RHEUMATOID ARTHRITIS: PATHOGENESIS, CLINICAL COURSE, AND MODERN TREATMENT APPROACHES

Toshmurzayeva Asila Zahiriddin qizi
Samarkand State Medicial University
zahiriddinova402@gmail.com
Hamroyeva Dilbar Ulug'bekovna
Samarkand State Medicial University
hamroyeva2007@icloud.com
Akhtamova Intizor Bobirjonovna
Samarkand State Medicial University
intizoraxtamova8@gmail.com
Rakhimberdiyeva Rukhshona Sherzodovna
Samarkand State Medicial University
sherzodovnaruxshona07@gmail.com

Abstract: Rheumatoid arthritis (RA) is a chronic, systemic autoimmune disease characterized by symmetric inflammatory polyarthritis, progressive synovial proliferation, and destruction of cartilage and juxta-articular bone, frequently accompanied by extra-articular manifestations affecting the lungs, skin, cardiovascular system, and hematologic profile. This narrative review synthesizes current evidence on the immunopathogenesis, clinical course, classification, and contemporary management of RA, drawing on the 2010 ACR/EULAR classification criteria and the 2021 American College of Rheumatology (ACR) guideline for the treatment of rheumatoid arthritis. Disease pathogenesis reflects the interaction of genetic susceptibility (notably the HLA-DRB1 shared epitope) and environmental triggers, principally cigarette smoking, which promote citrullination of self-proteins, loss of immune tolerance, and production of rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA). These autoantibodies, together with activated T and B lymphocytes, drive synovial inflammation, fibroblast-like synoviocyte proliferation and pannus formation, and cytokine-mediated amplification through tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1, culminating in osteoclast-mediated bone erosion and cartilage destruction. Management has shifted decisively toward early diagnosis and a treat-to-target strategy: methotrexate remains the anchor drug for patients with moderate-to-high disease activity, with prompt escalation to biologic or targeted synthetic disease-modifying antirheumatic drugs (DMARDs) for patients with an inadequate response, while glucocorticoids are reserved for short-term bridging use only. A mechanism-based understanding of RA, combined with early, individualized, guideline-directed treatment, is central to preventing irreversible joint damage and improving long-term functional outcomes, including within the healthcare system of Uzbekistan.

Keywords: Rheumatoid arthritis, autoimmunity, citrullination, anti-citrullinated protein antibodies, synovitis, methotrexate, biologic DMARD, treat-to-target.

Methods

This work was prepared as a narrative literature review. A literature search was conducted in August 2026 using PubMed, the ACR and EULAR publication databases, and the websites of major rheumatology societies, with the search terms "rheumatoid arthritis," "pathogenesis," "citrullination," "ACPA," "DMARD," and "treat-to-target," combined with filters for publication in English between 2016 and 2026. Priority was given to the 2021 ACR guideline for the treatment of rheumatoid arthritis, the 2010 ACR/EULAR classification criteria, systematic reviews, and peer-reviewed original research; narrative summaries from established clinical reference sources were included for foundational background. Case reports and articles without accessible full text were excluded. A total of twelve sources meeting these criteria were selected and synthesized for this review.

Introduction

Rheumatoid arthritis is the most common chronic inflammatory arthritis, affecting approximately 0.5-1% of the adult population worldwide, with a female-to-male predominance of roughly 3:1. The disease typically presents as a symmetric, additive polyarthritis affecting the small joints of the hands and feet, and follows a variable course ranging from mild, well-controlled disease to progressive, erosive joint destruction and disability if left inadequately treated.

Contemporary understanding frames RA not merely as a disease of the joints but as a systemic autoimmune process in which genetic susceptibility and environmental triggers converge to break immune tolerance to citrullinated self-proteins years before clinical synovitis becomes apparent. This mechanistic insight has directly informed the shift toward earlier diagnosis, a treat-to-target treatment philosophy, and the expansion of targeted biologic and small-molecule therapies over the past two decades.

