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REACTIVE ARTHRITIS: LITERATURE REVIEW, TARGET TREATMENTS IN THE ERA OF BIOLOGICS

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Abstract:
Reactive arthritis (ReA) is an autoimmune condition characterized by joint inflammation that typically arises following an infection, most commonly in the gastrointestinal or genitourinary tract. It is considered part of the broader spectrum of spondyloarthropathies, with hallmark symptoms including asymmetric arthritis, enthesitis, and dactylitis, often involving the lower limbs. The condition is triggered by bacterial infections, such as Chlamydia trachomatis, Salmonella, or Campylobacter, although the exact pathogenic mechanisms remain unclear. Reactive arthritis may manifest as acute, self-limiting inflammation, or progress to a chronic condition, leading to prolonged disability and joint damage in severe cases.[1]. This review explores the clinical presentation, pathophysiology, diagnostic criteria, and treatment strategies for ReA. Therapeutic interventions range from nonsteroidal anti-inflammatory drugs (NSAIDs) for pain management to disease-modifying antirheumatic drugs (DMARDs) and biologic agents like TNF inhibitors for persistent and severe cases. Recent advances in understanding the molecular mechanisms, particularly the role of HLA-B27 and cytokine dysregulation, offer new insights into potential therapeutic targets. Early diagnosis and appropriate management are crucial for preventing long-term complications and improving patient outcomes. This article also discusses emerging treatments and the challenges of managing ReA in the context of coexisting infections and chronic disease.[2].

Keywords: HLA-B27, Reactive arthritis, TNF inhibitors, JAK inhibitors.

Introduction

Reactive arthritis (ReA) is an inflammatory condition that occurs following an infection, typically in the gastrointestinal or genitourinary tract. Although the initial infection is typically resolved by the time arthritis develops, a maladaptive immune response continues, triggering inflammation primarily in the joints. ReA is classified under the group of **spondyloarthritides (SpA),** a family of disorders characterized by inflammation of the spine and peripheral joints, and is closely linked to the genetic marker **HLA-B27.** The pathogenesis of ReA is complex and involves a combination of genetic predisposition, microbial infection, and immune dysregulation. In this section, we will explore the intricate immunological processes and factors that contribute to the development and progression of ReA. **Genetic predisposition:** A critical component of ReA pathogenesis is the strong association with the HLA-B27 gene, a class I major histocompatibility complex (MHC) molecule. HLA-B27 is present in approximately 60-80% of patients with ReA, compared to 6-8% in the general population. However, not all individuals carrying this allele develop ReA, indicating that other factors such as infection and immune dysregulation also play significant roles. The exact mechanism by which HLA-B27 contributes to disease susceptibility is still debated. Several hypotheses have been proposed: 1)Misfolding Hypothesis: HLA-B27 has a tendency to misfold, leading to endoplasmic reticulum (ER) stress. This can activate the unfolded protein response (UPR), leading to inflammation. 2)Molecular Mimicry: HLA-B27 might present bacterial peptides that resemble self-antigens, leading to an autoimmune response where the immune system mistakenly attacks healthy joint tissues. 3)Abnormal Antigen Presentation: HLA-B27 may present certain bacterial antigens in an abnormal way, provoking a heightened immune response. **Microbial triggers:** The development of reactive arthritis is typically preceded by infections with certain Gram-negative bacteria. Common causative organisms include: Chlamydia trachomatis (genitourinary infections), Salmonella, Shigella, Yersinia, and Campylobacter (gastrointestinal infections). Although the infection is resolved, components of the bacterial pathogen persist in the body and act as chronic triggers for the immune system. These bacterial antigens are believed to be transported to the synovial fluid via blood or lymphatics. There, they are recognized by the immune system, stimulating chronic inflammation. Some bacterial proteins mimic human proteins, leading to cross-reactivity where the immune system mistakenly attacks both the bacterial antigen and the body's own tissues. Bacterial antigens or remnants can persist in synovial fluid, where they stimulate an ongoing immune response despite the clearance of the primary infection. Bacterial infections upregulate pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-17 (IL-17), and interleukin-6 (IL-6), which play central roles in driving inflammation in ReA. The immune response in ReA is primarily mediated by innate and adaptive immune cells that recognize and react to bacterial antigens. CD8+ T cells are critical for the cytotoxic response in the synovial fluid, recognizing bacterial antigens presented by HLA-B27. Th1 and Th17 responses are elevated in ReA, contributing to the pro-inflammatory environment by producing cytokines like

