Review Article

Autoimmune Disorder: A Review on Rheumatoid Arthritis

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ABSTRACT

The human immune system is a complex defense mechanism that protects the body from microbial infections and foreign substances. However, in autoimmune diseases, the immune system mistakenly attacks healthy cells and tissues, leading to chronic inflammation and tissue damage. Autoimmune diseases include insulin dependent diabetic mellitus, rheumatoid arthritis, systemic lupus erythematosus, scleroderma, thyroiditis, and multiple sclerosis. Rheumatoid arthritis (RA) is a common autoimmune disorder characterized by symmetric polyarthritis, joint discomfort, and inflammation. The etiology of RA involves the interaction of genetic and environmental susceptibility factors, including the periodontal bacterium Porphyromonas gingivalis. Women are more likely to develop RA than men, with a female-to-male incidence ratio that increases with age. The disease can be classified into seropositive and seronegative RA, with seropositive RA being the most prevalent form. Treatment options for RA include disease-modifying antirheumatic drugs (DMARDs), nonsteroidal anti-inflammatory drugs (NSAIDs), and corticosteroids.

Keywords: Autoimmune Disorders, Rheumatoid Arthritis, Immune System, Genetic Factors.

INTRODUCTION

The human immune system is a "double edged sword" that can both help and hurt our physiological processes. By using soluble mediators to maintain a balance between different cells and tissues, this system's integrity is preserved. Additionally, this immune system has a protective role in keeping our bodies free from microbial illnesses [1]. By identifying and getting rid of foreign substances, the immune system shields the host from illness. Immune cells that respond against self-tissues are removed as the immune system matures, resulting in an immune system that is "tolerant" of itself [2]. Normally, the immune system fights off antigens and mounts an attack in retaliation. The immune system cannot distinguish between foreign antigens and its own host cells in autoimmune diseases [3]. The immune system's inability to distinguish between potentially hazardous antigens and healthy tissue is a defining feature of autoimmune illnesses. The idea of molecular mimicry can be used to explain immune system attacks on host cells [4]. Because of their chronic nature, high healthcare costs, and predominance among young populations at the prime of their working and reproductive years, autoimmune disorders represent a serious clinical challenge [5]. There are more than 80 different autoimmune disorders that impact hundreds of millions of people around the world. After cancer and heart disease, these systemic or organ-specific disorders are the third most common cause of morbidity and death in the industrialized world [6]. Most of these variables are still up for debate, but genetic and environmental factors interact in a complicated way to cause AI illnesses [7].

Immunologic tolerance is compromised in autoimmune illnesses, triggering an immunological reaction to self-molecules. Most of the time, it is unknown what triggers the immune response to self-molecules; nevertheless, several studies have linked certain infections, environmental, and genetic factors to this process [8]. When the immune system mistakenly targets healthy cells for foreign intruders, autoimmune diseases result. Organ dysfunction, tissue damage, and inflammation are the results of this pathological misidentification [9]. There are currently around 80 known autoimmune disorders. They can be organ-specific, like type 1 diabetes, which mostly affects the pancreas, or systemic, like systemic lupus erythematosus, which can affect the skin, joints, kidneys, and central nervous system [10]. Women are more likely than men to experience autoimmune illnesses, which can lead to long-term illness, a low quality of life, and significant medical expenses [11].