The aim of this review is to summarize current evidence on the pathogenesis, clinical course, classification, and stepwise management of rheumatoid arthritis, with particular emphasis on recently updated international guidelines and their relevance to clinical practice.

Understanding the modern approach to RA is relevant across several areas of clinical practice, including:

- Rheumatology (diagnosis, classification, disease activity assessment, long-term management)
- Family and internal medicine (early recognition and timely referral)
- Pulmonology (evaluation of interstitial lung disease)
- Cardiology (assessment of accelerated cardiovascular risk)
- Orthopedics (management of joint deformity and need for surgical intervention)
- Pharmacology (monitoring of DMARD toxicity and drug interactions)

Pathogenesis

The pathogenesis of RA begins with a genetic predisposition, most strongly linked to HLA-DRB1 alleles encoding the "shared epitope," combined with environmental triggers

— principally cigarette smoking, but also periodontal disease (Porphyromonas gingivalis) and alterations in the lung and gut microbiome — that promote citrullination, a post-translational modification of arginine residues in self-proteins such as fibrinogen, vimentin, and collagen. In genetically susceptible individuals, these citrullinated proteins are recognized as foreign by the immune system, resulting in a loss of tolerance and the generation of anti-citrullinated protein antibodies (ACPA) and rheumatoid factor (RF), often detectable in the serum years before the onset of clinically apparent joint symptoms.

Once autoimmunity is established, immune complexes and activated autoreactive T cells (particularly Th17 cells) migrate to the synovium, where they activate resident dendritic cells and macrophages. This triggers proliferation of fibroblast-like synoviocytes, which, together with infiltrating inflammatory cells, form an invasive, tumor-like tissue known as pannus. The pannus directly invades adjacent cartilage and subchondral bone, while a cascade of pro-inflammatory cytokines — most notably tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1 (IL-1) — amplifies synovial inflammation, promotes systemic acute-phase responses (elevated CRP, ESR, anemia of chronic disease), and drives osteoclast differentiation via the RANK/RANKL pathway.

Osteoclast activation, combined with suppression of bone-forming osteoblast activity by inflammatory cytokines, results in the characteristic radiographic findings of RA: juxta-articular osteopenia in early disease, followed by marginal bone erosions and joint space narrowing as cartilage is progressively destroyed. Left untreated, this self-amplifying cycle of autoantibody production, synovial inflammation, and cytokine-driven bone resorption leads to irreversible joint deformity and functional disability, as illustrated in Figure 1.