IFN-γ and IL-17. Macrophages and Dendritic Cells: These antigen-presenting cells (APCs) play an essential role by engulfing bacterial remnants and presenting them to T cells, perpetuating the inflammatory response. Neutrophils are recruited to the joints in response to pro-inflammatory cytokines. They release reactive oxygen species (ROS) and enzymes that cause tissue damage and amplify inflammation. Natural Killer (NK) Cells: NK cells are implicated in the early response to infection and their dysregulated activation may contribute to ongoing joint inflammation in ReA. [2,3]. Cytokines are crucial mediators of the inflammatory response in ReA. The dysregulation of pro-inflammatory cytokines leads to chronic inflammation, joint damage, and disease progression. Tumor Necrosis Factor-alpha (TNF-α): TNF-α is a master regulator of inflammation, promoting the recruitment of immune cells to the synovial joints and the production of other pro-inflammatory cytokines. Interleukin-17 (IL-17): IL-17, produced by Th17 cells, has emerged as a key player in autoimmune diseases, including ReA. It promotes the recruitment of neutrophils and enhances tissue inflammation. Interleukin-6 (IL-6): IL-6 promotes local inflammation and is responsible for inducing acute-phase responses and systemic effects such as fever and fatigue. Interleukin-23 (IL-23): IL-23 is involved in the differentiation and maintenance of Th17 cells, which are central to the IL-17-mediated inflammatory response. The TNF-α/IL-23/IL-17 axis is particularly critical in the pathogenesis of ReA and has become a target for biologic therapies such as TNF inhibitors and IL-17 inhibitors. [3,4]

In ReA, immune dysregulation is specifically localized in the synovium, the membrane lining the joints. Once bacterial antigens are introduced into the synovium, they are presented by synovial macrophages and dendritic cells, which activate CD4+ and CD8+ T cells. This leads to local inflammation characterized by the following processes: Synovial Hyperplasia: Prolonged inflammation causes the thickening of the synovial membrane, leading to the characteristic swelling and pain seen in ReA. Cartilage and Bone Damage: Persistent inflammation results in the activation of osteoclasts (cells that break down bone tissue) and damage to cartilage, potentially leading to joint erosion and deformities.[5]. The immune mechanisms involved in ReA are not confined to the joints. Extra-articular manifestations such as conjunctivitis, uveitis, and skin lesions are common, reflecting the systemic nature of the immune dysregulation. These manifestations are driven by the same immune pathways (e.g., TNF-α, IL-17) and often involve similar immune cells infiltrating extra-articular tissues. In many patients, ReA is self-limiting, but in 15-30% of cases, it becomes chronic or recurrent. The reasons for chronicity are not fully understood but may involve: Persistent Infection: In some cases, the causative pathogen may not be fully eradicated, allowing for ongoing antigen presentation and immune activation. Autoimmunity: Continued immune activation, possibly driven by molecular mimicry, may lead to an autoimmune process where the immune system attacks the body's own tissues long after the infection has been cleared. Genetic Factors: HLA-B27-positive individuals are more likely to develop chronic or recurrent ReA.[6]. A systematic literature search was conducted using PubMed, Scopus, and Cochrane databases for studies published from

2018 to 2024. The search terms included "Reactive Arthritis," "prevalence," "HLA-B27," "treatment," "biologics," and "DMARDs." Inclusion criteria were: 1.ReA diagnosed according to established clinical criteria. 2.Studies including at least 30 patients with follow-up of 6 months or more. 3.Reported outcomes on treatment efficacy or genetic associations. A random-effects model was applied due to expected heterogeneity among studies. Prevalence rates, relative risks (RR), and odds ratios (OR) were calculated with 95% confidence intervals (CIs). Heterogeneity was quantified using I^2 statistics, with values >50% indicating substantial heterogeneity.

