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RHEUMATOID ARTHRITIS: A CONTEMPORARY REVIEW OF ETIOLOGY, PATHOGENESIS, AND THERAPEUTIC STRATEGIES

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ABSTRACT

Background: Rheumatoid arthritis (RA) is a chronic, systemic autoimmune disease characterised by synovial inflammation, progressive cartilage and bone erosion, and extra-articular organ involvement. Despite major therapeutic advances over the past two decades, a substantial proportion of patients fail to achieve sustained remission, underscoring the need for a continuously updated understanding of its multifactorial etiology, complex immunopathogenesis, and the mechanistic basis of current and emerging therapies.

Objectives: To provide a comprehensive and integrated review of the established and emerging etiological factors of RA, to delineate the cellular and molecular mechanisms underlying its pathogenesis, and to systematically evaluate current pharmacological treatment strategies including conventional synthetic, biological, and targeted synthetic disease-modifying antirheumatic drugs (DMARDs).

Methods: A structured narrative review was conducted using searches of PubMed/MEDLINE, Scopus, and the Cochrane Library (2005–2025). Search terms included 'rheumatoid arthritis etiology', 'RA pathogenesis', 'synovial inflammation', 'anti-citrullinated protein antibodies', 'biological DMARDs', and 'JAK inhibitors'. Priority was given to systematic reviews, meta-analyses, randomised controlled trials, and landmark mechanistic studies.

Results: RA aetiology involves complex interactions among genetic susceptibility (HLA-DRB1 shared epitope, PTPN22, STAT4), environmental triggers (cigarette smoke, oral dysbiosis, gut microbiome alterations), and epigenetic modifications. Pathogenesis is driven by citrullination-induced autoimmunity, synovial fibroblast transformation, and a cytokine network dominated by TNF-α, IL-6, IL-17, and GM-CSF. Treatment has evolved from non-selective immunosuppression to targeted molecular inhibition: biological DMARDs (TNF inhibitors, IL-6 receptor antagonists, B-cell depletion, T-cell co-stimulation blockade) and JAK inhibitors have fundamentally altered disease outcomes, with treat-to-target strategies achieving clinical remission in 30–50% of patients.

Conclusion: RA is an immunologically heterogeneous disease whose therapeutic management has been transformed by mechanistic insight. Future directions include precision medicine approaches based on molecular endotyping, microbiome modulation, and next-generation targeted therapies. Central Asian populations, including those of Uzbekistan, remain understudied and warrant dedicated epidemiological and pharmacogenomic investigation.

Keywords: *rheumatoid arthritis, etiology, pathogenesis, synovial inflammation, anti-citrullinated protein antibodies, disease-modifying antirheumatic drugs, JAK inhibitors, biological therapy.*

1. INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune inflammatory disease that primarily targets diarthrodial joints, producing a characteristic pattern of symmetric polyarthritis with synovial membrane hyperplasia, pannus formation, and progressive destruction of articular cartilage and subchondral bone. Globally, RA affects approximately 18 million people, with a prevalence of 0.5–1.0% in the adult population and a female-to-male ratio of approximately 3:1. The disease carries a substantial burden of functional disability, reduced quality of life, increased cardiovascular morbidity, and premature mortality, with a life expectancy reduced by an estimated 5–10 years relative to the general population [1].

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The past two decades have witnessed a revolution in our understanding of RA pathophysiology and, consequently, in its treatment. The identification of anti-citrullinated protein antibodies (ACPAs) as highly specific serological markers and drivers of autoimmunity, the delineation of the TNF-α and IL-6 signalling axes as therapeutic targets, and the development of targeted synthetic DMARDs—particularly Janus kinase (JAK) inhibitors—have collectively transformed RA from a disease managed with palliative intent into one for which remission is an achievable and routinely pursued clinical goal [2].

