increased disease risk.

In addition to joint involvement, RA may produce systemic manifestations affecting organs such as the cardiovascular system, eyes, skin, and other tissues. The disease can therefore have a substantial impact on physical functioning, work capacity, and overall quality of life. Early recognition and appropriate treatment are important to control inflammation, prevent irreversible joint damage, and improve long-term outcomes.

Advances in diagnostic techniques, biomarkers, imaging, and disease-modifying antirheumatic drugs (DMARDs) have significantly improved the management of RA. Modern RA management focuses on initiating treatment early, monitoring disease activity at regular intervals, and following a treat-to-target strategy to achieve lasting remission or maintain low disease activity.

Autoimmune changes can develop well before clinically recognizable arthritis. RF and ACPA may become detectable during this preclinical interval. Persistent joint inflammation is thought to arise when inherited susceptibility, outside triggers, immune reactions at mucosal surfaces, and abnormal citrullination of proteins act together over time.[4,5]

RA involves multiple components of innate and adaptive immunity, including T and B lymphocytes, macrophages, neutrophils, and fibroblast-like cnidocytes. Cytokines such as TNF and IL-6 help to maintain synovial inflammation, whereas osteoclast activation and matrix-degrading pathways contribute to cartilage and bone injury.[5,6]

The usual clinical picture includes persistent inflammatory arthritis of the hands and feet, accompanied by pain, swelling, stiffness, fatigue, and functional limitation. Disease severity varies among individuals, and systemic complications can include rheumatoid nodules, pulmonary involvement, ocular disease, vasculitis, and cardiovascular manifestations.[1,2]

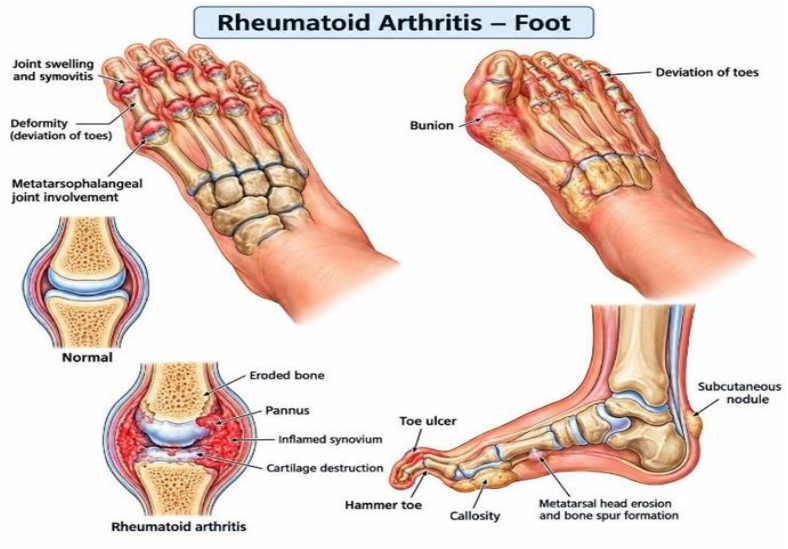
Because ongoing inflammation may produce irreversible structural damage, early evaluation is important. Diagnosis incorporates clinical findings, RF and ACPA, inflammatory markers, and imaging. Radiographs, ultrasonography, and MRI provide complementary information regarding Inflammatory activity and structural abnormalities.[7]

The 2010 ACR/EULAR classification system considers joint involvement, serology, acutephase reactants, and symptom duration. Although developed primarily for classification and research, it has supported more systematic recognition of early RA.[8] Treatment is directed toward suppressing inflammation, limiting structural damage, preserving function, improving quality of life, and achieving remission or low disease activity. Among traditional disease-modifying drugs, methotrexate is still the first choice, and patients whose disease stays active despite it can move on to biologic agents or targeted synthetic drugs.[1,9] Current care commonly uses a treat-to-target approach, with repeated assessment of disease activity and modification of treatment when targets are not reached. Prognostic factors, comorbidities, safety considerations, treatment response, and patient preferences are incorporated into therapeutic decisions. Persistent disease activity in some patients continues to drive research into more individualized treatment.[9,10]

RA therefore remains an important global health problem because of chronic disability, Systemic complications, treatment-associated risks, and socioeconomic consequences. Research continues to focus on earlier detection, improved understanding of mechanisms, clinically useful biomarkers, Prediction of treatment response, and precision-oriented therapies.

2. Epidemiology of Rheumatoid Arthritis

RA is a chronic systemic autoimmune disease whose population distribution is not uniform. Differences in geographic setting, age, sex, inherited susceptibility, environmental exposures, and case-identification methods contribute to variation in reported epidemiological estimates.[11]



(Fig2. Foot manifestations of rheumatoid arthritis, including synovitis, toe deformities, bunions, cartilage destruction, bone erosion, callosities, ulcers, and subcutaneous nodules.)

