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Pharmacotherapeutic Approaches of Rheumatoid Arthritis

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Abstract

Rheumatoid arthritis is an autoimmune inflammatory disease primarily characterized by synovitis accompanied by clinical manifestations which include fever, malaise, edema, pain, and stiffness in several joints. It is also associated with the damage of extra- articular organs like eyes, heart, lungs and blood vessels. The epidemiology of RA indicates a population prevalence of about 0.5% to 1% and can lead to severe joint damage and disability. Thus, the understanding of disease pathology, proper diagnosis and treatment are required from the early stages of the disease. The genome-wide analyses of the nucleotide sequences in the patients diagnosed with RA have identified the human leukocyte antigen D-related B1 gene (HLA-DRB1) as the most relevant disease-susceptible gene. While anti-inflammatory drugs and glucocorticoids were used as palliative therapy earlier, disease-modifying antirheumatic drugs (DMARDs) are currently used to repress the immune abnormalities and to control disease severity. DMARDs are classified into synthetic and biological DMARDs among which synthetic group is further classified as conventional synthetic DMARDs (e.g., methotrexate) and targeted synthetic DMARDs (eg., JAK inhibitors). Proper use of this class of drugs has resulted in remission of Rheumatoid arthritis. These drugs aim to prevent structural damage to the joints and to prevent the worsening of the condition. By maintaining remission, the appropriate administration of these drugs has also been showed to prevent the disease progression over a long period. In the coming times, safer and more effective therapeutic measures are expected along with the precision medicine.

Conclusion: In conclusion, the pharmacotherapeutic landscape of RA continues to evolve rapidly, driven by advances in our understanding of disease mechanisms and therapeutic targets. Moving forward, efforts must focus on refining existing treatments, exploring novel therapeutic avenues, and implementing personalized approaches to enhance the overall management of RA and improve patient outcomes.

Keywords: Rheumatoid Arthritis; Autoimmune Disease; Diagnosis; HLA-DRB1 Dene; Treatment; DMARDs

Abbreviations: RA: Rheumatoid Arthritis; DMARDs: Disease-Modifying Antirheumatic Drugs; NSAIDs: Nonsteroidal Anti-Inflammatory Drugs; HLA: Human Leukocyte Antigen; FLS: Fibroblast Like Synoviocytes; ROS: Oxygen Reactive Species; APC: Antigen Presenting Cells; GC: Germinal Cells; AS: Ankylosis Spondylitis; PS: Psoriatic Spondylitis; SLE: Systemic Lupus Erythematosus; TNF: Tumor Necrosis Factor; TLRs: Toll-Like Receptors; ESR: Erythrocyte Sedimentation Rate; CRP: C-Reactive Protein

Introduction

Rheumatoid arthritis (RA) is a chronic, autoimmune disease that mostly affects joints, which means the arthritis results from the immune system attacking the body's own tissues. It is characterized by the inflammation of the synovial membrane (the soft connective tissue, found inside the movable joints which produce fluid to help the joint move smoothly) [1]. The synovial inflammation causes bone erosion, pain and only affects the joints but also associated with the damage of extra- articular organs like eyes, heart, lungs and blood vessels [2].

Rheumatoid arthritis mostly occurs in women when compared to men i.e., 70% of people living with RA is women. The epidemiological estimates of RA has shown that RA effected population is higher in the United States and northern European countries, usually between 0.5 to 1%. In individuals with RA, ultrasonography shows the major abnormalities which include tendon sheath broadening, bone deformities, joint space widening, synovium hypertrophy, fluid buildup, bone erosions, and cartilage deformities. Disease-modifying antirheumatic drugs (DMARDs) are currently used to repress the immune abnormalities and to control disease severity [3]. This article furtherly provides an overview of the pathophysiology, clinical manifestations, diagnostic techniques, and best treatment of rheumatoid arthritis, from the basic to the latest information.

Over the years, significant strides have been made in understanding the pathophysiology of RA, paving the way for the development of diverse pharmacotherapeutic approaches aimed at mitigating disease progression, alleviating symptoms, & improving patients' quality of life [4]. The therapeutic landscape of RA has evolved considerably, transitioning from conventional disease-modifying antirheumatic drugs (DMARDs) to more targeted and biologic therapies, with the emergence of novel small molecule inhibitors. Key pharmacotherapeutic approaches in RA encompass nonsteroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, conventional synthetic DMARDs (csDMARDs), biologic DMARDs (bDMARDs), and targeted synthetic DMARDs (tsDMARDs) [5]. Each class of medications targets specific components of the immune response cascade implicated in RA pathogenesis, aiming to achieve disease remission or low disease activity while minimizing adverse effects [6].

