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Drug treatment of Rheumatoid arthritis

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ABSTRACT

Rheumatoid arthritis (RA) is a chronic autoimmune disorder marked by progressive joint inflammation that results in the destruction of cartilage and bone. With a global prevalence of 0.5-1%, the disease exhibits a significant female predominance, occurring at a 2-3:1 ratio compared to males. The pathogenesis of RA involves a complex interplay of genetic factors, particularly HLA-DRB1 alleles, environmental triggers such as smoking, and dysregulated immune responses. Diagnosis relies on a combination of clinical evaluation, serological testing for rheumatoid factor (RF) and anti-citrullinated peptide antibodies (ACPAs), and advanced imaging techniques including X-ray, ultrasound, and MRI.

Contemporary management of RA follows a treat-to-target paradigm, with the primary goal of achieving remission or low disease activity. The therapeutic arsenal includes nonsteroidal anti-inflammatory drugs (NSAIDs) for symptomatic relief, corticosteroids as short-term bridge therapy, and disease-modifying antirheumatic drugs (DMARDs) as foundational treatment. DMARDs encompass conventional agents like methotrexate, targeted synthetic drugs such as JAK inhibitors, and biologic therapies including anti-TNF and anti-IL6 agents. First-line treatment typically begins with methotrexate, with escalation to combination therapies or biologics in cases of inadequate response. Regular monitoring every three months is essential to prevent irreversible joint damage and functional disability.

Although RA remains incurable, advancements in treatment have substantially improved patient outcomes. Future directions in RA management emphasize personalized medicine strategies and the development of safer, more targeted therapies. Ongoing research continues to unravel the underlying mechanisms of RA, paving the way for novel and more effective treatment modalities.

Keywords: Rheumatoid arthritis, Autoimmune disease, DMARDs, RF.

INTRODUCTION

A. Definition of Rheumatoid Arthritis (RA)

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune disorder characterized by persistent inflammation, predominantly targeting the synovial joints. This condition results in progressive joint deterioration and loss of function, affecting an estimated 0.5%–1% of adults globally, with women being two to three times more likely to develop RA than men. While the disease exhibits clinical heterogeneity, its defining feature in advanced stages is sustained synovial inflammation, often presenting with symmetrical involvement of peripheral joints

The pathogenesis of RA involves a complex interaction of genetic susceptibility, environmental factors, and immune system dysfunction. Autoimmune responses mistakenly target

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synovium, triggering chronic inflammation and synovial hyperplasia (pannus formation), which ultimately contribute to joint destruction [1,2].

In addition to joint manifestations, RA is a systemic condition capable of affecting extra-articular tissues, including the cardiovascular system, lungs, blood vessels, and eyes [3].