2.1 Prevalence of RA in Epidemio Studies

In many populations, RA affects approximately one-half to one percent of adults, Although the measured prevalence can change with demographic composition, environmental factors, genetic background, diagnostic definitions, and study design.[12]

RA generally occurs more frequently in women, with female-to-male ratios commonly reported around 2–3:1, although this proportion can vary among populations. The incidence tends to increase with age, particularly in later adulthood. Familial susceptibility also contributes to disease occurrence, while environmental factors such as tobacco exposure and obesity may further modify individual risk. The WHO-ILAR COPCORD study performed in rural western India found an RA prevalence of approximately 0.5%, showing that RA is also relevant in rural community[12] Indian studies have reported geographic differences in prevalence. Such differences may arise from variations in population structure, case definitions, access to healthcare, and the approaches used to identify people with disease.[12]

(2.2)Epidemiological Assessment of Rheumatoid Arthritis Incidence

The occurrence of newly diagnosed RA varies across populations and is affected by age, sex, geographic context, and case-ascertainment procedures. Epidemiological research indicates that RA occurs more frequently in women, and its incidence generally increases with advancing age.[13]

In Rochester, Minnesota, the estimated overall annual incidence during 1955–1994 was 44.6 per 100,000 adults. Rates declined from 61.2 per 100,000 in 1955–1964 to 32.7 per 100,000 in 1985–1994, demonstrating that incidence can change over time.[14]

(3) Factors Associated with the Development of Rheumatoid Arthritis

Rheumatoid arthritis (RA) results from the interaction of genetic predisposition with environmental and lifestyle-related influences. Several factors are associated with an increased risk of developing the disease, including female sex, advancing age, a family history of RA, tobacco smoking, obesity, and certain occupational exposures. The associations between these factors may vary between seropositive and seronegative forms of RA.[15]

The development of RA involves multiple contributing factors rather than a single identifiable cause. Genetic susceptibility, environmental conditions, and immune system disturbances collectively influence disease onset. Major risk factors include female sex, older age, a familial history of RA, genetic variations such as HLA-DRB1 alleles, cigarette smoking, obesity, and particular workplace or environmental exposures. These factors may contribute to the initiation and progression of the disease by disrupting normal immune regulation and promoting persistent inflammation.

Genetic predisposition is an important contributor to RA development. Variants of the HLADRB1 gene that carry the shared epitope are closely associated with increased disease susceptibility. Other genetic variations, including those in the PTPN22 gene, may also influence the likelihood of developing RA. The extent of these genetic effects may differ across populations and may be influenced by environmental conditions.[15]

Cigarette smoking is a major modifiable risk factor, especially for anti-citrullinated protein antibody (ACPA)-positive RA. It may interact with HLA-DRB1 genetic susceptibility and promote protein citrullination, potentially triggering abnormal autoimmune responses before the clinical signs of arthritis appear.[16]

Obesity has also been identified as a factor associated with an increased risk of RA. Populationbased cohort studies have reported a relationship between a body mass index (BMI) of 30 kg/m² or higher and the occurrence of RA. These findings suggest that body weight is a potentially modifiable factor that may influence disease susceptibility.[16]

(4). Pathophysiology of Rheumatoid Arthritis

RA results from sustained immune activation that produces chronic inflammation within the synovium. Genetic factors, together with environmental influences, contribute to abnormal protein modifications, disruption of immune tolerance, and the activation of innate and adaptive immune responses. Over time, these pathological processes can cause progressive cartilage loss, bone erosion, joint deformities, and impairment of physical functioning.[17,18]

(4.1) Genetic and environmental Predisposition

HLA-DRB1 shared-epitope alleles represent important inherited risk factors. Environmental stimuli such as smoking and mucosal inflammatory conditions may encourage abnormal protein modification and immune activation in susceptible Individuals.[17]

(42)Protein citrullination and loss of immune tolerance

Peptidyl arginine deiminase (PAD) enzymes facilitate the modification of arginine residues into citrulline, a process known as citrullination. This modification may be enhanced in mucosal tissues, particularly those of the respiratory tract and periodontal region. In genetically susceptible people, modified proteins can become targets of adaptive immunity, promoting T- and B-cell activation and RF/ACPA formation.[17,18]

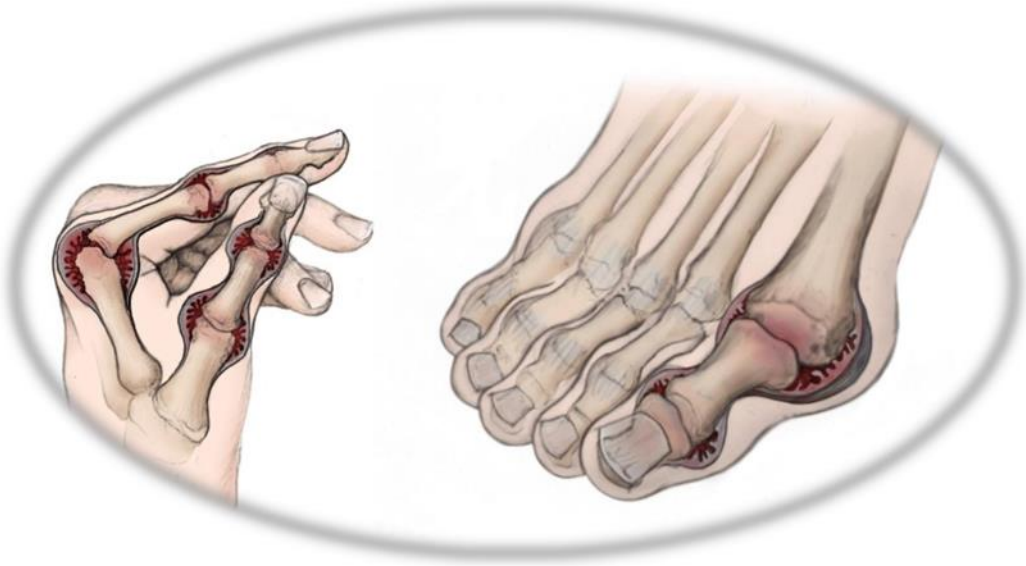
(4.3)Formation and role of autoantibodies