Despite these advances, RA remains an incompletely understood condition. Approximately 15–20% of patients are seronegative (ACPA-negative and rheumatoid factor-negative), exhibiting distinct immunopathological features. A further 20–30% of seropositive patients demonstrate inadequate responses to multiple lines of biological therapy, suggesting the existence of distinct immunological endotypes that are not yet fully characterised. Moreover, the contribution of the gut and oral microbiomes to disease initiation and perpetuation has emerged as a rapidly evolving area of research with potential implications for novel preventive and therapeutic strategies [3].

Central Asian populations, including those of Uzbekistan, have been largely excluded from large-scale RA epidemiological and pharmacogenomic studies. The prevalence, clinical phenotype, genetic risk architecture, and treatment response patterns of RA in this region may differ from Western cohorts due to distinct HLA haplotype frequencies, environmental exposures (including occupational dust and silica), and dietary microbiome-modulating factors. Generating regionally relevant evidence in RA is therefore a scientific and public health priority.

The present review was undertaken with three objectives: (1) to synthesise the current evidence on RA etiology, encompassing genetic, environmental, and epigenetic factors; (2) to provide an integrated mechanistic account of RA pathogenesis at the cellular and molecular level; and (3) to systematically evaluate the pharmacological treatment landscape, including conventional synthetic DMARDs, biological agents, JAK inhibitors, and emerging therapeutic modalities.

2. METHODS

2.1 Search Strategy and Source Selection

A structured narrative review was conducted using PubMed/MEDLINE, Scopus, Cochrane Library, and ClinicalTrials.gov, covering publications from January 2005 to March 2025. The following MeSH and free-text search terms were employed in Boolean combination: 'rheumatoid arthritis'[MeSH] AND ('etiology' OR 'aetiology' OR 'risk factors' OR 'pathogenesis' OR 'synovitis' OR 'ACPA' OR 'citrullination' OR 'disease-modifying antirheumatic drugs' OR 'biologics' OR 'JAK inhibitors' OR 'treat-to-target'). Reference lists of included articles were hand-searched for additional relevant sources.

2.2 Inclusion and Exclusion Criteria

Sources were included if they: (a) addressed human RA (not juvenile idiopathic arthritis or other inflammatory arthritides); (b) reported original data, systematic reviews, meta-analyses, or clinical practice guidelines; (c) were published in peer-reviewed English-language journals; and (d) were of sufficient methodological quality (Jadad score ≥ 3 for randomised trials; AMSTAR-2 'moderate' or higher for systematic reviews). Sources were excluded if they reported exclusively animal model data without clinical translation, were published in non-indexed journals, or were inaccessible in full text. A total of 187 sources were screened; 8 are formally cited in this review.

2.3 Data Synthesis

Given the heterogeneous nature of the reviewed literature—encompassing genetic studies, mechanistic immunology, and clinical trial data—a narrative synthesis approach was adopted. Evidence was organised thematically into three main domains: etiology, pathogenesis, and treatment. Within each domain, the hierarchy of evidence (randomised controlled trials and meta-analyses > prospective cohort studies > cross-sectional studies > expert opinion) was applied to grade the strength of conclusions.

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3. RESULTS

3.1 Etiology of Rheumatoid Arthritis

3.1.1 Genetic Factors

RA is a polygenic disease with estimated heritability of 50–60%. The HLA region, particularly HLA-DRB1 alleles encoding the 'shared epitope' (SE)—a conserved amino acid sequence at positions 70–74 of the DRβ1 chain—confers the largest known genetic risk, with odds ratios of 2–4 for heterozygous SE carriers and up to 11 for SE homozygotes in ACPA-positive RA. The SE is hypothesised to shape the thymic T-cell repertoire, promoting the survival of autoreactive $CD4^+$ T cells that recognise citrullinated peptides presented by SE-bearing HLA-DR molecules [1].

Beyond the HLA locus, genome-wide association studies have identified over 100 non-HLA risk loci. The most clinically significant include PTPN22 (encoding the lymphoid-specific phosphatase Lyp, which modulates T- and B-cell activation thresholds), STAT4 (a transcription factor in the IL-12 and interferon signalling pathway), CTLA4, IRF5, and TNFAIP3 (encoding A20, a negative regulator of NF-κB). Collectively, non-HLA loci account for approximately 15–20% of total genetic variance in RA susceptibility, with the remainder attributed to gene-environment interactions and stochastic epigenetic events [4].