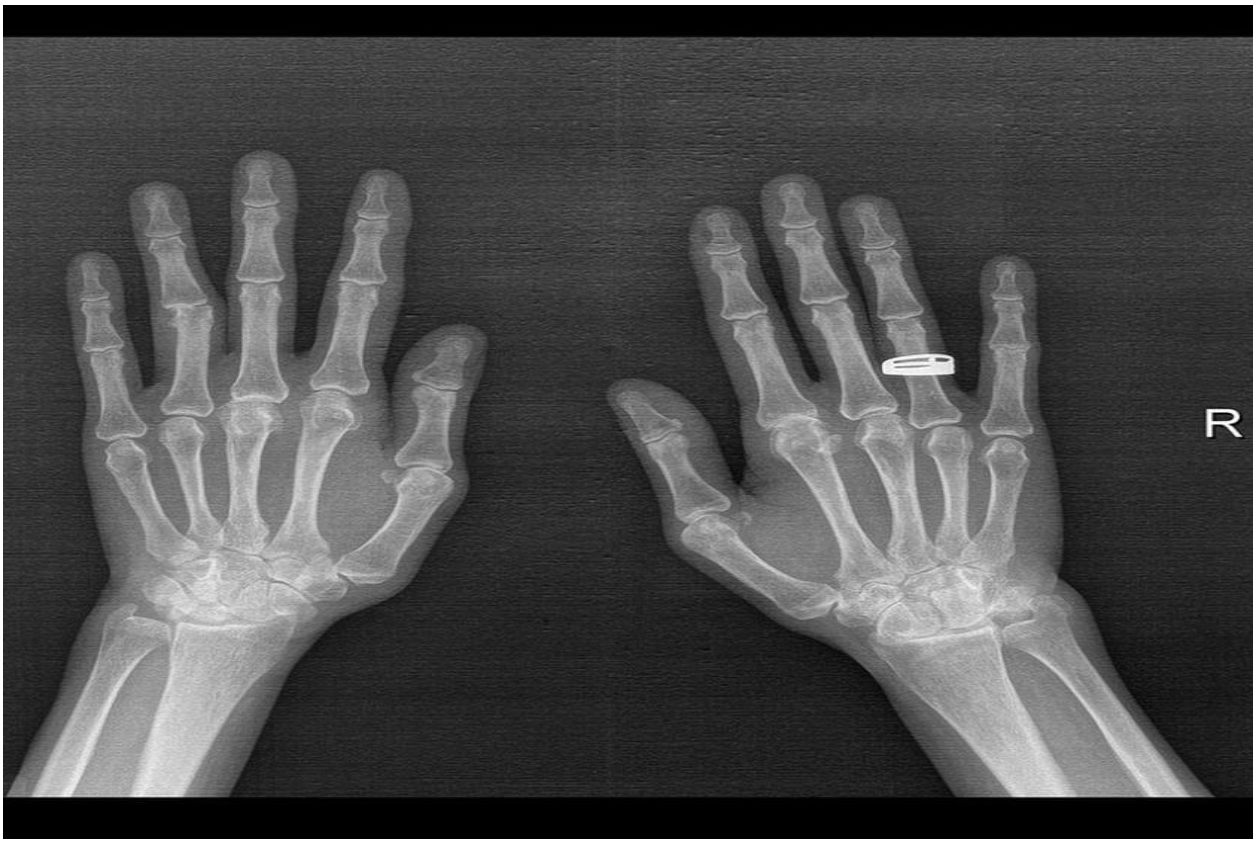

Fig.1. X-ray image of both hands showing possible early signs of rheumatoid arthritis, such as joint space narrowing and soft tissue swelling, with an external metallic object on the fourth digit of the right hand that does not interfere with diagnostic evaluation.[2]

B. Epidemiology of Rheumatoid Arthritis

Rheumatoid arthritis (RA), a systemic autoimmune disorder marked by chronic synovial joint inflammation, exhibits considerable heterogeneity in prevalence and incidence across global populations. Epidemiological investigations are critical for assessing disease burden, delineating risk factors, and informing early diagnosis, therapeutic approaches, and preventive strategies [4].

Incidence of Rheumatoid Arthritis

Incidence denotes the number of new RA cases emerging within a defined population during a specific timeframe [5]. While prevalence studies are more abundant, community-based incidence studies remain limited due to challenges in longitudinal population tracking and incomplete medical documentation [6]. Available evidence indicates temporal and geographical variability in RA incidence.

In certain populations, RA incidence increased during the late 1960s but later declined, notably among White populations in Europe [7] and the United States from the early 1990s onward [8]. This reduction was most evident in women and correlated with decreased overall RA prevalence and a lower proportion of rheumatoid factor (RF)-positive cases among younger individuals [9]. In contrast, rising RA incidence has been observed in regions such as Africa. However, comparisons with high-income countries require caution, as disparities in age demographics in developing nations may contribute to underreported incidence rates relative to North American and Northern European populations [10].

Prevalence of Rheumatoid Arthritis

Prevalence reflects the total number of RA cases within a population at a given time, encompassing both incident and existing diagnoses [5]. The Global Burden of Disease (GBD) 2017 study estimated a worldwide RA prevalence of 0.27% (95% CI: 0.24–0.30%), with marked regional variation [11]: North America (0.38%; 95% CI: 0.36–0.40%), Western Europe (0.35%; 95% CI: 0.31–0.38%), Caribbean (0.34%; 95% CI: 0.30–0.37%), Oceania (0.14%; 95% CI: 0.12–0.15%), Western sub-Saharan Africa (0.13%; 95% CI: 0.11–0.15%), and Southeast Asia (0.10%; 95% CI: 0.089–0.11%) [12].