Results

Prevalence of ReA following infection. Eight studies evaluated the prevalence of ReA following infection with common pathogens. The pooled prevalence of ReA was **11.6% (95% CI: 9.2–14.4%)** across 7,582 patients who experienced enteric or genitourinary infections. The breakdown by pathogen was:

- **Chlamydia trachomatis: Prevalence of 7.4% (95% CI: 5.8–9.3%) .**
- **Salmonella spp.: Prevalence of 12.3% (95% CI: 9.0–16.5%) .**
- **Shigella spp.: Prevalence of 10.2% (95% CI: 7.5–13.5%) .**
- **Campylobacter spp.**: Prevalence of **14.1% (95% CI: 11.0–17.8%).**[7,8,9]

Heterogeneity was moderate (I^2 = 56%) due to the differences in the study populations and geographical variability. Six studies investigated the association between **HLA-B27** and ReA. The pooled estimate for the frequency of HLA-B27 positivity in ReA patients was **72% (95% CI: 68–77%),** compared to 8% in the general population . HLA-B27 positivity was associated with a significantly increased risk of chronicity or recurrence (RR = 2.5, 95% CI: 2.0–3.1) . Heterogeneity across studies was low (I^2 = 37%).[7,8,9]. Four studies evaluated the efficacy of NSAIDs in the acute management of ReA. Pooled data showed that NSAIDs provided symptomatic relief in **76% (95% CI: 71–82%)** of patients, although **40% (95% CI: 34–47%)** experienced recurrence upon discontinuation of NSAID treatment . The effectiveness of NSAIDs in preventing chronicity was limited, and recurrence rates were higher in patients with HLA-B27 positivity. [9]**.** Five studies assessed the role of DMARDs, particularly methotrexate and sulfasalazine, in chronic or severe ReA. Pooled results showed a **60% remission rate (95% CI: 53–67%)** after 6 months of DMARD therapy. DMARDs were associated with a relative risk reduction for long-term joint damage (RR = 0.68, 95% CI: 0.56–0.83) compared to NSAIDs alone . Heterogeneity was moderate (I^2 = 45%).[7,8,9,10]. Seven studies evaluated biologic agents, mainly **TNF-α inhibitors** (etanercept, infliximab), in patients with refractory ReA. The response rate for biologic therapy was **68% (95% CI: 61–75%)**, with a significant reduction in inflammatory markers (CRP and ESR). Biologics were more effective in HLA-B27-positive patients compared to HLA-B27-negative patients (OR = 2.1, 95% CI: 1.4–3.2) . Heterogeneity was substantial (I^2 = 61%), likely due to varying biologic agents and patient characteristics.[10]

Discussion. Diagnosis and management

- Recognition of the rheumatological clinical picture
- Evidence of genitourinary infection and identification of genital pathogens
- Research on the specificity and activity of arthritis

Management

- Information, education, care and testing of partners and other STIs
- Further investigations:

Systematically: Synovial fluid analysis, screening for other STIs, biological markers of inflammation, blood count, urinalysis.

According to the case: Imaging, HLA-B27, electrocardiogram, ophthalmologic consultation, exclusion tests for other rheumatic diseases, blood cultures, stool cultures, echocardiography.

Treatment:

Arthritis, enthesitis:

- First line:

Rest, physical treatment (cryotherapy)

NSAIDS

Intra-articular corticosteroid therapy/enthesis

- Second line (moderate to severe arthritis, first line failure)

Systemic corticosteroids

DMARDs (sulfasalazine, methotrexate)

Biological anti-TNF agents (place to be specified)

Antibiotics: standard treatment of active infection; prolonged antibiotic treatment not established

Cutaneous, mucosal and ophthalmological damage:

- Specific dermatological and ophthalmological treatment.[10,11].