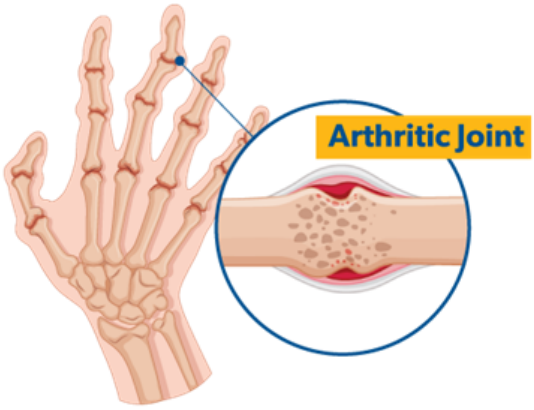

Figure 1: Rheumatoid Arthritis- Joint Inflammation.

Causes

The exact cause of Rheumatoid Arthritis is not known yet but few research studies illustrate that a combination of the following factors may lead to the condition:

- **Environment:** Environmental factors such as cigarette smoke and some inhalants like bacteria, viruses may add up the risk of the disease [7].
- **Sex:** Woman is more likely than men to develop the risk of the disease.
- **Age:** It mostly begins in the middle age [8].
- **Family History:** Having a family member with RA increases the odds of developing RA [9].

Clinical manifestations of the disease

- Swelling of the joints while after performing daily activities.
- Morning stiffness which persists more than 30 minutes to several hours [10].
- Difficulty in joint movement usually after long periods of sitting or inactivity.
- Occasional low-grade fever.
- Fatigue and loss of appetite.

Diagnosis of the disease

Rheumatoid arthritis can be difficult to diagnose in the early

stages as the symptoms of this disease are the characteristics of many other medical conditions. Few blood tests and Imaging tests are done in-order to diagnose Rheumatoid Arthritis.

The Blood tests of the patients with Rheumatoid arthritis often have an elevated erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) level, which may indicate the presence of an inflammatory process in the body.

The other ways of diagnosing RA is through imaging techniques which include X Ray, MRI scanning and Ultrasound scanning [11].

Pathophysiology

Synovitis, arthritis and joint damage that characterizes the active rheumatoid arthritis.

The active rheumatoid arthritis is the end results of auto immune rejection and complex Inflammatory reactions. This is generally triggered by alterations in some of the genes such as HLA [Human Leukocyte Antigen] which is responsible for coding of proteins that differentiates between self and nonself antigen and antibodies and there are also some bacteria called Porphyromungs gingivitis that leads to Gingivitis these causes modifications of auto antigens including citrullination [12].

"Synovial membrane" which is present in the joints capsule produces a synovial fluid which is responsible for lubrication. In case of active rheumatoid arthritis, synovitis takes place where the synovial membrane undergoes inflammation that causes pain and swelling and the synovitis also leads to bone and cartilage erosion. Angiogenesis takes place in the patients with active rheumatoid arthritis. At cellular level, synovium is made up of cells called FLS (fibroblast like synoviocytes) and they play a major role in rheumatoid arthritis [13].

Some of the genes especially [HLA, STAT4] and environmental infections trigger macrophages and dendritic cells, thought to present instigating antigens to T cells, those results in the activation of T Cells and proliferation of T cells. The activated T Cells produce cytokines [i.e. IL-6, TNF-α, IL-1] which probably leads to inflammation. The inflammatory cytokines stimulate the FLS as they gets activated and begins to proliferate, the inflammatory cytokines and activated FLS together stimulates [RANKL] expression which leads to osteoclast activity that causes bone erosion, the activated [FLS] also begins to secrete proteases, they essentially causes the breakdown of cartilage [cartilage degradation] the activated [FLS] migrate from joint to joint [symmetrical arthritis] [14].

Plasma cells in the area of synovial membrane accumulates only 5%of immune cells and they assist in inflammation through cytokines and antibodies ,in the 'synovial fluid' we found neutrophils they essentially produces proteases and oxygen reactive species [ROS] they causes bone and cartilage erosion they contribute to inflammation ,in case of angiogenesis the cytokines produced by all the cells increases vascular permeability and increases adhesion molecules allowing the immune cells to migrate to the joints when there is a synovial injury /hyperplasia (or) infection that trigger the cytokine release and leads to inflammation & modification of auto antigens. Due to the modifications of autoantigens, they are recognised by the APC [antigen presenting cells] to initiate the immune response and the APC gets migrates to the lymph nodes the APC activates CD4+ cells present in the lymph nodes, the activated CD4+ cells activated the B cells in the germinal cells [GC] which is present within the lymph node [costimulation].the activated B cells proliferates and produces plasma cells and they produce autoantibodies [15].