ACPAs can be present before arthritis is clinically apparent and recognize citrullinated proteins. RF and ACPA can contribute to immune-complex formation and inflammator signaling. ACPA-associated processes can also enhance osteoclast activation, contributing to bone destruction and loss.[18,19]

(4.4)Activation of innate and adaptive immunity

T cells, B cells, macrophages, neutrophils, dendritic cells, and synovial fibroblasts participate in the inflammatory response. Th1/Th17 pathways, B-cell activation, and macrophagederived TNF-α, IL-1, and IL-6 help maintain the inflammatory environment.[17,18]

(4.5) Synovial inflammation and hyperplasia



(Fig4. Rheumatoid arthritis–associated inflammation of the hand and foot joints, showing synovitis and inflammatory tissue proliferation.).

Immune-cell infiltration leads to release of cytokines, chemokines, growth factors, and tissue-degrading enzymes. TNF-α, IL-1, and IL-6 promote vascular activation, leukocyte recruitment, fibroblast stimulation, and expansion of synovial tissue. Fibroblast-like synoviocytes produce MMPs and related mediators that damage cartilage and bone.[17,18]

(4.6) Formation of pannus

Persistent synovitis results in formation of a thick, vascular inflammatory tissue known as pannus. It can extend over cartilage and into neighboring bone, while angiogenesis supports continued expansion and recruitment of inflammatory cells.[18]

(4.7) Cartilage destruction

MMPs and aggrecanases break down extracellular-matrix components such as collagen and proteoglycans. Progressive loss of the cartilage matrix weakens the cartilage, narrows the joint space, and impairs normal joint movement and function.[17,18]

(4.8) Osteoclast activation and bone erosion:

Inflammatory cytokines and stromal signals increase RANKL-dependent osteoclast differentiation. TNF-α, IL-1, IL-6, IL-17, and RANKL participate in osteoclastogenesis, leading to the marginal erosions typical of RA. ACPA-related mechanisms may further enhance osteoclast-mediated bone loss.[18,19]

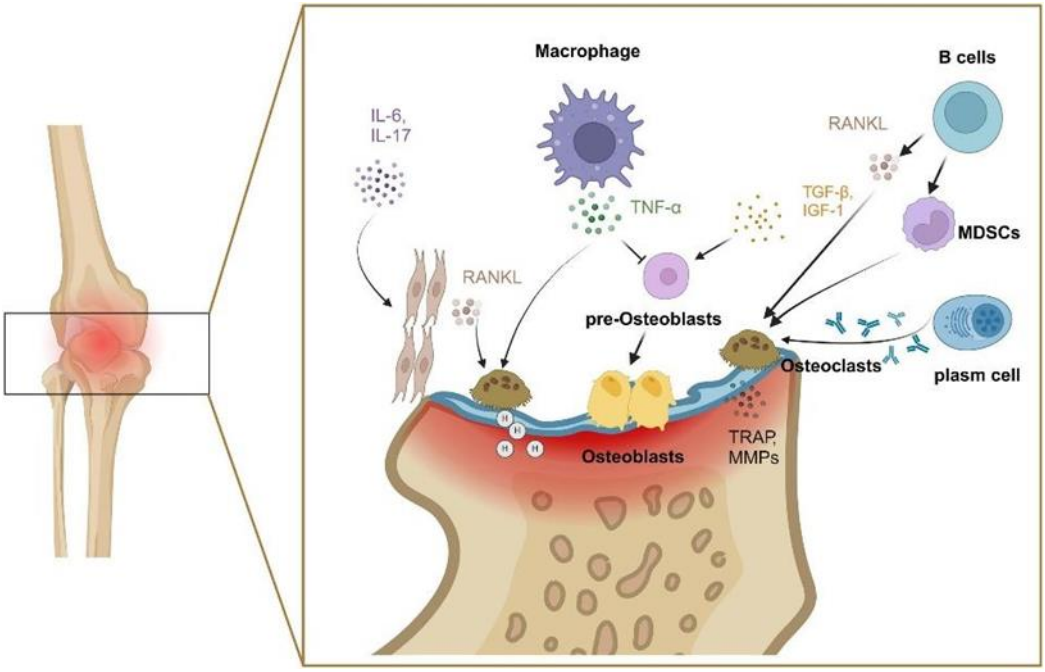
(4.9) Role of major cytokines

TNF-α, IL-1, IL-6, and IL-17 form a connected inflammatory network that promotes leukocyte recruitment, synovial activation, matrix degradation, and osteoclastogenic signaling. The effectiveness of therapies directed at these pathways supports their importance in RA inflammation.[17,18]

(4.10) Neutrophil Activity and the Formation of neutrophil extracellular traps (NETs)

Neutrophils in RA synovial fluid can form NETs containing DNA, histones, and granular proteins. NET release can expose the immune system to modified proteins, potentially strengthening the links between citrullination, anti-citrullinated protein antibodies (ACPAs), and inflammatory cells.[18,19]

4.11 Final pathway leading to joint destruction



(Fig5. Mechanisms of bone erosion in rheumatoid arthritis involving inflammatory cytokines, osteoclast activation, and bone destruction.)