Discussion and research gaps in Reactive arthritis

Reactive arthritis (ReA) is a clinically heterogeneous disease that poses significant challenges in both diagnosis and management. This meta-analysis consolidates current knowledge on its prevalence, risk factors, and treatment efficacy, but it also highlights several gaps in the literature that warrant further investigation. These gaps are particularly crucial for improving clinical outcomes and optimizing treatment strategies.

Genetic predisposition beyond HLA-B27. While HLA-B27 is a well-established genetic marker associated with ReA, its presence does not explain the entire disease spectrum. Approximately 20-30% of patients with ReA are HLA-B27 negative, and these patients may exhibit different disease courses and responses to treatment is needed to explore the genetic factors that predispose individuals to ReA in the absence of HLA-B27,

potentially involving genome-wide association studies (GWAS) to identify novel susceptibility loci.[13,14]

Pathogen-specific disease mechanisms. Reactive arthritis is commonly triggered by infections with *Chlamydia trachomatis*, *Salmonella*, *Shigella*, *Campylobacter*, and *Yersinia*. However, the exact mechanisms by which these pathogens trigger an aberrant immune response remain poorly understood. Emerging evidence suggests that molecular mimicry, persistent infection, and altered gut microbiota may play roles in the pathogenesis . Differences in to these pathogens may also affect disease severity and chronicity, but detailed immunological studies remain limited.[13,14]

Chronicity and recurrence. A major challenge in ReA is the transition from acute, self-limiting arthritis to chronic, recurrent disease. Approximately 30-50% of patients with ReA develop a chronic form, often associated with HLA-B27 positivity . The factors that predict chronicic, immunological, and environmental factors, are not well defined. Additionally, the long-term outcomes of patients who develop chronic ReA are not well documented, especially in terms of joint damage, quality of life, and disability.[12,13,14]

Optimizing treatment strategies. The treatment of ReA often begins with NSAIDs for acute symptoms, followed by DMARDs or biologics in chronic or refractory cases. While NSAIDs provide symptomatic relief, they do not prevent chronicity. DMARDs, such as methotrexate and sulfasalazine, have shown moderate efficacy, but evidence for their long-term benefits remains limited . Biologics, particularly TNF inhibitors, have demonsicacy in chronic ReA, but data on other biologic agents, such as IL-17 or JAK inhibitors, are sparse. Moreover, there is limited guidance on when to escalate trebiologics, especially in HLA-B27-negative patients, who may respond differently. Given the expense and side effects of biologic therapy, understanding the best timing and patient selection criteria for these treatments is critical.[15,16]

Antibiotics and preventive therapies. Prophylactic antibiotics in preventing ReA after bacterial infections remain a controversial area. Recent studies on the use of antibiotics in the treatment of Chlamydia-induced ReA suggest mixed results . The role of antibiotics, especially in preventing long-term sequelaeshed. Furthermore, understanding which patients may benefit from preventive therapies or early interventions remains unclear.[17]

Biomarkers for disease activity. Currently, there are no reliable biomarkers that can predict the onset, severity, or recurrence of ReA. While inflammatory markers such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are commonly used, they lack specificity and sensitivity for ReA. Advances in understanding the molecular pathways

of spondyloarthritis could help identify novel biomarkers for disease activity, treatment response, and prognosis.

Impact of lifestyle and environmental factors There is limited research on the role of lifestyle factors (such as diet, smoking, and exercise) and environmental exposures in the development and progression of ReA. These factors have been implicated in other forms of spondyloarthritis and may also influence outcomes in ReA. The gut microbiome, for instance, has gained attention as a potential modulator of inflammatory diseases, and its role in ReA should be explored.

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