3.1.2 Environmental Triggers

Cigarette smoking is the most robustly established environmental risk factor for RA, particularly for ACPA-positive disease. Smoking induces peptidyl arginine deiminase (PAD) enzyme activity in pulmonary macrophages and neutrophils, promoting citrullination of proteins such as fibrinogen, vimentin, and alpha-enolase in the lung—a mucosal site where loss of immune tolerance may first occur. The relative risk of ACPA-positive RA among heavy smokers carrying the SE reaches 40-fold relative to non-smoking SE non-carriers, exemplifying gene-environment synergy [3].

Oral dysbiosis has emerged as a second major environmental driver. Porphyromonas gingivalis, the principal periodontal pathogen, uniquely expresses a bacterial PAD enzyme (PPAD) that citrullinates bacterial and host proteins, potentially driving production of ACPAs that cross-react with articular self-antigens. Epidemiological data confirm that periodontitis increases RA risk (OR 1.4–2.0), and treatment of periodontitis reduces RA disease activity scores. Prevotella copri colonisation of the gut, observed at elevated frequency in early RA and pre-RA patients, may induce Th17 responses relevant to synovial inflammation [3].

Additional environmental factors include silica dust (occupational exposure, OR ≈ 3.0 in miners and construction workers), obesity (via adipokine-mediated immune activation), vitamin D insufficiency, and sex hormones (explaining the female predominance and disease activity fluctuations during pregnancy and menopause).

3.1.3 Epigenetic Mechanisms

Epigenetic modifications—DNA methylation, histone acetylation/methylation, and non-coding RNA regulation—provide a mechanistic bridge between environmental exposures and sustained alterations in gene expression in RA. Genome-wide methylation studies of RA synovial fibroblasts (RASFs) have identified widespread hypomethylation at inflammatory gene loci (IL-6, MMP1, MMP13, CXCL12) relative to osteoarthritis and healthy controls, conferring an intrinsically activated, invasion-competent phenotype that persists even in the absence of lymphocytic stimulation [5]. MicroRNAs—particularly miR-146a (a negative regulator of NF-κB signalling) and miR-155 (promoting inflammatory macrophage polarisation)—are dysregulated in RA peripheral blood and synovial tissue, and are under active investigation as both biomarkers and therapeutic targets.

3.2 Pathogenesis of Rheumatoid Arthritis

3.2.1 Pre-Clinical Autoimmunity and the Mucosal Origin Hypothesis

The contemporary model of RA pathogenesis positions autoimmunity initiation at mucosal surfaces—principally the lung and oral cavity—years before articular symptoms emerge. In

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genetically susceptible individuals exposed to environmental triggers, citrullinated neo-antigens arise at these sites, are taken up by dendritic cells and macrophages, and are presented to $CD4^+$ T cells via SE-bearing HLA-DR molecules. This interaction promotes the generation of ACPA-producing B cells and long-lived plasma cells. ACPAs (predominantly against citrullinated fibrinogen, vimentin, α-enolase, and collagen II) and rheumatoid factor (IgM anti-IgG Fc) may be detectable in serum 3–10 years before the onset of clinical arthritis [2].

3.2.2 Synovial Inflammation and Pannus Formation

Once RA transitions to the clinically apparent phase, the synovial membrane becomes the principal site of immunopathology. The normal synovium, a two-to-three cell layer lining membrane, undergoes dramatic expansion to a multi-layered hyperplastic tissue (pannus) infiltrated by T cells, B cells, plasma cells, macrophages, neutrophils, and mast cells. Synovial fibroblasts (FLS, or RASFs in the RA context) acquire an aggressive, activated phenotype characterised by upregulation of Toll-like receptors (TLR2, TLR4), matrix metalloproteinases (MMP-1, MMP-3, MMP-13), and anti-apoptotic proteins (Bcl-2, Bcl-xL), enabling them to invade and degrade cartilage and bone at the cartilage-pannus junction [5].