A 2021 meta-analysis reported a higher pooled prevalence of *0.46% (95% CI: 0.37–0.57%)*, nearly double the GBD 2017 estimate. Methodological differences, diagnostic criteria variability, and healthcare access disparities likely explain this discrepancy. Additionally, urban areas exhibit higher RA prevalence than rural settings, potentially linked to environmental exposures, lifestyle factors, and healthcare infrastructure [13, 14].

By elucidating these epidemiological patterns, healthcare systems and researchers can refine disease management protocols, allocate resources effectively, and enhance patient outcomes globally.

C. Impact on Quality of Life

Rheumatoid arthritis (RA) is a progressive and disabling condition that profoundly diminishes patients' overall well-being and socioeconomic functioning. Among chronic illnesses, RA ranks as one of the most detrimental to health-related quality of life (HRQoL). Persistent pain, chronic fatigue, and progressive physical disability frequently impair occupational performance—reducing workplace attendance, diminishing productivity in both professional and domestic settings, and restricting engagement in social, familial, and recreational activities.

Modern therapeutic strategies, including advanced pharmacologic interventions, focus on alleviating symptoms, preventing structural joint deterioration, and restoring functional capacity. By mitigating disease progression, these treatments contribute to meaningful improvements in HRQoL, enabling patients to regain independence and resume daily activities [15].

2- Pathophysiology of Rheumatoid Arthritis (RA)

Rheumatoid arthritis is a complex autoimmune disorder characterized by immune dysregulation leading to persistent synovial inflammation and progressive joint destruction. The disease develops through three distinct phases of pathogenesis. In the initial phase of immune tolerance breakdown, genetic predisposition involving HLA class II gene variants disrupts T-cell regulation, causing failure to recognize self-antigens and subsequent production of autoantibodies, including rheumatoid factor and anti-citrullinated protein antibodies by B cells. The second phase features immune-mediated synovial invasion where dysfunctional T cells acquire tissue-invasive properties, migrate into the synovium, and initiate unresolved inflammation clinically manifesting as active arthritis with joint

swelling, pain, and stiffness. The final phase involves chronic inflammation and structural damage where dysregulated innate immunity worsens autoimmune responses, leading to irreversible tissue destruction through abnormal proliferation of fibroblast-like synoviocytes forming pannus tissue that causes cartilage breakdown, bone erosion, and joint deformity.

Metabolic disturbances significantly contribute to RA pathology through several mechanisms. Mitochondrial dysfunction occurs as RA synoviocytes exhibit impaired function even when derived from healthy donors under inflammatory conditions, with increased mitochondrial membrane potential shifting metabolism toward aerobic glycolysis. This metabolic reprogramming elevates reactive oxygen species production and mitochondrial DNA mutations, while oxidative stress mediated by molecules like 4-hydroxy-2-nonenal inhibits oxidative phosphorylation complexes III and IV, creating a self-sustaining cycle of oxidative and metabolic stress that accelerates joint destruction. The hypoxic RA synovial microenvironment stabilizes hypoxia-inducible factor-1α, which upregulates pro-angiogenic factors like VEGF and matrix metalloproteinases, connecting hypoxia to both neovascularization and cartilage degradation, with inflammatory mediators including IL-1β, TNF-α, and reactive oxygen species further activating HIF-1α to reinforce this feedback loop of metabolic dysfunction and chronic inflammation [16,17].

The cytokine network in RA pathogenesis involves complex interactions between multiple inflammatory mediators. Central drivers include TNF-α and IL-6, which promote synovitis, cartilage breakdown, and bone erosion, while IL-1β and IL-18 activate macrophages and synovial fibroblasts to amplify inflammation. The IL-17/IL-21/IL-23 axis promotes Th17 cell responses, exacerbating joint inflammation and bone loss, with GM-CSF enhancing macrophage and neutrophil activity to sustain synovitis, and IL-7 and IL-33 supporting T-cell survival and activation to perpetuate chronic immune responses. Certain cytokines exhibit dual roles - IL-27 promotes Th1 responses while suppressing Th17-mediated inflammation and stimulating IL-10 production, though it remains elevated in RA patients and correlates with disease severity. IL-35 suppresses T-cell proliferation while enhancing regulatory T-cell function and inhibiting Th17 differentiation to reduce synovial inflammation, though clinical studies present conflicting data about its precise role. Additional pro-inflammatory mediators include IL-32, which induces multiple cytokines through NF-κB and p38-MAPK pathways while promoting inflammatory macrophage differentiation and synergizing with RANK-L to enhance osteoclast activity, with anti-TNF therapy reducing its levels to confirm involvement in RA inflammation. IL-34 binds CSF-1R to support monocyte/macrophage survival and activation while driving immunosuppressive polarization and accelerating osteoclast formation, with preclinical studies showing IL-34 inhibition reduces arthritis severity [18-20].

