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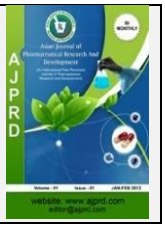

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Review Article

Role of Microsponge Drug Delivery Systems In Improving Therapeutic Outcomes In Rheumatoid Arthritis

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A B S T R A C T

Rheumatoid arthritis (RA) is a chronic systemic autoimmune inflammatory disorder primarily affecting synovial joints and leading to progressive joint destruction, disability, and reduced quality of life. In addition to joint involvement, RA is associated with multiple extra-articular manifestations involving the cardiovascular, pulmonary, ocular, and nervous systems. The etiology of RA is multifactorial, involving genetic predisposition, environmental factors such as smoking, and immune dysregulation. This review article provides a comprehensive overview of rheumatoid arthritis, including its historical background, etiology, pathophysiology, clinical manifestations, diagnostic criteria, and current therapeutic strategies. Special emphasis is given to the role of cytokines, immune cells, autoantibodies, and inflammatory mediators in disease progression. The review also discusses conventional and biological disease-modifying antirheumatic drugs (DMARDs), their mechanisms of action, and associated adverse effects. Understanding the complex pathogenesis and evolving treatment options of RA is essential for improving disease management, minimizing complications, and enhancing patient outcomes.

KEYWORDS: Rheumatoid arthritis; Autoimmune disease; Inflammation; Pathophysiology; DMARDs; Biological therapy

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INTRODUCTION

Rheumatoid Arthritis (RA)

Rheumatoid arthritis (RA) is defined as a systemic autoimmune pathology associated with a chronic inflammatory process, which can damage both joints and extra-articular organs, including the heart, kidney, lung, digestive system, eye, skin and nervous system [1,2]. Numerous types of arthritis have been investigated and described in order to classify them into non-inflammatory arthritis (osteoarthritis) and inflammatory arthritis caused by crystal deposition (pseudogout, basic calcium phosphate disease, gout), by bacterial and viral infections (Staphylococcus aureus, Neisseria gonorrhea, complications of Lyme disease, Parvovirus, Enterovirus) or by autoimmune processes.

Although a number of biomolecular mechanisms have been proposed, the etiology of RA is not yet fully elucidated, a current hypothesis being that dysregulated citrullination leads to the production of anti-citrullinated protein antibodies (ACPAs) [3,4]. The evolution of RA is fluctuant with episodic exacerbations and in the absence of optimal treatment symptoms gradually worsen until the joints are irreversibly damaged and physical and psychological functioning is affected [5]. Moreover, RA complications and comorbidities reduce the life expectancy of patients by a few years [6].

Existing statistical analysis and interpretation of quantitative data show that RA represents not only a medical feature, but also a public health issue. The most common medical cause of mobility-related functionality loss among United States (US) adults is arthritis [7,8]. Furthermore, several health

economic studies have measured the economic burden of RA and, and as a result, have demonstrated that the costs of preventing RA by reducing the risk factors or treating incipient cases are much lower than those generated by hospitalization and surgeries[9,10].

Origins of rheumatoid arthritis

Although intermittent case series were subsequently reported, the disease was not fully recognized until it was defined by Garrod in 1859. He named it 'rheumatoid' arthritis to distinguish it from the two well-known forms arthritis, rheumatic fever and gout. By the early 20th century, RA was viewed as separate from osteoarthritis ('arthritis deformans'). In 1957, Charles Short described RA definitively and clearly set it apart as a defined clinical entity distinct from the seronegative spondyloarthropathies, crystal-induced disease, osteoarthritis, systemic lupus erythematosus, and many other conditions.

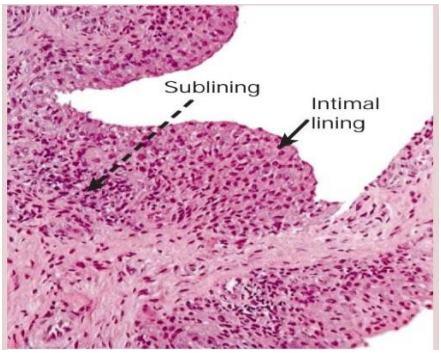

Figure 23: Synovial histology in rheumatoid arthritis.

Synovial histology in rheumatoid arthritis. A photomicrograph (magnification x 200) shows the redundant folds of the synovial lining and intense infiltration with inflammatory cells in RA. The intimal lining layer (solid arrow) is hyperplastic, with multiple layers of cells compared with a normal lining that is one or two cell layers deep. The sublining region (dashed arrow) is marked by accumulation of mononuclear cells such as CD4+T cells, macrophages and B cells[11,12]

Etiology

- The etiology of RA has a significant basis in genetics. It is thought to result from the interaction between patients' genotypes and environmental factors[13].
- The risk of developing rheumatoid arthritis has been associated with HLA-DRB1 alleles: HLA-DRB1*04, HLA-DRB1*01, and HLA-DRB1*10. These HLA-DRB1 alleles contain a stretch of a conserved sequence of 5 amino acids referred to as the "shared epitope" (SE) in the third hypervariable region of their DRB1 chain, which has been associated with the risk of developing RA[14-17].
- Some genetic polymorphisms are associated with RA in different ethnic groups [16,18].
- Cigarette smoking is the strongest environmental risk factor associated with rheumatoid arthritis. Studies have shown in anti-citrullinated protein antibody (anti-CCP) positive individuals, there is an interaction between the shared epitope (SE) and smoking that increases the risk of RA[19-25]
- Other environmental triggers may play a role as a trigger for RA, these include silica, asbestos, textile dust, and P gingivalis may be entered through mouth ,lungs and gut[26].
- Changes in the composition and function of the intestinal microbiome have been related to rheumatoid arthritis as well[23].

