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CLINICAL PROGNOSTIC ASPECTS OF THE DEVELOPMENT OF REACTIVE ARTHRITIS: A LITERATURE REVIEW

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This article reviews the clinical prognostic aspects of the development of ReA, in particular, the potential role of the microRNA (miR)-146a molecule in the pathogenesis of the disease.. In recent years, the role of miR-146a in modulating the anti-inflammatory immune response has been widely studied in a number of rheumatic diseases, including rheumatoid arthritis and osteoarthritis. However, the direct relationship between miR-146a and ReA has not yet been sufficiently studied. This review covers literature published between 2020 and 2026, and attempts are made to extrapolate potential mechanisms in the pathogenesis of ReA through the role of miR-146a in other types of arthritis. The etiology, pathogenesis, clinical manifestations, and current treatment methods of the disease are also reviewed.

Key words
reactive arthritis, miR-146a, microRNA, prognostic factors, HLA-B27, spondyloarthropathy, inflammation, cytokines, biomarkers, postinfectious arthritis.

In the 21st century, modern rheumatology has gained a lot of information in determining the basis of RA. It is known that the pathogenetic basis of RA lies in the autoimmune process with uncontrolled activation of the immune system, which leads to chronic inflammation of the connective tissue .Reactive arthritis (ReA) is an immune-mediated inflammatory disease that develops after an infectious process in the body, but in which the infectious agent is not detected in the joint fluid. The disease was first described in 1969 as "reactive arthritis", and in the following years many studies were conducted on its etiology, pathogenesis and clinical features. ReA belongs to the group of seronegative spondyloarthropathies and occurs most often in young men, it is associated with the HLA-B27 antigen. In the last decade, there has been increasing interest in the role of microRNA (miRNA) molecules in autoimmune and inflammatory diseases. In particular, miR-146a has been recognized as an important regulator in controlling the pro-inflammatory immune response. Changes in miR-146a expression and its interaction with inflammatory

cytokines (TNF-α, IL-6, IL-17) have been widely studied in diseases such as rheumatoid arthritis (RA) and osteoarthritis (OA). However, the role of miR-146a in the pathogenesis of ReA and its clinical prognostic significance have not been sufficiently studied to date.

The aim of this literature review is to study the clinical prognostic aspects of the development of ReA, in particular from the perspective of the potential role of the miR-146a molecule, and to conduct a comprehensive analysis based on the literature from 2020 to 2026. The analysis also considers the etiology, pathogenesis, clinical manifestations, and treatment methods of the disease. MicroRNAs (miRNAs) are small non-coding RNA molecules of approximately 22 nucleotides that regulate gene expression at the post-transcriptional level. In recent years, the role of miRNAs in the pathogenesis of autoimmune and inflammatory diseases has been intensively studied. In particular, miR-146a has been identified as one of the central regulators in the control of the pro-inflammatory immune response [1]. The role of miR-146a in rheumatoid arthritis. A number of studies have demonstrated the importance of miR-146a in the pathogenesis of rheumatoid arthritis (RA). A study by Tan et al. (2025) found that miR-146a expression was higher in peripheral blood Th17 cells of RA patients compared to healthy controls. In addition, miR-146a expression was positively correlated with the levels of inflammatory cytokines — TNF-α, IL-6 and IL-17. The expression of these cytokines was significantly reduced after transfection with miR-146a mimic, suggesting that miR-146a may function as a compensatory anti-inflammatory mechanism [2]. In a study conducted in an Egyptian population by Ali et al. (2024), the miR-146a (rs2910164C/G) polymorphism was found to be associated with the risk of developing RA. The authors assessed the miR-146a CG genotype as a risk factor for RA (OR = 2.190). Also, the expression of miR-146a was higher in RA patients compared to controls [3]. The role of miR-146a in osteoarthritis. In a study conducted in osteoarthritis (OA) chondrocytes by Cheleschi et al. (2025), the role of the lncRNA XIST/miR-146a axis in matrix degradation and apoptosis was investigated. In OA chondrocytes, miR-146a expression was decreased, while XIST was elevated. XIST silencing increased miR-146a expression, improved cell viability, and reduced apoptosis. This suggests that miR-146a may play a chondroprotective role [4]. Role of miR-146a in gout. A study by Song et al. (2026) found that Clostridium butyricum and its metabolites exert anti-gouty arthritis effects by regulating macrophage polarization through miR-146a. Decreased butyrate levels resulted in impaired miR-146a expression and imbalanced macrophage polarization. The SOCS7/JAK2-STAT3 signaling pathway was identified as an important mediator in the regulation of macrophage polarization