The CD4+, Tcells, B cells &autoantibodies from lymph node gets migrate to joint tissue and destroys enzymatically and it leads to severe rheumatoid arthritis which affect the entire body by extraarticular involvement. Some of the antibodies such as igM (rheumatoid factor) it is present in 75% of people with rheumatoid arthritis ,they target the FC position of igG antibodies and results in the formation of immune complexes and igM antibodies also form complexes with complementary proteins such as fibrin and Filburn, anti-citrullinated antibody helps in the diagnosis of active rheumatoid arthritis [16].

Treatment for Rheumatoid Arthritis (RA)

There is no cure for rheumatoid arthritis has been found so far, but treatment and management for rheumatoid arthritis can begin at the early onset of the disease to reduce the risk of permanent damage to joints and disease progression. Most likely treatment for RA begins with medications known as disease-modifying antirheumatic drugs (DMARDs), and other drugs such as non-steroidal anti-inflammatory drugs (NSAIDs), and corticosteroids [17].

Disease-Modifying Antirheumatic Drugs (DMARDs)

Disease-modifying antirheumatic drugs are a class of immunosuppressants and immunomodulatory agents indicated for the treatment of rheumatoid arthritis and other conditions such as ankylosis spondylitis (AS), psoriatic spondylitis (PS), and systemic lupus erythematosus (SLE). These DMARDs act by suppressing the overactivity of the body's immune, and inflammatory systems [18]. The choice

between DMARD depends on various factors such as the stage and severity of the disease and a sense of equal balance between probable side effects, toxicities, and comorbidities. DMARDs are classified into-

- ✓ Conventional DMARDs
- ✓ Biological DMARDs
- ✓ Target synthetic DMARDs

Conventional DMARDs (csDMARD)

These are the drugs that can slow down the progression of rheumatoid arthritis by blocking inflammation and prevent from causing permanent damage to joints, and other tissues. Conventional DMARDs work by suppressing the immune system to control inflammation. The most commonly used conventional DMARDs are Methotrexate, hydroxychloroquine, sulfasalazine and leflunomide.

Methotrexate (MTX): Anti-metabolite that was initially used in the chemotherapy treatment of cancer. Methotrexate is a folic acid antagonist approved by the FDA due to its high efficacy and potential in the treatment of rheumatoid arthritis and can also be useful in treating patients with juvenile idiopathic arthritis. Many studies observed the overexpression of adenosine receptors on immune cells in patients suffering from RA, choosing methotrexate as a drug of choice as it inhibits the enzyme AICAR transformylase which leads to the accumulation of adenosine. Anti-inflammatory actions of adenosine lead to down-regulation of B cells and binding of beta-1 interleukin to its cell surface receptors is inhibited. Even low doses of methotrexate are not free from side effects; the major adverse effect of methotrexate is hepatotoxicity. Methotrexate is contraindicated in pregnant women with its teratogenic effect [19].

Hydroxychloroquine: Belongs to the class of antimalarial and antirheumatic drugs (DMARDs). It is an immunomodulatory drug that is used to treat malaria and autoimmune diseases such as inflammatory arthritis, and systemic lupus erythematosus. Over a long time use of hydroxychloroquine can help reduce pain, swelling, and stiffness of the joints. Hydroxychloroquine acts by suppressing the toll-like receptors (TLRs), these receptors are essential inflammatory mediators of the inflammatory pathway. Initial dosing of hydroxychloroquine is given as 200-400 mg per day as a single dose or divided into two doses. Usually, hydroxychloroquine is often taken in combination with other drugs such as methotrexate. On long-term treatment of the drug, it is important to note the side effects caused by hydroxychloroquine which include nausea, vomiting, tinnitus, and diarrhea. On higher doses serious complications such as retinal toxicity/ ocular toxicity can be caused due to hydroxychloroquine therapy [20].

Sulfasalazine: Effective DMARD that shows effectiveness in treating RA, inflammatory bowel diseases, moderately active Crohn's disease, and psoriatic arthritis. Sulfasalazine is cheaper, easier to administer, and lacks teratogenic activities in comparison to other DMARDs. The metabolites of sulfasalazine are 5-aminosalicylic acid and sulfapyridine, these two metabolites are responsible for the anti-inflammatory effect. Sulfasalazine also works by inducing the conversion of adenine nucleotide to adenine, as adenine mediates the anti-inflammatory effect. It is typically available as a 500mg oral tablet or taken as 1g per day to a maximum of 3g per day. The most common side effects are vomiting, variations in blood count, renal/hepatic/hematologic toxicities, hypersensitivity reactions, oligospermia, etc. It is important to take plenty of oral fluids on the administration of sulfasalazine and avoid taking them on an empty stomach [21].