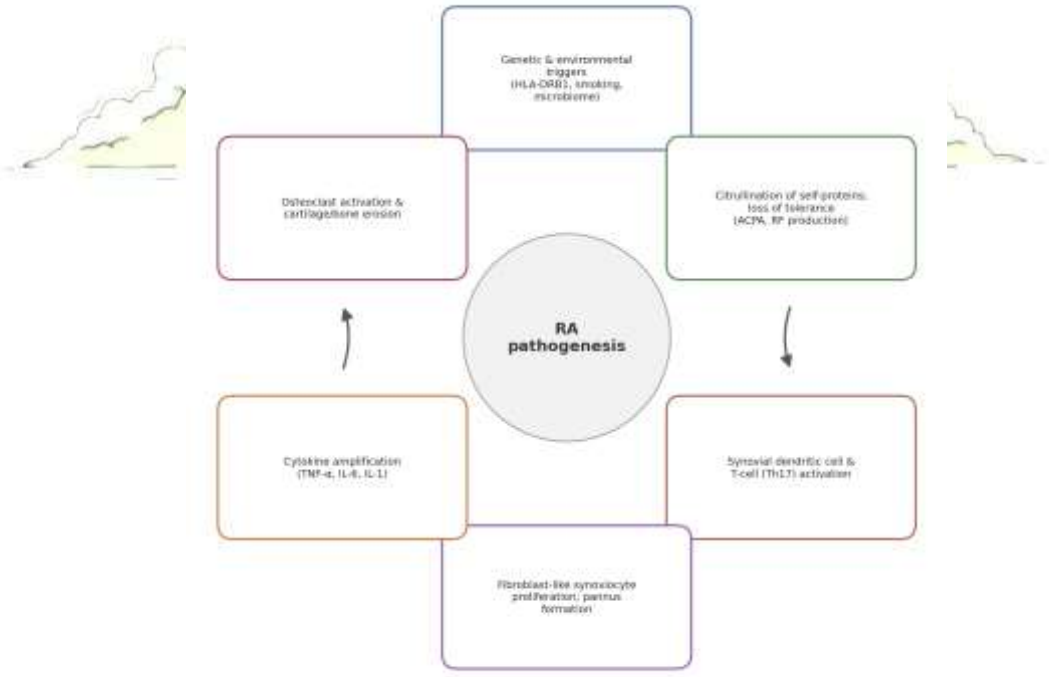

Figure 1. The self-amplifying pathogenic cycle of rheumatoid arthritis: genetic and environmental triggers drive citrullination and loss of tolerance, activating synovial dendritic cells and T cells, promoting fibroblast-like synoviocyte proliferation and pannus formation, amplifying pro-inflammatory cytokine production, and ultimately activating osteoclasts to erode cartilage and bone.

Beyond the joints, the same systemic inflammatory milieu — sustained elevation of TNF-α, IL-6, and acute-phase proteins — underlies the extra-articular manifestations of RA, including accelerated atherosclerosis, interstitial lung disease, and rheumatoid nodules, which contribute substantially to overall morbidity and mortality independent of joint damage itself.

Extra-Articular and Systemic Manifestations

Although RA is defined primarily by its articular manifestations, systemic and extra-articular involvement is common, particularly in patients with long-standing, seropositive, and poorly controlled disease, and is an important determinant of overall prognosis. The principal extra-articular systems affected are summarized in Table 1.

Table 1. Extra-Articular and Systemic Manifestations of Rheumatoid Arthritis

System	Manifestation	Clinical Note
● **Cutaneous / Nodules**	Rheumatoid nodules over extensor surfaces (elbows, forearms)	Occur in ~20-30% of seropositive patients; associated with high RF/ACPA titers
● **Pulmonary**	Interstitial lung disease, pleuritis, rheumatoid nodules in lung parenchyma	Leading cause of RA-related mortality after cardiovascular disease
● **Cardiovascular**	Accelerated atherosclerosis, pericarditis, increased risk of myocardial infarction	Chronic systemic inflammation is an independent cardiovascular risk factor
● **Hematologic / Ocular**	Anemia of chronic disease, Felty syndrome, secondary Sjögren syndrome, scleritis	Felty syndrome: RA + splenomegaly + neutropenia, seen in long-standing seropositive disease
● **Skeletal**	Periarticular osteoporosis, bone erosions, generalized osteoporosis	Compounded by long-term glucocorticoid exposure

Classification and Diagnosis

The 2010 ACR/EULAR classification criteria were developed to identify patients with early, undifferentiated inflammatory arthritis who are at high risk of persistent or erosive disease, replacing the older 1987 ACR criteria, which were better suited to identifying established, late-stage RA. The criteria are applied to patients presenting with synovitis in at least one joint that is not better explained by an alternative diagnosis such as systemic lupus erythematosus, psoriatic arthritis, or gout.

Points are assigned across four domains — joint involvement (0-5 points, based on the number and size of affected joints), serology (0-3 points, based on RF and ACPA titers), acute-phase reactants (0-1 point, based on CRP and ESR), and symptom duration (0-1 point, for symptoms lasting six weeks or longer) — for a maximum possible score of 10. A cumulative score of 6 or greater, in the presence of confirmed synovitis, classifies a patient as having definite rheumatoid arthritis. Patients with a score below 6 are not excluded from a diagnosis of RA but may need reassessment over time as cumulative criteria are met.