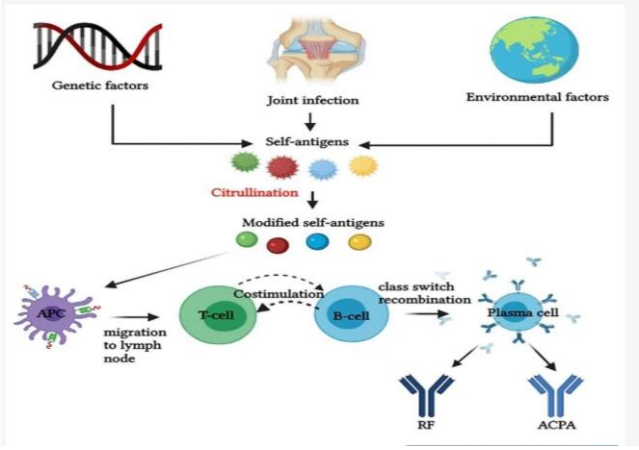

Figure 24: Immunological processes in the pre-RA phase. ACPA, anti-citrullinated protein antibodies; APC, antigen-presenting cells; RF, rheumatoid factor [27]

Pathophysiology

- RA risk is influenced by a genetic predisposition, environmental factors, or a combination of both. It is clear that immune cells, such as lymphocytes, neutrophils,and macrophages, play an important role in the pathophysiology of RA [28].
- Within the synovium of RA patients are macrophages and T cells that produce cytokines which promote inflammation and cell migration.
- Cytokines tumor necrosis factor-α (TNF-α),interleukin-1 (IL-1), and interleukin-6 (IL-6), produced by macrophages, and cytokine interleukin-17 (IL-17), produced byCD4+ cells, are commonly involved in the inflammatory response and subsequent cartilage destruction.
- These cytokines activate synoviocytes and cause them to proliferate, creating proteases in the synovial fluid, which lead to the breakdown of cartilage and hypertrophied synovial tissue, known as pannus [29].
- Pannus can be further exacerbated by angiogenesis. The additional blood supply to invaded cartilage and bone allows immune cells to infiltrate the joints, worsening the synovial hyperplasia [28].
- Cytokines also combine with receptor activator of nuclear factor kappa-β ligand (RANKL) to stimulate osteoclast activity, which leads to bone erosion. The expression of RANKL is also affected by T cells [30].
- Synovial dendritic cells stimulate immune response by attracting T lymphocytes and activating antigen-specific T cells and, in turn, B cells. In this positive feedback loop, activated Bcells stimulate CD4+ T cells, producing more cytokines [31,32].
- B cell proliferation can also lead to the creation of plasma cells,which produce autoantibodies, including rheumatoid factor (RF)and anti-citrullinated protein antibodies (ACPAs) [33].
- These autoantibodies infiltrate the joint through newly developed bloodvessels and are currently used in the diagnosis and prognosis of RA [34].

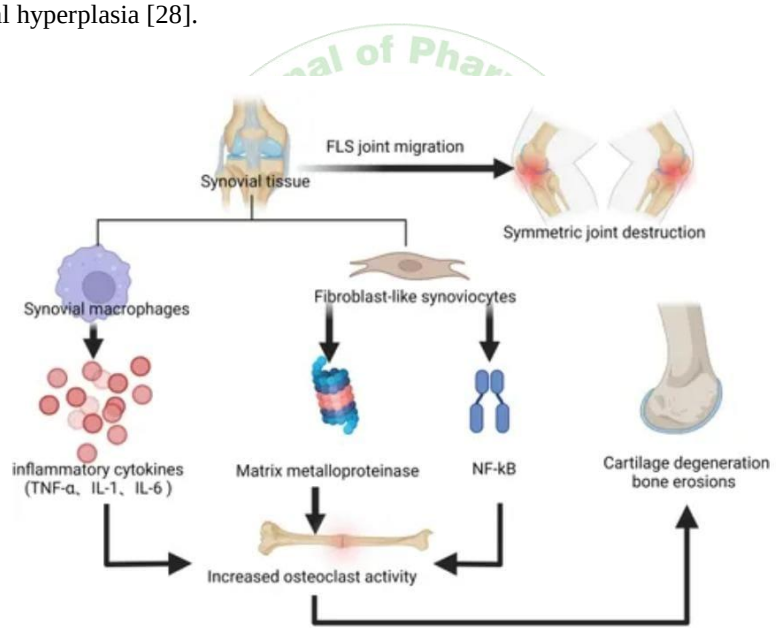

Figure 25: The immune processes that occur in the joint synovium and synovial fluid, leading to the progress of bone erosion and cartilage degeneration [35,36]