Leflunomide: Drug with anti-inflammatory and immunomodulatory characteristics that is helpful in the treatment of rheumatoid arthritis by delaying irreversible joint damage and disintegration of bone. This medication is also used to prevent synovitis and is indicated in the treatment of psoriatic arthritis. Leflunomide metabolizes in the body into a metabolite called teriflunomide, this metabolite will inhibit the mitochondrial enzyme, which promotes the activation of the P53 gene. This further restricts the proliferation of lymphocytes promoting the anti-inflammatory effect along with immunomodulation. The initial dosage for patients with a low risk of liver disease and bone marrow complications is 100mg daily for three consecutive days, and 20mg per day depending on the patient. If the dose exceeds more than 25mg then serious adverse effects can be observed such as elevation in liver enzymes, hypertension, alopecia, and mouth ulcers. Leflunomide is contraindicated in pregnant women and patients with interstitial lung diseases [22].

Biological DMARDs (bDMARD)

Biological DMARDs are more powerful and complex than conventional DMARDs which may probably stop the inflammation that damages the joints and other autoimmune diseases. If the patient does not respond well to conventional DMARD, the physician prescribes biological DMARD as they are effective and targets the molecules that cause inflammation at high specificity [23]. These drugs block inflammatory proteins called tumor necrosis factor (TNF), and pro-inflammatory cells (B cells and T cells), inhibit interleukins. Some of the common biological DMARDs used are-

- ➢ Adalimumab
- ➢ Infliximab

- Abatacept
- Rituximab
- Certolizumab
- Golimumab
- Tocilizumab
- Etanercept

Target- Synthetic DMARDs (tsDMARD)

Target-synthetic DMARDs also called Janus kinase inhibitors (JAK inhibitors) bind to the cytokines. Cytokines are essential to host defenses and immunoregulators that play a vital role in the immunopathogenesis of autoimmune diseases. These drugs are used to treat chronic inflammatory disorders- rheumatoid arthritis, axial spondylarthritis, juvenile idiopathic arthritis, and atopic dermatitis. These drugs inhibit the family of Janus kinase enzymes – JAK1, JAK2, JAK3, etc, and intervene in the JAK/STAT signaling pathway in lymphocytes. The JAK/STAT pathway is a significant cascade of transducing signals for cell proliferation, multiple growth factors, and cytokines [24]. These drugs are used when conventional and biological may not be effective. Targeted synthetic DMARDs include-

- ✓ Baricitinib
- ✓ Tofacitinib
- ✓ upadacitinib

Higher doses of targeted synthetic DMARD can increase the risks of serious cardiovascular diseases and may also cause blood clots in the lungs, upper respiratory tract infections, nasopharyngitis, and cancer [25].

Non-Steroidal Anti-Inflammatory Drugs

Patients suffering from rheumatic diseases which include rheumatoid arthritis, and osteoarthritis describe pain and inflammatory stiffness. NSAIDs are very effective anti-inflammatory drugs that help in managing chronic pain and inflammation due to their ability to inhibit prostaglandin and cyclooxygenase pathways (COX 1 and COX 2). Naproxen is the most suitable NSAID that is used in the treatment of rheumatoid arthritis. A few common NSAIDs prescribed are – ibuprofen, naproxen, aspirin, ketorolac, fenoprofen, diclofenac, ketoprofen, and celecoxib (selective COX 2 inhibitor). All NSAIDs are associated with causing a risk of heart attack and stroke, but common side effects of this class of drugs are- gastrointestinal problems, excessive bleeding, stomach ulcers, diarrhea, and anemia [26].

Corticosteroids

Corticosteroids are predominantly used in relieving pain and inflammation. They have a higher potential for anti-inflammatory effects when compared with those of non-steroidal anti-inflammatory drugs (NSAIDs). These drugs are put to use when the NSAIDs are no longer managing the symptoms. Corticosteroids regulate the gene expression by binding to the glucocorticoid receptors [27]. These drugs work by specifically up-regulating the anti-inflammatory gene and down-regulating the pro-inflammatory genes. Steroids usually mimic the activity of the hormone produced by the body's adrenal glands which helps in suppressing immune cells that attack the synovial joints. Examples of steroids that are prescribed to treat RA-