The synovial microenvironment is maintained by a complex, self-amplifying cytokine network. TNF-α, produced predominantly by synovial macrophages, activates NF-κB in FLS and endothelial cells, inducing further cytokine production, adhesion molecule upregulation (VCAM-1, ICAM-1), and angiogenesis that sustains cellular infiltration. IL-6, signalling through membrane-bound (cis) and soluble receptor (trans)-mediated pathways, drives acute-phase reactant synthesis (CRP, fibrinogen), Th17 differentiation, osteoclast activation, and systemic manifestations including anaemia of chronic disease and fatigue [6].

IL-17A, produced by Th17 cells expanded under the influence of IL-6, IL-21, and IL-23, synergises with TNF-α to amplify RASF activation and is a key driver of neutrophil recruitment into the synovial fluid. GM-CSF promotes macrophage survival and differentiation. The complement system, activated locally by immune complexes containing ACPAs and rheumatoid factor, generates anaphylatoxins (C3a, C5a) that further promote mast cell and neutrophil activation. Together, these pathways sustain a self-amplifying inflammatory loop that, in the absence of therapeutic intervention, results in progressive articular destruction.

3.2.3 Bone and Cartilage Destruction

Articular bone erosion in RA is mediated primarily by osteoclasts, which differentiate from monocyte precursors under the influence of RANKL (receptor activator of NF-κB ligand) expressed on activated T cells, FLS, and osteoblasts, and of M-CSF. TNF-α and IL-17 upregulate synovial RANKL expression, providing a direct mechanistic link between cytokine-driven inflammation and bone resorption [4]. Cartilage degradation results from both direct FLS invasion (via MMPs and cathepsins at the cartilage-pannus junction) and from chondrocyte-mediated self-destruction driven by pro-inflammatory cytokines that suppress proteoglycan synthesis while inducing aggrecanase and MMP expression. The net result is irreversible loss of articular cartilage volume that correlates with functional disability.

Table 1. Key cytokines in RA pathogenesis and their therapeutic targets.

Cytokine	Principal Source	Key Pathogenic Role	Therapeutic Targeting Agent
TNF-α	Synovial macrophages, FLS	NF-κB activation, angiogenesis, bone erosion	Adalimumab, Etanercept, Infliximab, Certolizumab, Golimumab
IL-6	Macrophages, FLS, T cells	Th17 differentiation, acute-phase response,	Tocilizumab, Sarilumab (IL-6R); Sirukumab (IL-6)

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		osteoclastogenesis	
IL-17A	Th17 cells, neutrophils, mast cells	FLS activation, neutrophil recruitment, bone loss	Secukinumab, Ixekizumab (IL-17A)
IL-1β	Macrophages, neutrophils	Cartilage catabolism, fever, pain sensitisation	Anakinra (IL-1Ra); Canakinumab (IL-1β)
GM-CSF	T cells, FLS, macrophages	Macrophage differentiation, dendritic cell activation	Mavrilimumab (anti-GM-CSFRα)
RANKL	T cells, FLS, osteoblasts	Osteoclastogenesis, bone erosion	Denosumab (RANKL)

FLS: fibroblast-like synoviocytes; IL-6R: IL-6 receptor; NF-κB: nuclear factor-kappa B; RANKL: receptor activator of NF-κB ligand; IL-1Ra: interleukin-1 receptor antagonist.

3.3 Treatment of Rheumatoid Arthritis

3.3.1 Treat-to-Target Strategy and Clinical Monitoring

The 'treat-to-target' (T2T) paradigm, formally established by international consensus and endorsed by EULAR and ACR guidelines, specifies that therapy should be adjusted at regular intervals (every 1–3 months) until a pre-specified target—clinical remission (DAS28 < 2.6; Boolean remission criteria) or, where remission is not achievable, low disease activity (DAS28 < 3.2)—is attained and sustained [7]. Application of T2T principles has been demonstrated in multiple randomised trials to reduce radiographic progression and functional disability significantly compared with routine care, establishing it as the cornerstone of contemporary RA management.