RA can be described as a progressive process in which genetic predisposition and environmental influences contribute to altered immune responses, leading to autoantibody production and ongoing inflammation of the synovial membrane.. Cytokine release, immune-cell recruitment, fibroblast activation, pannus development, cartilage breakdown, and osteoclast activation eventually produce erosions, joint-space loss, deformity, pain, stiffness, and functional limitation.[17–19]

(5.1) Diagnosis of Rheumatoid Arthritis

RA diagnosis is based on an integrated assessment of symptoms, physical findings, serology, inflammatory markers, and imaging. Persistent inflammatory synovitis is a key feature, while alternative causes of inflammatory arthritis need to be considered before a diagnosis is assigned [20] Assessment includes joint pain, swelling, tenderness, morning stiffness, and restricted movement. The wrists and small joints of the hands and feet are frequently involved, and both the number and distribution of affected joints contribute to the ACR/EULAR classification approach.[20]

(5.1.1) Diagnostic, Prognostic and Predictiv markers in Rheumatoid Artritis

Biomarkers are useful for detecting RA at an early stage, evaluating disease severity and joint damage progression, monitoring inflammatory activity, and investigating variations in patients'responses to different treatments.Established laboratory measures include RF, ACPA, CRP, and ESR; other investigated markers include 14-3-3η, calprotectin, anticarbamylated protein antibodies,and composite multi-biomarker scores.[21]

1.Diagnosticbiomarkers: Rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA) are the two major serological indicators commonly used in the evaluation of rheumatoid arthritis (RA). AntiCCP2 has high specificity and may be detectable before clinical arthritis, making ACPA useful in early or undifferentiated inflammatory arthritis. RF is less specific because it can occur in other autoimmune and infectious disorders. Combining RF with ACPA can improve diagnostic identification. Serum 14-3-3η has been investigated as a supplementary biomarker, especially when used in combination with conventional serological tests.

2. Prognostic biomarkers: RF and ACPA can provide information about subsequent disease behavior and structural injury. Higher levels of ACPA have been linked to more pronounced radiographic joint damage over time in several patient groups; however, these findings should be evaluated alongside clinical assessments and imaging results. Calprotectin reflects innate inflammatory activity and has been linked with active disease and later erosive progression. Higher initial levels of 1433η have been linked to increased radiographic disease progression; however, further studies are required before it can be routinely used as an independent biomarker.[22]

3. Predictive biomarkers: RF and ACPA have been examined as potential predictors of response to biologic therapies, including TNF inhibitors, but current evidence does not establish them as independent tools for selecting a particular treatment. Multibiomarker disease activity scores combine several serum markers to estimate inflammatory activity and have been associated with later disease activity and structural progression; their ability to guide selction of The effectiveness of a particular biologic agent or targeted therapy is still being studied.[23]

4. Emerging biomarkers: Anti-carbamylated protein antibodies, microRNAs, and other molecular signatures are being studied for additional diagnostic and predictiv information, including in seronegative disease. Wider clinical use will require validation in independent populations and standardized testing methods.[23]

(5.2.1)Imaging-Based Assessment of Rheumatoid Arthritis

Imaging is particularly useful when clinical assessment leaves uncertainty or when early Inflammatory abnormalities are suspected. Radiography, ultrasonography, and MRI are the principal modalities, and their findings should be interpreted alongside clinical and laboratory information.[24]

Conventional radiographs are widely used to evaluate established structural damage. RA May produce marginal erosions, periarticular osteopenia, relatively uniform joint-space narrowing, and progressive destruction, although plain radiography is less sensitive for early synovitis and small erosions.[24]

Ultrasonography can identify synovial hypertrophy, effusion, tenosynovitis, and erosions. Power Doppler assessment provides information about vascular activity associated with active synovitis and may detect inflammation that is not readily apparent during physical examination.[24]

MRI is highly sensitive for early inflammatory and structural abnormalities, including synovitis, tenosynovitis, bone-marrow edema, and erosions. MRI-visible bone-marrow edema has also been associated with later radiographic progression and may have prognostic relevance.[24]

CT is more sensitive than standard radiography for cortical bone abnormalities and erosions, but its use is constrained by ionizing radiation and its lower sensitivity for soft-tissue

inflammation compared with MRI or ultrasound. It may be useful when detailed cortical bone assessment is required.[24]

(5.2) Therapeutic Management Approaches for Rheumatoid Arthritis

treatment is intended to suppress inflammation, limit structural damage, preserve physical function, and maintain remission or low disease activity.[25] Table X. Classification, Target Molecules, Developmental Progress, and Frequently Reported.