- Dexamethasone
- Prednisolone
- Prednisone
- Methylprednisolone

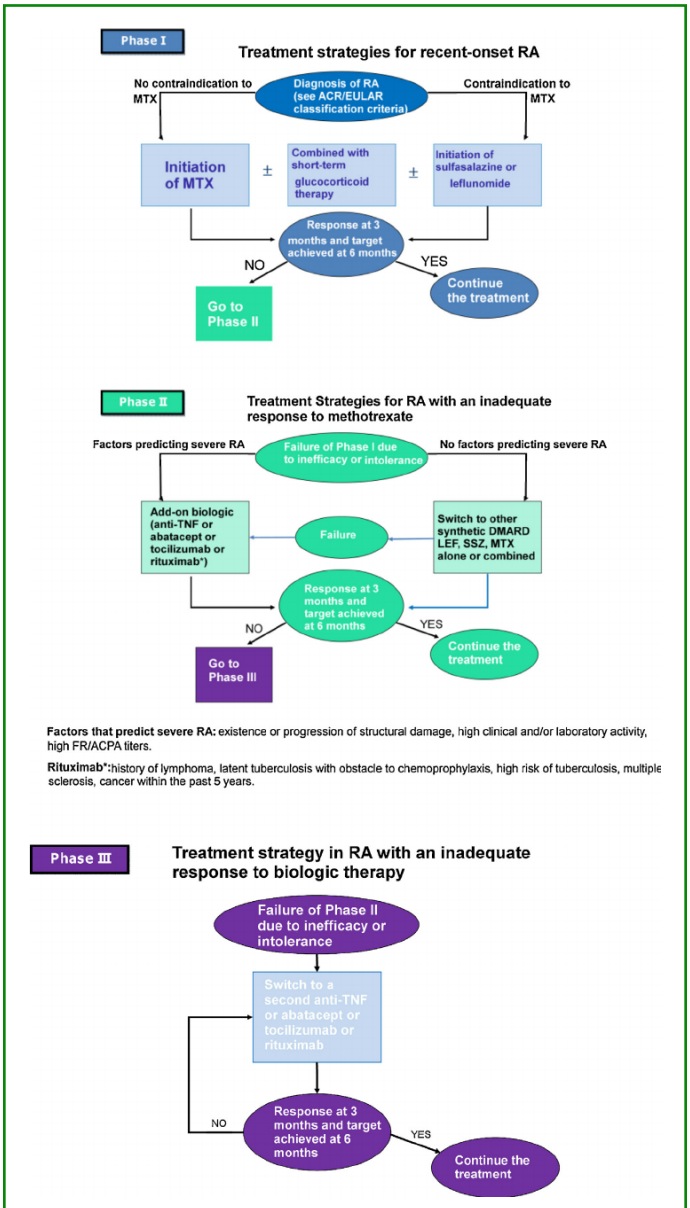

Figure 2: Treatment algorithm of Rheumatoid Arthritis.

The available preparations of corticosteroids that are available are intra-articular injections, intramuscular

injections, intravenous injections, and oral medications. A typical dosage of prednisolone is around 5-10 mg per day. Possible common adverse effects caused due to corticosteroids include hypertension, hyperkalemia, edema, steroid-induced diabetes, risk of cataracts, fragile skin, and osteoporosis [28].

Conclusion

RA is a chronic, inflammatory disease characterized with joint damage and if left untreated can lead to long term disability. Early diagnosis and therapeutic treatment are essential for the prevention of serious outcomes and reduce the serious outcomes of the disease. With the advancement in the molecular medical field, we have a better understanding of the disease causing mechanisms and can help in the designing of more effective treatments. One such most effective treatment for RA can be achieved by DMARDs. DMARD's are crucial in preventing the joint deformities and injuries that can lead occur as a result of RA. Essentially they interfere with the cellular signalling cascade which causes inflammation in RA. Once the patient has been diagnosed with RA, the best possible prognosis can be achieved by starting DMARD therapy. There are different types of DMARDs among which the traditional ones are methotrexate, hydroxychloroquine, sulfasalazine, leflunamide as well as biological DMARDs such as etanercept, adalimumab, infliximab and rituximab. The choice of DMARD and its combination therapy depends upon the severity of the condition and the individual's characteristics [29].

Despite the expanding armamentarium of RA therapies, challenges persist in optimizing treatment outcomes, including drug tolerability, long-term safety concerns, economic considerations, and the risk of treatment resistance. Furthermore, the advent of precision medicine holds promise in tailoring therapy based on individual genetic, molecular, and immunological profiles, potentially revolutionizing RA management by optimizing efficacy and minimizing adverse effects [30].

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