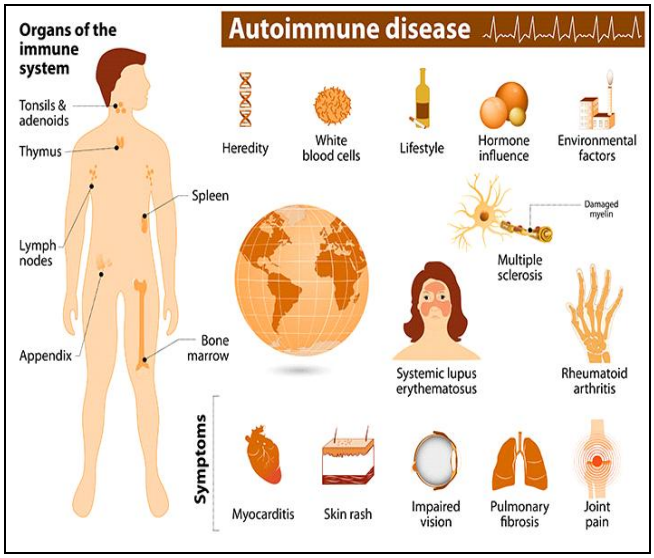

Figure 1: Various Autoimmune Diseases related to Immune System [11]

About 6% of the population suffers from an array of diverse conditions collectively known as autoimmune disorders

(Siatskas et al., 2006). Based on the clinical symptoms and the target antigen's location, they can be broadly categorized as systemic or organ specific (Sakaguchi, 2000) [12]. Systemic autoimmune diseases encompass a wide spectrum of linked conditions that are defined by immune system dysregulation. This dysregulation leads to the activation of immune cells against autoantigens, causing inappropriate inflammation and tissue damage Systemic lupus erythematosus (SLE), rheumatoid arthritis, systemic sclerosis, ankylosing spondylitis, and polymyositis are common examples of systemic autoimmune diseases. Additionally, Addison's disease, Hashimoto thyroiditis, Graves disease, Sjogren's syndrome, vitiligo, pernicious anemia, glomerulonephritis, myasthenia gravis, Goodpasture's syndrome, autoimmune hemolytic anemia, idiopathic thrombocytopenia purpura, and pulmonary fibrosis are instances of organ-specific autoimmune diseases [13].

1. Rheumatoid Arthritis

The synovial membrane of diarthrodial joints is impacted by the chronic autoimmune inflammatory condition known as rheumatoid arthritis (RA) [14]. The initial signs of RA may be fatigue, fever, and systemic weight loss. Chronic, dual, symmetric polyarthritis, joint discomfort, and inflammation that can cause deformity, instability, and synovial joint degeneration are the hallmarks of this condition [15]. The etiology of RA most likely entails the interaction of environmental and genetic susceptibility factors, one of which is the periodontal bacterium Porphyromonas gingivalis. Anti-citrullinated protein antibodies were produced in response to P. gingivalis, and this is what will ultimately raise the risk of RA [16].

Chronic synovial inflammation, hyperplasia, bone loss, joint damage, and increased PAD activity in inflammatory joints have all been linked to RA-related disability. It has also been suggested that monocytes and macrophages that are attracted to the joints are the source of PAD enzymes [17]. In 1981, Fujisaki and Sugawara partially isolated the enzyme that was causing this process, which they called peptidylarginine deiminase (PAD). Since then, five PADs have been found in humans (PAD1-4 and 6), and they are grouped together on a chromosome [18].

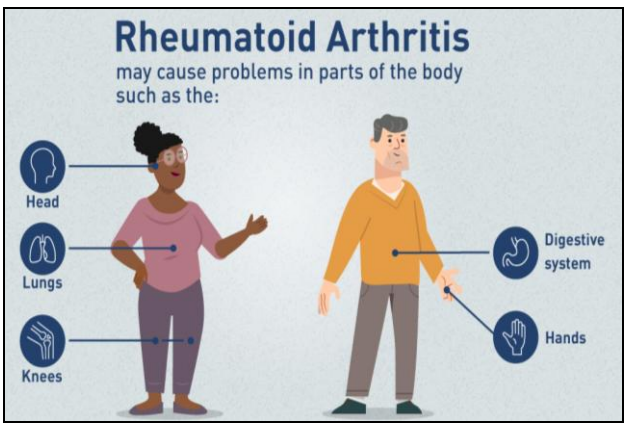

Figure 2: Rheumatoid Arthritis effects on body part [18]