by miR-146a.Reactive arthritis usually develops 1-4 weeks after genitourinary or gastrointestinal infections.

Main etiological factors: Genitourinary infections: Chlamydia trachomatis (most common), Ureaplasma urealyticum, Neisseria gonorrhoeae (less common) Gastrointestinal infections: Campylobacter jejuni (most common), Salmonella enterica,Shigella flexneri,Yersinia enterocolitica and Y. pseudotuberculosis, Clostridioides difficile, Escherichia coli. Other etiological factors: Chlamydia pneumoniae (pulmonary infection), SARS-CoV-2 (COVID-19), HIV infection increases the risk of developing ReA. The clinical manifestations of ReA are divided into three main groups: articular, extraarticular and general symptoms. Peripheral arthritis: Manifested as asymmetric oligoarthritis, mainly affecting the large joints of the lower extremities (knees, ankles). The joints are painful, swollen and warm. Enthesitis: Inflammation of the attachment site of a tendon, ligament or joint capsule to the bone. Most often occurs at the attachment site of the Achilles tendon and plantar fascia to the calcaneus. Dactylitis: Also known as "sausage toe", it is manifested by complete swelling of the fingers. The classic triad of ReA (arthritis, conjunctivitis, urethritis) is seen in approximately one-third of patients. Ocular: Conjunctivitis (most common), anterior uveitis, keratitis Mucocutaneous: Circinar balanitis, keratoderma blennorrhagicum, oral ulcers. Urethritis, prostatitis, cervicitis Cardiac: Aortitis, aortic regurgitation, AV block. Neurological: Rarely, peripheral neuropathy. General symptoms: Fever, fatigue, weight loss. Genetic predisposition. The HLA-B27 antigen is found in 70-90% of patients with ReA. Persistence of bacterial antigens. Although the infectious agent cannot be cultured in the joint fluid in ReA, bacterial antigens (e.g., Chlamydia lipopolysaccharides) have been detected in synovial tissues and synovial fluid. The persistence of these antigens stimulates the immune response for a long time. Molecular mimicry. A cross-reactive immune response develops as a result of the similarity between bacterial antigens and the body's own tissues (e.g., articular cartilage). The inflammatory cascade and the potential role of miR-146a. As discussed above, miR-146a plays an important role in regulating the inflammatory response. In ReA, activation of TLRs by infectious agents results in the production of inflammatory cytokines (TNF-α, IL-1, IL-6, IL-17) via the NF-κB pathway. At the same time, miR-146a is induced and acts to limit inflammation by suppressing the IRAK1/TRAF6 pathway. Disruption of this mechanism, due to genetic predisposition or other factors, can lead to chronic inflammation. The treatment of ReA is based on a stepwise approach: Symptomatic treatment. NSAIDs: First-line treatment, started at a high dose and titrated to the lowest effective dose. Long-acting NSAIDs such as naproxen provide good compliance. Glucocorticoids: Used when NSAIDs fail to

respond or have contraindications. Intraarticular glucocorticoids in monoarthritis, systemic glucocorticoids in polyarthritis Genitourinary infections: Antibiotics are used in all patients with confirmed chlamydial infection. Gastrointestinal infections: Antibiotics are recommended for severe bacterial gastroenteritis, especially in immunocompromised patients. Long-term antibiotics (up to 6 months) are used by some experts, but the evidence base is mixed. DMARDs (disease-modifying antirheumatic drugs): Used in chronic ReA (symptoms >6 months) or severe disease.