Modern Treatment Approaches

Management of RA is guided by a treat-to-target strategy, in which disease activity is regularly measured using validated composite indices (such as the Disease Activity Score in 28 joints, DAS28, or the Clinical Disease Activity Index, CDAI) and therapy is escalated in a stepwise fashion until remission, or at minimum low disease activity, is achieved and sustained. Early initiation of disease-modifying antirheumatic drug (DMARD) therapy is essential, as the window between symptom onset and irreversible joint damage may be measured in months.

According to the 2021 ACR guideline, methotrexate monotherapy is strongly recommended as first-line therapy for DMARD-naïve patients with moderate-to-high disease activity, preferred over hydroxychloroquine or sulfasalazine monotherapy and over combination therapy with a biologic or targeted synthetic DMARD at treatment initiation. For patients with low disease activity who have not previously received DMARDs, hydroxychloroquine is conditionally favored, followed by sulfasalazine, with methotrexate reserved as a later option in this lower-risk group.

For patients who do not achieve an adequate response to methotrexate monotherapy, the guideline supports two comparably effective strategies: addition of a biologic DMARD (such as a TNF inhibitor, IL-6 receptor antagonist, or T-cell costimulation modulator) or a targeted synthetic DMARD (a Janus kinase inhibitor), or escalation to triple conventional therapy with methotrexate, sulfasalazine, and hydroxychloroquine. Triple therapy offers a lower-cost alternative with a comparable rate of disease control, although the onset of benefit is typically slower than with biologic or targeted synthetic agents.

Glucocorticoids retain a role as short-term bridging therapy during periods of active disease or while awaiting the full effect of a newly initiated DMARD, but the 2021 guideline explicitly discourages long-term use, given well-established risks of osteoporosis, infection, and cardiovascular disease with prolonged exposure. The stepwise treatment approach is summarized in Table 2.

Table 2. Stepwise Treat-to-Target Approach in Rheumatoid Arthritis (2021 ACR Guideline)

Step	Recommended Approach	Goal / Note
① **Low disease activity, DMARD-naïve**	Hydroxychloroquine conditionally preferred; sulfasalazine over methotrexate; methotrexate over leflunomide	**Start monotherapy as early as possible**
② **Moderate-to-high activity, DMARD-naïve**	Methotrexate monotherapy strongly preferred over hydroxychloroquine, sulfasalazine, or a biologic/tsDMARD alone	**Methotrexate is the anchor drug**
③ **Inadequate response to MTX**	Add a biologic DMARD or tsDMARD, or switch to triple therapy (MTX + sulfasalazine + hydroxychloroquine)	**Triple therapy is a reasonable, lower-cost alternative**
④ **Treat-to-target monitoring**	Reassess disease activity (e.g., DAS28, CDAI) every 1–3 months; escalate therapy if target not met	**Target: remission or low disease activity**
⑤ **Glucocorticoid use**	Use lowest possible dose for shortest duration as bridge therapy only; avoid long-term use	**Long-term use raises fracture, infection, and cardiovascular risk**

Non-pharmacologic management — physical and occupational therapy to preserve joint function, patient education, smoking cessation, and cardiovascular risk factor modification — is recommended as an integral complement to pharmacotherapy for every patient with RA. Regular monitoring for medication toxicity (hepatic, hematologic, pulmonary, and infectious complications) and for the development of extra-articular manifestations is essential throughout the course of long-term treatment.

Conclusion

Rheumatoid arthritis arises from a self-amplifying autoimmune and inflammatory cycle in which genetic susceptibility and environmental triggers drive citrullination of self-proteins, loss of immune tolerance, autoantibody production, and cytokine-mediated synovial inflammation, culminating in progressive cartilage and bone destruction.

Accurate, early classification using validated criteria and systematic assessment of both articular and extra-articular disease activity are essential to guide individualized, treat-to-target management. Contemporary therapy centers on methotrexate as the anchor

drug, with timely escalation to biologic or targeted synthetic DMARDs for inadequate responders, and judicious, short-term use of glucocorticoids only.

Continued application of mechanism-based classification and guideline-directed, individualized treatment holds the potential to increase rates of sustained remission, prevent irreversible joint damage, and improve long-term functional outcomes and quality of life for patients with rheumatoid arthritis.

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