This comprehensive pathophysiology highlights the multifaceted nature of RA involving interconnected genetic, immunological, metabolic, and cytokine-mediated mechanisms that collectively drive disease progression and joint destruction, while identifying numerous potential therapeutic targets for intervention. The detailed understanding of these pathogenic processes continues to inform the development of more effective treatment strategies aimed at modifying disease course and improving clinical outcomes for RA patients.

3- Treatment of Rheumatoid arthritis

Once RA is diagnosed in a patient, the overall treatment target is to either reach full remission or at least significantly lower disease activity within a span of approximately 6 months in order to prevent joint damage, disability, and systemic

manifestations of RA. The importance of prompt and targeted RA treatment is underlined by the fact that 80% of insufficiently treated patients will have misaligned joints and 40% of patients will be unable to work within 10 years of disease onset [21].

To achieve the treatment goals, treatment should be initiated promptly and continuously with frequent reassessment of both the state of the disease and the effectiveness of the applied treatment strategy. Until the early 1990s, the common treatment strategy of RA was based on a treatment pyramid consisting of bed rest, the administration of non-steroidal anti-inflammatory drugs (NSAIDs), and, if these treatments failed, disease-modifying anti-rheumatic drug (DMARD) therapy. However, the efficacy of this treatment strategy was limited, and within years, rheumatoid arthritis frequently resulted in joint destruction, disability, inability to work, and increased mortality [22].

Fortunately, the repertoire of therapeutic drugs with benefits in the treatment of RA has grown steadily in the last 30 years. Currently, the available drug classes include NSAIDs, immunosuppressive glucocorticoids, and DMARDs. Drug treatment is typically supplemented by non-pharmacological treatment, which includes physical therapy to sustain joint mobility and patient counselling to slow down disease progression. NSAIDs, like for example aspirin, diclofenac, or ibuprofen, effectively reduce pain and swelling and improve joint function but are not disease-modifying since they do not prevent additional joint damage [23].

Mechanistically, the anti-inflammatory properties of NSAIDs can be mainly attributed to the inhibition of prostanoid biosynthesis [24]. Prostanoids, such as for example prostaglandin (PG) E2, PGD2, PGF2a, thromboxane A2, and prostacyclin, are second messengers that interact with and activate surface-expressed G-protein coupled receptors, thereby modulating many cellular functions. While effectively reducing RA symptoms, the application of NSAIDs is frequently accompanied by renal-, hepatic-, gastrointestinal-, and cardiovascular side-effects (reviewed in [25]).

Glucocorticoids like prednisolone are highly potent anti-inflammatory drugs that delay radiologic progression in early disease stages by general suppression of gene expression. Despite these beneficial effects, the disease-modifying effects of glucocorticoids were described to be minimal, and the long-term application of glucocorticoids is hampered by severe multisystemic metabolic side effects such as gastrointestinal bleeding, osteoporosis, and ulcer formation [26, 27].

Finally, DMARDs are drugs that target rheumatoid inflammation and thereby prevent further joint damage. By definition, DMARDs are drugs that, in contrast to drugs that do not prevent disease progression (e.g., NSAIDs or pain medication). interfere with the signs and symptoms of RA, improve physical function, and inhibit the progression of structural joint damage.