(5.3)Adverse Effects of Selected Janus Kinase Inhibitors Used in Rheumatoid Arthritis

1. Conventional synthetic DMARDs: Conventional DMARD therapy, particularly methotrexate, is a central component of RA management. These medicines reduce inflammatory activity and can slow structural progression.[25]

2. Glucocorticoids as bridging therapy: A brief course of low-dose glucocorticoids can provide rapid symptom improvement while DMARDs take effect. Longer exposure is generally minimized because cumulative toxicity increases with duration.[26]

3. Biological DMARDs: When conventional DMARD treatment does not adequately control disease, Biologic agents targeting pathways such as TNF-α or IL-6 can be considered.[27]

4. Targeted synthetic DMARDs: JAK inhibitors such as tofacitinib, baricitinib, filgotinib, and upadacitinib acts on intracellular signaling pathways and offers oral targeted treatment options.[28]

5. Treat-to-target strategy: Disease activity is measured at planned intervals, and treatment is adjusted when the intended target is not reached. The overall goal is sustained remission or low disease activity while limiting progression.[29]

6.Non-pharmacological measures: Exercise, physiotherapy, and rehabilitation help maintain mobility, muscle strength, physical function, and quality of life and therefore form an important part of comprehensive RA care.[29]

(6). Pharmacological Therapies in Rheumatoid Arthritis

1. Conventional synthetic DMARDs: These agents reduce disease activity and help prevent structural injury. Methotrexate is generally central to initial treatment, while leflunomide or sulfasalazine may be alternatives when methotrexate cannot be used or is not tolerated.[29]

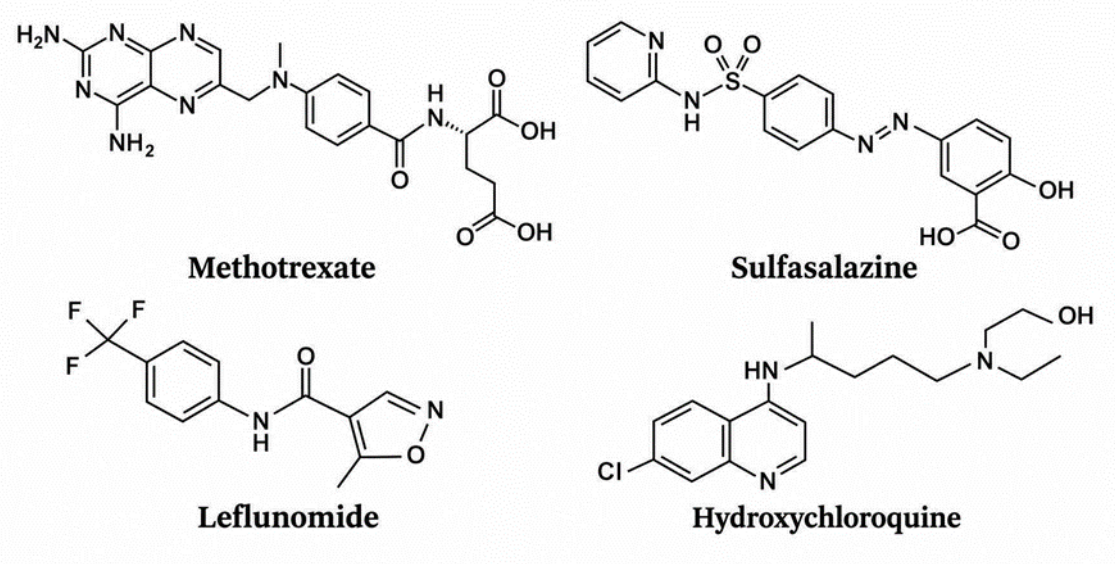
2. Hydroxychloroquine: Hydroxychloroquine can be considered in selected patients, particularly in less severe disease or within conventional DMARD regimens. Appropriate ophthalmic monitoring is required because retinal toxicity is a recognized risk.[30]

3. Glucocorticoids: Short courses may be used when rapid suppression of inflammation is required, especially during DMARD initiation or adjustment. Long-term exposure is restricted because adverse effects accumulate with continued use.[30]

4. Biological DMARDs: Patients with insufficient response to conventional DMARDs may receive biologic treatment. Options include TNF inhibitors such as adalimumab, etanercept, and infliximab, as well as abatacept, rituximab, tocilizumab, and sarilumab.[31]

5. Targeted synthetic DMARDs: JAK inhibitors including tofacitinib, baricitinib, filgotinib, and upadacitinib provides oral targeted treatment. Individual cardiovascular, malignancy, and thromboembolic risk factors should be considered when these agents are used.[31]

6. Treattotarget therapy: Treatment is reviewed repeatedly against predefined disease-activity goals and changed when those goals are not achieved, with sustained remission or low disease activity as the therapeutic aim.[31]



1) Methotrexate

Methotrexate is a folate antagonist and an important csDMARD used in the management of RA. It reduces inflammation, helps manage ongoing synovial inflammation, and may slow the progression of the disease. Methotrexate acts by blocking dihydrofolate reductase and disrupting folate-dependent metabolic pathways in cells. However, the exact mechanism responsible for its anti-inflammatory effects in rheumatoid arthritis (RA) has not yet been fully clarified. Methotrexate is commonly used as an initial DMARD and may be administered orally or subcutaneously.

2) Sulfasalazine

Sulfasalazine is a csDMARD with anti-inflammatory and immunomodulatory properties. After oral administration, intestinal bacteria metabolize it mainly into sulfapyridine and 5aminosalicylic acid. Although its exact mechanism in RA remains incompletely defined, these metabolites may contribute to its anti-inflammatory effects. Sulfasalazine can be used alone or as part of combination csDMARD therapy.