Events in the CR have an impact on multiple facets of RA. IL-6 and other inflammatory cytokines usually cause the hypothalamus to produce corticotropin-releasing hormone, which in turn causes the pituitary glands to release corticotropin and the adrenal gland to secrete glucocorticoids [19]. Four distinct instances of mechanistic models used to investigate RA illness and related therapies were found throughout our search. Published in 2005, Ruhlmann's initial study details the use of the Entellus® RA Physio Lab® platform to predict the impact of hypothetical anti-IL-15 and anti-IL-12 treatments on cartilage degradation rate and synovial cell density, as well as to validate potential biological targets [20]. But according to recent research, women are four times more likely than men to have RA overall. The female to male incidence ratio of RA also rises with age, reaching three to five times higher in the perimenopausal and reproductive age groups. Furthermore, in three global regions America, Europe, and the Western Pacific more than four out of every five RA patients are female [21]. Numerous theories have been put forth, such as microchimerism, the X chromosome, sex hormones, environmental variables, and the microbiome. The exact cause of this autoimmune sex prejudice is yet unknown, though [12].

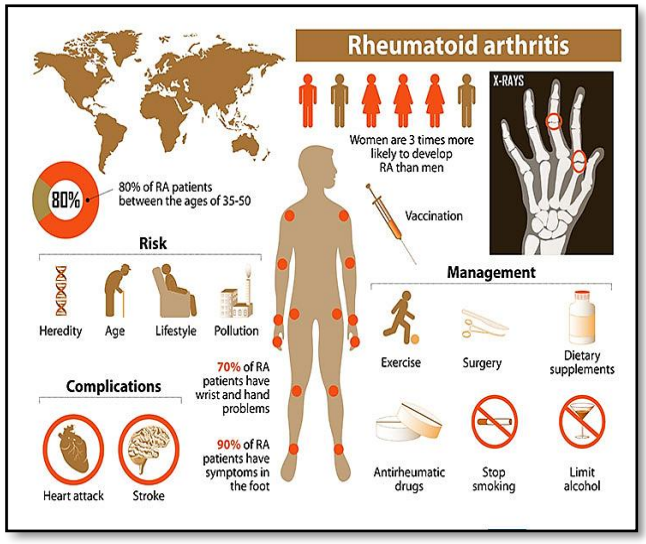

Figure 3: RA affect more in women and its Risk factors of RA and their various types of management [21]

3. Types of Rheumatoid Arthritis

3.1 Seropositive RA

60 to 80% of RA patients are seropositive, making this the most prevalent form. If you have seropositive RA, your blood contains antibodies that can cause inflammation in your joints and assault your body. They are known as anti-citrullinated protein antibodies (ACPAs) or anti-cyclic citrullinated peptides (your doctor may refer to them as anti-CCPs). You can get a blood test from your doctor to check for anti-CCPs. However, they are not always indicative of RA. Once your doctor has determined what is causing your symptoms, they will make that call [22]. Your body may be actively generating an immune response to

your normal tissues if your blood tests positive for the protein known as Rheumatoid Factor (RF) or the antibody anti-cyclic citrullinated peptide (anti-CCP). You don't necessarily get RA just because you have these proteins. Nevertheless, if you do, it can help experts identify the classification [23].

3.2 Seronegative RA

Being seronegative means that your blood levels of anti-CCPs and rheumatoid factor are either very low or non-existent. If your anti-CCP test results are negative yet you still have RA symptoms, you probably have seronegative RA or even another diagnosis. A person may still have RA even if their blood tests for RF and anti-CCP are negative [24]. The diagnosis is made using more than just these tests. Your PCP will also take into account clinical complaints, X-rays, and other laboratory tests. People who test negative for both RF and anti-CCP usually have a milder form of RA than those who test positive for RF [22].