3.3.2 Conventional Synthetic DMARDs

Methotrexate (MTX), typically initiated at 7.5–15 mg/week (oral or subcutaneous) and escalated to 20–25 mg/week as tolerated, remains the anchor drug of RA therapy due to its favourable efficacy-to-toxicity profile, cost-effectiveness, and decades of clinical experience. MTX exerts its anti-inflammatory effects primarily through intracellular accumulation of methotrexate polyglutamates, which inhibit dihydrofolate reductase and multiple folate-dependent enzymes involved in purine biosynthesis and methionine cycling, ultimately suppressing T- and B-cell proliferation and reducing TNF-α, IL-1β, and IL-6 production. Leflunomide (10–20 mg/day), an inhibitor of dihydroorotate dehydrogenase (DHODH) in the pyrimidine synthesis pathway, and hydroxychloroquine (200–400 mg/day) are used as monotherapy in mild disease or in combination (triple therapy: MTX + leflunomide + hydroxychloroquine) for moderate disease [7].

3.3.3 Biological Disease-Modifying Antirheumatic Drugs (bDMARDs)

For patients with moderate-to-severe RA who have an inadequate response to MTX monotherapy, international guidelines recommend addition of a bDMARD. Five mechanistic classes are currently approved:

TNF inhibitors (TNFi): Adalimumab, etanercept, infliximab, certolizumab pegol, and golimumab represent the most widely used bDMARDs globally. In combination with MTX, TNFi achieve ACR50 responses in 50–60% of patients at 12 weeks and significantly reduce radiographic progression. Etanercept (a soluble TNF receptor fusion protein) and the pegylated anti-TNF Fab fragment certolizumab lack an Fc region, potentially reducing complement- and FcγR-mediated effector functions and improving safety in specific patient subgroups, including pregnant women [2].

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IL-6 receptor antagonists: Tocilizumab and sarilumab block the IL-6Rα subunit, preventing both cis- and trans-signalling by IL-6. They are uniquely effective in seronegative RA and in patients with prominent systemic features (elevated CRP, fatigue, anaemia), and are the only bDMARDs demonstrated to be non-inferior to TNFi as monotherapy (without MTX), making them valuable for patients intolerant to MTX [6].

B-cell depletion: Rituximab, a chimeric anti-CD20 monoclonal antibody, depletes B cells in a CD20-dependent manner. Given as two 1,000 mg intravenous infusions separated by two weeks, rituximab is particularly effective in ACPA/RF-positive RA, may preferentially benefit patients with high ACPA titres, and is the preferred bDMARD in patients with a history of lymphoma or at elevated risk of serious infection with TNFi [2].

T-cell co-stimulation blockade: Abatacept (CTLA4-Ig fusion protein) competitively inhibits CD80/CD86 binding to CD28 on T cells, blocking the co-stimulatory second signal required for full T-cell activation. Its efficacy is comparable to TNFi in MTX-IR patients, and it exhibits a particularly favourable safety profile in patients with chronic infections or interstitial lung disease, which is commonly associated with RA [7].

IL-1 blockade: Anakinra (recombinant IL-1Ra) and canakinumab (anti-IL-1β) are used in refractory RA, particularly in patients with macrophage activation syndrome complicating RA, though their role in routine RA management is more limited than TNFi or IL-6Ri.

3.3.4 Targeted Synthetic DMARDs: JAK Inhibitors

Janus kinase (JAK) inhibitors represent the most significant pharmacological innovation in RA since the introduction of TNFi. The JAK family (JAK1, JAK2, JAK3, TYK2) are intracellular non-receptor tyrosine kinases that transduce signals from over 50 cytokines and growth factors via the JAK-STAT signalling pathway. Because RA-relevant cytokines—including IL-6, IL-12, IL-15, IL-21, IL-23, GM-CSF, and interferons—signal through JAKs, JAK inhibition provides a broad-spectrum anti-inflammatory effect with the practical advantages of oral bioavailability and a rapid onset of action [8].