3) Leflunomide

Leflunomide is an immunomodulatory csDMARD used to reduce inflammatory disease activity in RA. It is converted to the active metabolite teriflunomide, which inhibits dihydroorotate dehydrogenase, an enzyme required for de novo pyrimidine synthesis. This reduces proliferation of activated lymphocytes and contributes to its immunomodulatory effect.

4) Hydroxychloroquine

Hydroxychloroquine is a 4-aminoquinoline drug with antirheumatic and immunomodulatory activity. Its precise anti-inflammatory mechanism in RA is not completely established, but it modifies immune and inflammatory processes. It is generally considered among the csDMARD options for RA, particularly in patients with lower disease activity. Long-term treatment requires attention to retinal toxicity and appropriate ophthalmic monitoring.

(7) New perspectives and future directions in the treatment of rheumatoid arthritis

RA treatment is increasingly moving toward individualized care in which disease characteristics, molecular mechanisms, and patient-specific factors are considered when therapy is selected.[32]

Synovial tissue analysis and multi-omics technologies may help define molecular subgroups of RA and improve prediction of therapeutic response, potentially allowing more precise treatment selection.[33] Research is also exploring targets beyond established inflammatory pathways, including mechanisms involving immune cells, fibroblasts, and intracellular signaling networks[32,33] Cell-based strategies, including CAR-T-cell approaches, are being investigated in severe treatmentresistant autoimmune diseases and may eventually have a role in refractory RA.[32]

Artificial intelligence and machine-learning approaches may help combine clinical, imaging, and molecular information to investigate disease progression and treatment response.[33] An important emerging direction is the use of precision medicine in RA.

Patients with clinically similar disease may have different underlying molecular and immunological mechanisms and may therefore respond differently to the same treatment. Advances in genomics, transcriptomic, proteomics, metabolomics, and other multi-omics technologies may help identify biologically distinct subgroups of RA.[32] Combining these methods with clinical data may enhance the ability to predict therapeutic outcomes and support more personalized treatment decisions for individual patients.[32,33]

Analysis of synovial tissue is becoming increasingly valuable for identifying differences in disease characteristics among patients with rheumatoid arthritis. The synovia contains different populations of immune and stromal cells that contribute to persistent inflammation and joint destruction[32] Molecular examination of synovial tissue may help identify specific pathogenic pathways active in individual patients[32] In the future, synovial profiling could potentially be used to classify patients into treatment-relevant molecular groups and guide the selection of targeted therapies.[32,33]

The future of RA therapy may also involve combination and sequential treatment strategies that are tailored to disease activity and individual response.[29,31] Instead of maintaining the same treatment indefinitely, therapy may be adjusted according to clinical response, biomarker changes, imaging findings, and the occurrence of adverse effects[29] This approach could help maintain disease remission while minimizing unnecessary medication exposure.

The increasing use of artificial intelligence (AI) and machine learning may further transform RA management. AI-based models can potentially analyze large and complex datasets containing clinical, laboratory, imaging, genetic, and molecular information. These tools may help healthcare professionals forecast disease progression, identify individuals at increased risk of severe joint damage, assess the likelihood of treatment success, and determine which patients may respond best to specific therapeutic approaches.. Automated analysis of radiographic and ultrasound images may also improve the detection and quantification of structural changes.[24,33]

Advanced imaging techniques are another area of future development. Conventional radiography remains important for detecting structural damage, but ultrasound and magnetic resonance imaging can identify inflammatory changes and joint abnormalities at earlier stages. Improvements in imaging technology and automated image interpretation may allow more sensitive monitoring of synovitis, erosions, and treatment response. This may be particularly valuable when clinical symptoms and laboratory markers do not completely reflect the underlying joint inflammation.[24]

Future research increasingly emphasizes intervention earlier in the disease continuum, including prevention in people at high risk. Treatment during the preclinical stage is being studied as a possible strategy for delaying or preventing established RA.[34]

(8) Risk factors of rheumatoid arthritis – expanded:

1. Genetic predisposition: A family history of RA and susceptibility variants, particularly HLA-DRB1 alleles, are associated with an increased risk of developing the disease.[35,36]

2. Female sex: RA occurs more frequently in women, and differences in hormonal influences and immune regulation may contribute to this pattern.[37,38]

3. Increasing age: RA can develop at any age; however, its occurrence generally increases with advancing age.[37]

4. Cigarette smoking: Smoking is an important modifiable risk factor, particularly for seropositive RA, and may interact with genetic susceptibility.[35,36]

5. Obesity: Excess body weight has been associated with an increased risk of RA, potentially through inflammatory mediators released by adipose tissue.[36,39]

6.Periodontal disease: Chronic periodontal inflammation, including that associated with The periodontal bacterium Porphyromonas gingivalis has been studied for its potential involvement in the autoimmune processes associated with rheumatoid arthritis (RA).[38]

7.Environmental and occupational exposure: Occupational exposure to inhaled substances, particularly silica dust, has been associated with an increased risk of RA.[35,36]

8.Air pollution: Long-term exposure to fine particulate matter has been investigated as a potential contributor to inflammatory and autoimmune processes associated with RA.[36]

9.Family history: Individuals with a first-degree relative affected by RA may have a higher risk of developing the disease because of inherited susceptibility and shared environmental exposure[35,37]

10.Hormonal and reproductive factors: Pregnancy, postpartum hormonal changes, and other reproductive factors may influence RA susceptibility and disease activity.[38]

11.Infections: Certain infectious exposures may act as environmental triggers in genetically susceptible individuals, although no single microorganism has been established as the direct causeofRA.[36]

12.Gene–environment interaction: Environmental exposures may increase disease susceptibility in genetically predisposed individuals. The interaction between cigarette smoking and HLA-DRB1 susceptibility alleles is a well-described example.[35,36]

CONCLUSION

Rheumatoid arthritis (RA) is a multifaceted chronic systemic autoimmune disorder that predominantly involves synovial joints but may also affect multiple organ systems and substantially influence physical function and quality of life. Sustained synovial inflammation can progressively injure cartilage and bone, leading to pain, stiffness, deformity, and functional limitation. Disease presentation and progression vary among individuals because of differences in genetic susceptibility, environmental exposures, immune regulation, and lifestyle factors.