The available DMARDs are further subdivided into (1) conventional synthetic DMARDS (methotrexate, hydrochloroquine, and sulfadiazine), (2) targeted synthetic DMARDs (pan-JAK- and JAK1/2-inhibitors), and (3) biologic DMARDs (TNF-α inhibitors, TNF-receptor inhibitors, IL-6 inhibitors, IL-6R inhibitors, B cell depleting antibodies, and inhibitors of co-stimulatory molecules)[21,23].

Side Effects of RA medication: (DMARDs, NSAIDs, and Corticosteroids):

1. Disease-Modifying Antirheumatic Drugs (DMARDs)

As the cornerstone of rheumatoid arthritis therapy, DMARDs demonstrate disease-modifying properties that can alter the natural history of the condition. The pharmacological spectrum encompasses conventional agents (methotrexate, leflunomide, sulfasalazine) alongside advanced biologic therapies (TNF-α inhibitors, JAK inhibitors).

Methotrexate, the most widely prescribed DMARD, frequently induces gastrointestinal disturbances including nausea and stomatitis, while chronic administration may precipitate hepatotoxicity and myelosuppression. Leflunomide therapy commonly manifests with alopecia, diarrhea, and potential hepatic impairment. Sulfasalazine administration may result in cephalalgia, cutaneous eruptions, and gastrointestinal intolerance [28,29].

Biologic agents, particularly TNF-α antagonists, significantly increase susceptibility to opportunistic infections, including mycobacterial reactivation, while JAK inhibitors demonstrate thrombogenic potential and dyslipidemic effects [30].

Fig.2. Methotrexate 2.5 mg oral tablets (Ebewe Pharma), a commonly prescribed dose in the treatment of rheumatoid arthritis and other autoimmune diseases [29].

2. Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

NSAIDs provide symptomatic relief through their analgesic and anti-inflammatory properties without influencing disease progression. The therapeutic class includes both non-selective COX inhibitors (ibuprofen, naproxen) and COX-2 selective agents (celecoxib).

These medications commonly produce gastropathy, ranging from dyspepsia to severe ulceration with hemorrhage. Cardiovascular considerations include elevated blood pressure and increased thrombotic risk, particularly with prolonged use. Nephrotoxic effects may manifest as reduced glomerular filtration rate and sodium retention [31].

3. Corticosteroids

Glucocorticoids offer potent anti-inflammatory effects with a rapid onset of action, though their utility is limited by an extensive adverse effect profile. Acute complications include hyperphagia, sleep disturbances, and affective lability. Chronic administration predisposes to metabolic derangements, including hyperglycemia and Cushingoid habitus. Musculoskeletal consequences encompass myopathy and accelerated osteoporosis. Ophthalmological monitoring is warranted due to risks of posterior subcapsular cataracts and elevated intraocular pressure [28].

Fig.3. Ibuprofen 400 mg tablets (Fourrts), a commonly used NSAID for oral administration. It helps relieve pain and reduce inflammation in patients with rheumatoid arthritis [32].

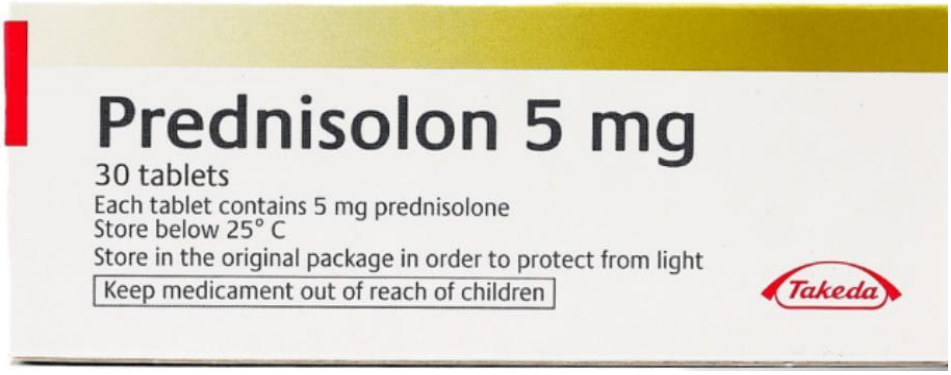

Fig.4. Prednisolone 5 mg tablets (Takeda), a corticosteroid commonly used in the treatment of rheumatoid arthritis. It helps reduce inflammation and suppress the immune response in active disease phases [33].

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