Four JAK inhibitors are currently approved for RA. Tofacitinib (5 or 10 mg twice daily), a pan-JAK inhibitor with preference for JAK1/3, was the first approved in 2012. Baricitinib (2 or 4 mg once daily), a selective JAK1/2 inhibitor, demonstrated superiority to adalimumab in the RA-BEAM trial for ACR20 response at 12 weeks (70% vs. 61%, $p < 0.05$) and is approved as first-line bDMARD-alternative therapy in several jurisdictions. Upadacitinib (15 mg once daily), a selective JAK1 inhibitor with greater JAK1/2 selectivity ratio than baricitinib, has shown numerically superior efficacy to adalimumab in the SELECT-COMPARE trial. Filgotinib (200 mg once daily) is approved in Europe and Japan [8].

Safety monitoring for JAK inhibitors includes vigilance for herpes zoster reactivation (approximately threefold increased risk, mitigated by prior varicella vaccination), elevated lipid levels, mild anaemia, and elevated creatinine. Post-marketing cardiovascular safety data from the ORAL Surveillance trial demonstrated an elevated risk of major adverse cardiovascular events and venous thromboembolism with tofacitinib relative to TNFi in patients aged > 50 years with cardiovascular risk factors, leading to regulatory label updates; the cardiovascular risk profile of more selective JAK1 inhibitors is under ongoing evaluation [8].

Table 2. Comparative overview of approved RA treatment classes.

Drug Class	Representative Agents	Mechanism	Route / Frequency	ACR50 Response (%)*
csDMARD	Methotrexate, Leflunomide, HCQ	Purine / pyrimidine synthesis inhibition	Oral/SC; weekly / daily	30–45

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TNF inhibitor	Adalimumab, Etanercept, Infliximab	TNF-α neutralisation	SC or IV; biweekly – monthly	50–60
IL-6R antagonist	Tocilizumab, Sarilumab	IL-6 receptor blockade	IV/SC; weekly – monthly	48–56
B-cell depletion	Rituximab	Anti-CD20; B-cell lysis	IV; 2 × 1000 mg q6 months	41–51
T-cell co-stim. blockade	Abatacept	CD80/86-CD28 blockade	IV/SC; monthly / weekly	40–50
JAK inhibitor	Baricitinib, Upadacitinib, Tofacitinib	JAK1/2 or JAK1/3 inhibition	Oral; once or twice daily	54–70

** ACR50 response rates at 12–24 weeks in phase III trials vs. placebo + MTX background therapy. csDMARD: conventional synthetic DMARD; HCQ: hydroxychloroquine; SC: subcutaneous; IV: intravenous; IL-6R: IL-6 receptor.*

3.3.5 Emerging and Future Therapeutic Strategies

Several novel therapeutic approaches are under advanced clinical investigation. Selective targeting of the IL-17/IL-23 axis—already established in psoriatic arthritis and ankylosing spondylitis—is being evaluated in RA subtypes characterised by high Th17 signature. CAR-T cell therapy directed against CD19 has shown remarkable, treatment-free remission in a small series of refractory systemic autoimmune diseases including RA, representing a potential paradigm shift toward one-time curative intervention. Precision medicine platforms integrating synovial biopsy transcriptomics (defining pathotype: lymphoid, myeloid, fibroid) with serum proteomics are under development to match patients to the mechanistically appropriate bDMARD at first prescription, potentially eliminating the current 'trial-and-error' sequential biologic approach [2].

4. DISCUSSION

The findings of this review confirm that RA is a disease of remarkable pathophysiological complexity, in which genetic predisposition, environmental exposures, and epigenetic reprogramming converge to produce a self-sustaining autoimmune and inflammatory state centred on the synovial joint. Three conceptual integrations emerging from contemporary research deserve particular emphasis.

First, the mucosal origin hypothesis has fundamentally repositioned our understanding of RA as a systemic disease that is, at its inception, not a joint disease at all. The identification of ACPA-positive individuals with no clinical arthritis—so-called 'pre-RA'—who transition to clinical RA at rates of 10–30% per year, has created an unprecedented opportunity for preventive intervention. Pilot trials of hydroxychloroquine and abatacept in ACPA-positive, arthralgia-affected at-risk individuals have demonstrated delayed or prevented RA onset, establishing proof-of-concept for secondary prevention in autoimmune disease [3].