Signs and symptoms

- The most common and predominant symptoms include joint pain and swelling. Initial joint involvement is typically in the small joints of the hands and feet, followed by larger joints. One of the hallmarks is stiffness, particularly morning stiffness[37].
- Usually, the onset of symptoms is slow and insidious; however, in some cases, an episodic pattern of symptoms can be seen and is defined as palindromic rheumatism[38]
- Although multiple small joint involvements are a frequent feature, some patients may present with monoarticular and extra articular involvement (lungs).
- typical signs and symptoms of carpal tunnel syndrome
- The classical physical findings of ulnar deviation, metacarpophalangeal joint subluxation, ulnar deviation, swan neck deformity, Boutonniere deformity, and the "bowstring" sign are seen in advanced chronic disease.
- Other findings in the later stages of RA include a reduced range of motion in the shoulders, elbows, and knees. In the feet, hallux valgus is common, as well as other toe deformities[39].
- Rheumatoid nodules are the most common extra articular manifestations of RA[40]. They are commonly found on pressure points such as the olecranon but may also occur over the joints of the hands and feet, the patella, and the Achilles tendons.

- Interstitial lung disease (ILD) affects 5 to 16% of patients with RA and is associated RA specific auto antibodies and increased mortality[41-43].
- Ophthalmological manifestations include secondary Sjogren syndrome with dry eyes and also dry mouth[44].
- Similarly, Felty syndrome, which is the combination of long-standing seropositive RA (including RF and ANA), leukopenia, and splenomegaly, is rarely seen today.
- These patients may have chronic non-healing ulcers and an increased risk of bacterial infection. Vasculitis involving both medium and small-sized blood vessels can also be seen as a presenting symptom of RA.[45]

Diagnosis and assessment

The presence of tenosynovitis, eg, at the flexor carpiulnaris tendon, and subclinical synovial inflammation can be detected by imaging with color Doppler sonography or gadolinium-enhanced magnetic resonance imaging, which demonstrate expansion of intra-articular soft tissue or hypervascularization of the synovial membrane.

No diagnostic criteria exist for RA [46,47]

The classification of RA requires presence of at least 1clinically swollen joint and at least 6 of 10 points from a scoring system (Table 1).

Table.1: Rheumatoid arthritis classification

Category	Criteria	Points
Joint Distribution (0–5 points)	1 large joint	0
	2–10 large joints	1
	1–3 small joints (large joints not counted)	2
	4–10 small joints (large joints not counted)	3
	>10 joints (≥1 small joint)	5
Serology (0–3 points)	Negative RF and negative ACPA	0
	Low positive RF or low positive ACPA	2
	High positive RF or high positive ACPA	3
Symptom Duration (0–1 point)	< 6 weeks	0
	≥ 6 weeks	1
Acute Phase Reactants (0–1 point)	Normal CRP and normal ESR	0
	Abnormal CRP or abnormal ESR	1

Joint involvement based on physical examination or imaging by ultrasound or magnetic resonance imaging contributes up to 5 points; elevated levels of RF, ACPAs, or both provides 2 additional points (or 3 points with levels >3 times the upper limit of normal); and elevated acute phase reactant (APR) response, such as increased CRP level or erythrocyte sedimentation rate, and duration of symptoms (-6 weeks) provide 1additional point each. These 2010 criteria have a sensitivity of 82% and specificity of 61%. Sensitivity of the new classification criteria was 11% greater and specificity 4% lower compared with the 1987 criteria[48].

Clinical management and treatment:[49-62]

Category	Drugs	Mechanism	Side effects
Symptomatic treatment: 1.NSAIDs	• Naproxen, • ibuprofen	Inhibition of COX enzyme	Bleeding, GI ulcerations, renal failure, rashes, confusion …etc
2.Glucocorticoids (GCs):	• celecoxib, • valdecoxib	Inhibition of COX-II enzyme	Nausea,Diarrhea..Etc
	• hydrocortisone • prednisolone • dexamethasone	Immune-suppressor	Long Term Side Effects Include , Weight Gain, Myalgia, Diabetes, Bone Thinning
Disease modifying anti-rheumatoid drugs (DMARDs)treatment: 1.Conventional DMARDs: 2.Biological DMARDs:	• Methotrexate • Leflunomide • Hydroxy Chloro- • Quine • Sulfasalazine	Non-targeted suppression of the over reactive Immune response	Diarrhoea, Nausea, Liver Damage, Thrombocytopenia, Leukopenia…Etc

	• Etanercept • Infliximab • Adalimumab • Golimumab	Inhibition of TNF-alpha	Herpes zoster, Hepatitis-B/C, Bone marrow - Suppression, Hepatotoxicity, Skin cancers …etc.
	• Anakinra • Tocilizumab	Inhibition of interleukins	
	• Rituximab	Depletion of B-cells	
	• Abatacept	Antagonism of T-cells	

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