Timely recognition and prompt initiation of disease-modifying treatment are essential to suppress inflammation and limit irreversible structural damage. Integrated assessment including clinical evaluation, serological markers such as rheumatoid factor and anticitrullinated protein antibodies, acute-phase reactants, and imaging modalities supports early diagnosis and monitoring. Ongoing advances in biomarker and imaging research may further enhance early detection, prognostic stratification, and prediction of therapeutic response.

Therapeutic management of RA has evolved from conventional synthetic disease-modifying antirheumatic drugs to biologic and targeted synthetic agents, thereby expanding options for achieving sustained remission or low disease activity. Methotrexate continues to be a cornerstone of initial therapy, while biologic and targeted therapies are considered when disease control remains inadequate. Complementary nonpharmacological measures including regular exercise, physiotherapy, occupational therapy, patient education, orthoses, and structured follow-up contribute to preservation of mobility, independence, and overall wellbeing.

REFERENCES

1. Smolen JS, Aletaha D, McInnes IB. Rheumatoid arthritis. Lancet, 2016; 388(10055): 2023-2038. doi: 10.1016/S0140-6736(16)30173-8.
2. Cross M, Smith E, Hoy D, et al. The global burden of rheumatoid arthritis: estimates from the Global Burden of Disease 2010 study. Ann Rheum Dis, 2014; 73(7): 1316-1322. doi: 10.1136/annrheumdis-2013-204627.
3. Malaviya AN, Kapoor SK, Singh RR, Kumar A, Pande I. Prevalence of rheumatoid arthritis in the adult Indian population. Rheumatol Int. 1993; 13(4): 131-134. doi: 10.1007/BF00301258.
4. Nielen MMJ, van Schaardenburg D, Reesink HW, et al. Specific autoantibodies precede the symptoms of rheumatoid arthritis: a study of serial measurements in blood donors. Arthritis Rheum, 2004; 50(2): 380-386. doi: 10.1002/art.20018.
5. Nielen MMJ, van Schaardenburg D, Reesink HW, et al. Increased levels of C-reactive protein in serum from blood donors before the onset of rheumatoid arthritis. Arthritis Rheum, 2004; 50(8): 2423-2427. doi: 10.1002/art.20431.
6. McInnes IB, Schett G. The pathogenesis of rheumatoid arthritis. N Engl J Med, 2011; 365(23): 2205-2219. doi: 10.1056/NEJMra1004965.
7. Østergaard M, Pedersen SJ, Døhn UM. Imaging in rheumatoid arthritis—status and recent advances for magnetic resonance imaging, ultrasonography, computed tomography and conventional radiography. Best Pract Res Clin Rheumatol, 2008; 22(6): 1019-1044. doi: 10.1016/j.berh.2008.09.014.
8. Aletaha D, Neogi T, Silman AJ, et al, 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis, 2010; 69(9): 1580-1588. doi: 10.1136/ard.2010.138461.
9. Fraenkel L, Bathon JM, England BR, et al, 2021 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. Arthritis Care Res, 2021; 73(7): 924-939. doi: 10.1002/acr.24596.
10. Smolen JS, Landewé RBM, Bergstra SA, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2022 update. Ann Rheum Dis, 2023; 82(1): 3-18.
11. Gabriel SE. The epidemiology of rheumatoid arthritis. Rheum Dis Clin North Am, 2001; 27(2): 269-281.