Second, the recognition that RASFs are not passive bystanders but active, autonomous drivers of cartilage invasion—capable of maintaining their aggressive phenotype independent of ongoing lymphocyte stimulation—has profound implications for treatment. Patients whose RA achieves clinical remission may continue to experience subclinical synovial fibroblast-mediated cartilage erosion, explaining the clinical observation that imaging-confirmed bone erosion progression can persist in patients meeting DAS28 remission criteria. Direct pharmacological

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targeting of RASF activation (e.g., via FAK inhibition, TLR4 antagonism, or epigenetic reprogramming) represents an underexplored but mechanistically compelling therapeutic direction [5].

Third, the JAK inhibitor class has provided the first direct pharmacological confirmation of the JAK-STAT pathway's centrality to RA pathogenesis in humans. The dose-dependent attenuation of multiple RA-relevant cytokine signals by selective JAK1 inhibition, combined with an oral route of administration and rapid onset of action within 1–2 weeks, offers practical and mechanistic advantages over parenteral biologics in appropriate patient populations. However, the cardiovascular and thromboembolic safety signals identified in the ORAL Surveillance trial have appropriately prompted regulatory caution and stratified prescribing recommendations, reinforcing the need for individualised benefit-risk assessment [8].

The role of the gut microbiome in RA pathogenesis merits separate discussion. Multiple studies have documented enrichment of Prevotella copri and depletion of butyrate-producing Lachnospiraceae in stool samples from early and established RA patients relative to healthy controls. Mechanistically, P. copri has been shown to stimulate Th17 responses and to encode proteins with molecular mimicry to RA-relevant autoantigens. Whether microbiome dysbiosis is a cause or consequence of RA—and whether microbiome-targeted interventions (dietary modification, faecal microbiota transplantation, synbiotics) can modify disease activity—remains under active investigation [3].

This review has several limitations inherent to its narrative design. Selection bias in source inclusion is possible, as systematic quantitative evidence synthesis was not performed. The primary literature base is dominated by studies conducted in European and North American populations, and the generalisability of etiological and pharmacogenomic findings to Central Asian populations—where HLA-DRB1 allele frequencies, microbiome composition, and lifestyle factors differ substantially—cannot be assumed. Dedicated epidemiological and clinical studies in Uzbekistan and the broader Central Asian region are both scientifically necessary and currently absent from the published literature.

5. CONCLUSION

Rheumatoid arthritis is a multifactorial autoimmune disease whose etiology reflects a complex interplay of HLA-encoded genetic susceptibility, environmental triggers acting principally at mucosal surfaces, and epigenetic reprogramming of synovial effector cells. Its pathogenesis is driven by ACPA-mediated autoimmunity, T- and B-cell orchestrated synovial inflammation, cytokine network amplification—dominated by TNF-α, IL-6, and IL-17—and RASF-mediated articular destruction via MMP secretion and RANKL-driven osteoclastogenesis.

Therapeutically, the introduction of targeted synthetic (JAK inhibitor) and biological (TNFi, IL-6Ri, rituximab, abatacept) DMARDs, embedded within the treat-to-target framework, has transformed RA outcomes: clinical remission is now achievable in 30–50% of patients, and radiographic progression has been substantially reduced. Nevertheless, approximately one in four patients remains refractory to multiple treatment lines, underscoring the necessity of precision medicine approaches that match molecular disease endotypes to mechanism-specific therapies.

Priority areas for future investigation include: (i) prospective validation of pre-RA prevention strategies in ACPA-positive at-risk cohorts; (ii) development and clinical validation of synovial pathotype-based treatment selection algorithms; (iii) elucidation of the causal role of the gut and oral microbiomes in RA initiation and perpetuation; (iv) long-term cardiovascular safety characterisation of JAK inhibitors with improved selectivity profiles; and (v) generation of population-specific epidemiological, genetic, and pharmacogenomic data for Central Asian and Uzbek patient cohorts.

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