Sulfasalazine, has the largest evidence base. Methotrexate: Used when there is no response to sulfasalazine. Biologics: TNF-α inhibitors (etanercept, adalimumab, infliximab) may be used in refractory cases. Treatment of extra-articular manifestations. Ocular: Topical glucocorticoids, dermatologic: Topical steroids and keratolytic, cardiac: Pacemaker for AV block, valve replacement for aortic regurgitation. ReA is usually self-limiting and symptoms resolve within 6-12 months. However, the recurrence rate is high. A small proportion of patients develop chronic arthritis. Poor prognostic factors include:HLA-B27 positivity,HIV infection,presence of the full ReA triad. Long duration of clinical symptoms,Non-response to NSAIDsThe relationship between miR-146a and arthritis. Studies conducted over the past 5 years have shown that miR-146a plays an important role in the pathogenesis of various types of arthritis. In rheumatoid arthritis, miR-146a expression is high and positively correlated with inflammatory cytokines (TNF-α, IL-6, IL-17). In osteoarthritis, miR-146a expression is reduced and this is associated with matrix degradation. In gout, disruption of miR-146a expression leads to an imbalance in macrophage polarization.Potential role of miR-146a in the pathogenesis of ReA. Although direct evidence is lacking, the above data suggest that miR-146a may play an important role in the pathogenesis of ReA. The inflammatory cascade that develops in response to infectious agents in ReA may be controlled by miR-146a. In particular:Activation of the TLR/NF-κB pathway leads to induction of miR-146aMiR-146a, in turn, suppresses IRAK1 and TRAF6, limiting inflammation,Disruption of this mechanism (genetic polymorphisms, persistent antigens) can lead to chronic inflammation. The importance of genetic polymorphisms. The miR-146a (rs2910164) polymorphism has been found to be associated with disease risk in RA. Similar associations may exist in ReA and may serve as a prognostic biomarker in the future. Evolution of treatment strategies. NSAIDs remain the first-line therapy in the treatment of ReA. Sulfasalazine and methotrexate are used in chronic cases. Biological drugs, in particular TNF-α inhibitors, are promising in refractory cases. MiR-146a-based therapies (e.g., miR-146a mimics or antagomiRs) may be explored as a novel treatment strategy in the

future.The clinical prognostic aspects of the development of reactive arthritis and the potential role of the miR-146a molecule were investigated through a literature review. Although the role of miR-146a in regulating the anti-inflammatory immune response has been widely studied in recent years in a number of rheumatic diseases, including rheumatoid arthritis, osteoarthritis, and gout, its role in reactive arthritis has not been sufficiently studied. The results of the analysis indicate that miR-146a is an important regulator in the inflammatory cascade, induced by the TLR/NF-κB pathway and acting as a negative feedback mechanism by suppressing IRAK1/TRAF6. A similar mechanism may be at work in the pathogenesis of ReA. The inflammatory response that develops after infection is controlled by miR-146a, and the disruption of this mechanism (due to genetic polymorphisms, persistent antigens, or other factors) leading to the transition to a chronic form of the disease has been discussed in many articles by scientists.

ReA is usually self-limiting and symptoms resolve within 6-12 months. Treatment is mainly symptomatic, with NSAIDs being the first-line drugs. In chronic cases, DMARDs such as sulfasalazine and methotrexate are used.

In the future, it was determined through a literature review that it would be appropriate to conduct studies in the following areas to study the relationship between miR-146a and ReA: to study the dynamics of miR-146a expression in ReA patients, to analyze the relationship between miR-146a polymorphisms and the risk of ReA, to evaluate the potential of miR-146a as a prognostic biomarker, and to test miR-146a-based therapeutic approaches in experimental models.

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