12. Joshi VL, Chopra A. Is there an urban-rural divide? Population surveys of rheumatic musculoskeletal disorders in the Pune region of India using the COPCORD Bhigwan model. J Rheumatol, 2009; 36(3): 614-622.
13. (Chopra A, Patil J, Bilampelly V, Relwani J, Tandle HS. The Bhigwan COPCORD: methodology and first information on prevalence and patterns of rheumatic musculoskeletal disorders in rural population. J Assoc Physicians India. 1997; 45: 747-749.
14. Myasoedova E, Crowson CS, Kremers HM, Therneau TM, Gabriel SE. Is the incidence of rheumatoid arthritis rising?: results from Olmsted County, Minnesota, 1955-2007. Arthritis Rheum, 2010; 62(6): 1576-1582.
15. Deane KD, Demoruelle MK, Kelmenson LB, Kuhn KA, Norris JM, Holers VM. Genetic and environmental risk factors for rheumatoid arthritis. Best Pract Res Clin Rheumatol, 2017; 31(1): 3-18.
16. Padyukov L, Silva C, Stolt P, Alfredsson L, Klareskog L. A gene-environment interaction between smoking and shared epitope genes in HLA-DR provides a high risk of seropositive rheumatoid arthritis. Arthritis Rheum, 2004; 50(10): 3085-3092. doi: 10.1002/art.20553.
17. Firestein GS. Evolving concepts of rheumatoid arthritis. Nature, 2003; 423(6937): 356361.
18. Klareskog L, Catrina AI, Paget S. Rheumatoid arthritis. Lancet, 2009; 373(9664): 659-672.
19. Schett G, Gravallese E. Bone erosion in rheumatoid arthritis: mechanisms, diagnosis and treatment. Nat Rev Rheumatol, 2012; 8(11): 656-664.
20. Aletaha D, Neogi T, Silman AJ, et al, 2010 rheumatoid arthritis classification criteria: an ACR/EULAR collaborative initiative. Ann Rheum Dis, 2010; 69(9): 1580-1588. doi: 10.1136/ard.2010.138461.
21. Abdelhafiz D, Baker T, Glascow DA, Abdelhafiz AH. Biomarkers for the diagnosis and treatment of rheumatoid arthritis—a systematic review. Postgrad Med, 2023; 135(3): 214-223. doi: 10.1080/00325481.2022.2052626.
22. Nordal HH, Fagerhol MK, Halse AK, et al. Calprotectin predicts 10-year radiographic progression in patients with rheumatoid arthritis. Scand J Rheumatol, 2009; 38(6): 427-432.

23. Curtis JR, van der Helm-van Mil AHM, Knevel R, et al. Validation of a biomarker-based disease activity score for rheumatoid arthritis. Arthritis Care Res, 2012; 64(12): 1791-1799.
24. Østergaard M, Møller-Bisgaard S, Willim M, et al. MRI and ultrasound in rheumatoid arthritis: imaging of synovitis, bone marrow edema and erosions. Best Pract Res Clin Rheumatol, 2019; 33(5): 101437.
25. Fraenkel L, Bathon JM, England BR, et al, 2021 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. Arthritis Care Res, 2021; 73(7): 924-939. doi: 10.1002/acr.24596.
26. Strehl C, Bijlsma JWJ, de Wit M, et al. Defining conditions where long-term glucocorticoid treatment has an acceptable benefit-risk ratio: viewpoints from an EULAR task force. Ann Rheum Dis, 2016; 75(6): 952-957.
27. Maini R, St Clair EW, Breedveld F, et al. Infliximab versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: the ATTRACT trial. Lancet. 1999; 354(9194): 1932-1939. doi: 10.1016/S0140-6736(99)05246-0.
28. Fleischmann R, Kremer J, Cush J, et al. Placebo-controlled trial of tofacitinib monotherapy in rheumatoid arthritis. N Engl J Med, 2012; 367(6): 495-507.
29. Smolen JS, Aletaha D, Bijlsma JWJ, et al. Treating rheumatoid arthritis to target: recommendations of an international task force. Ann Rheum Dis, 2010; 69(4): 631-637. doi: 10.1136/ard.2009.123919.
30. O'Dell JR, Leff R, Paulsen G, et al. Treatment of rheumatoid arthritis with methotrexate and hydroxychloroquine, methotrexate and sulfasalazine, or a combination of the three medications. Arthritis Rheum, 2002; 46(5): 1164-1170. doi: 10.1002/art.10228.
31. Smolen JS, Landewé RBM, Bergstra SA, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological DMARDs: 2022 update. Ann Rheum Dis, 2023; 82(1): 3-18.
32. Cheng Y, et al. New learnings from the molecular pathology of the synovial tissue in rheumatoid arthritis: from pathogenesis to therapeutic targeting toward precision medicine. Curr Opin Immunol, 2026; 82: 102785. doi: 10.1016/j.coi.2026.102785.
33. Artificial intelligence in rheumatoid arthritis: current applications and future perspectives. Rheumatology International, 2026.
34. Deane KD, Holers VM. Can rheumatoid arthritis be prevented? Best Pract Res Clin Rheumatol, 2014; 28(4): 467-485. doi: 10.1016/j.berh.2013.09.002.

35. Smolen JS, Aletaha D, McInnes IB. Rheumatoid arthritis. Lancet, 2016; 388(10055): 2023-2038. Doi: 10.1016/S0140-6736(16)30173-8.
36. Abdelhafiz D, Baker T, Glascow DA, Abdelhafiz AH. Biomarkers for the diagnosis and treatment of rheumatoid arthritis—a systematic review. Postgrad Med, 2023; 135(3): 214-223. Doi: 10.1080/00325481.2022.2052626.
37. Aletaha D, Neogi T, Silman AJ, et al, 2010 rheumatoid arthritis classification criteria. Ann Rheum Dis, 2010; 69(9): 1580-1588. Doi: 10.1136/ard.2010.138461.
38. Zangi HA, Ndosi M, Adams J, et al. EULAR recommendations for patient education for people with inflammatory arthritis. Ann Rheum Dis, 2015; 74(6): 954-962. Doi: 10.1136/annrheumdis-2014-206807.
39. Rausch Osthoff AK, Vliet Vlieland TPM, Ferreira RJO, et al. EULAR recommendations for physical activity in people with inflammatory arthritis and osteoarthritis: 2025 update. Ann Rheum Dis, 2026; 85(6): 1026-1038. Doi: 10.1016/j.ard.2026.03.006.