4. Etiology

The last few decades have seen a significant improvement in the prognosis of RA patients due to the growing body of knowledge regarding the genesis and pathophysiology of the disease, which has made it possible to produce several currently approved and efficacious medications [25]. Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease, impacted by both hereditary and environmental factors. A high-risk genetic background triggers a series of events that impact several extra-articular organs in addition to causing synovitis and destructive arthritis. These events are accompanied by epigenetic markings and environmental exposures [26]. Recent research has also demonstrated that viral infections raise the risk of RA, which may be especially significant considering the present coronavirus epidemic. Recently, mycoplasma pneumonia has also been associated with RA incidents, particularly in the elderly and in the two years after infection [27].

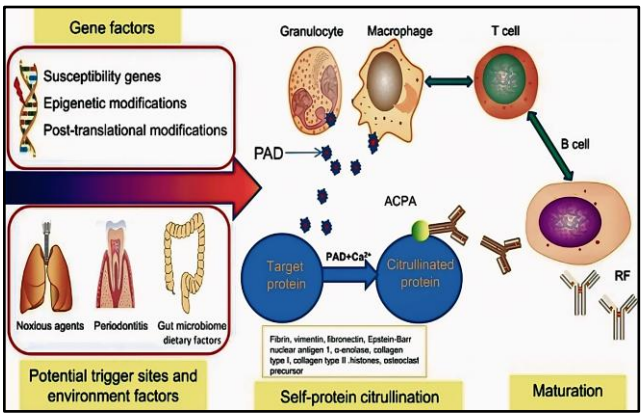

Figure 4: The initiation of self-protein citrullination, which results in the generation of autoantibodies against citrullinated peptides, is one of the ways that the interaction between genes and environmental variables might cause RA in the potential trigger sites (lung, mouth, gut).[28]

Numerous variables, including genetic, epigenetic, and environmental ones, are connected to the pathogenesis of RA. The inflammatory process is primarily initiated by a set of predisposing genes known as Human leukocyte antigen (HLA) class II, which includes more than 100 vulnerable loci, including CTLA4, TRAF1, PTPN22, and PADI4 [28]. The human leukocyte antigen D-related B1 gene (HLA-DRB1) has been found to be the most relevant disease-susceptible gene among individuals with rheumatoid arthritis. Other disease-susceptible genes have also been identified using genome-wide analysis of single nucleotide polymorphisms [29].

Also, inflammatory mediators such as proteases, cytokines, autoantibodies, and chemokines, nonimmune cells such as chondrocytes and fibroblasts, immune cells such as mast cells, T cells, B cells, dendritic cells, and macrophages, and various nongenetic factors such as sex hormones and smoking are also cooperatively involved in the inflammatory reactions that target the bone and cartilage, leading to impaired joint function [30].

5. Risk Factors of Rheumatoid Arthritis

There are two broad categories of risk factors for developing RA: host- and environment-related. A different respiratory exposure that was also identified as a risk factor for RA in 1987 was silica, which is confirmed by recent research to raise the likelihood of RA by more than double [31]. There are several factors that can raise one's risk of developing rheumatoid arthritis, including smoking, female sex, positive family history, aging, and silicate exposure. Drinking more than three cups of coffee a day, especially decaffeinated coffee, may also be a factor. Use of oral contraceptives, high vitamin D intake, and tea drinking are linked to lower risk [32].

5.1 Genetic Factors: Since autoimmune disorders do not always develop in identical twins, genetic variables alone cannot account for the origins of autoimmune diseases. Moreover, somatic mutation of B-cell receptors, differences in receptor assembly, and nonidentity in immunological repertoires due to TCR and Ig gene recombination may account for the relatively low concordance rates between identical twins, depending on the illness [6]. The initial evidence for a genetic component in RA came from twin and familial investigations. As a matter of fact, the risk of RA for a monozygotic twin of a patient with RA is 9-15%, which is significantly greater than the general population and up to four times that of dizygotic twins [relative risk (RR) [33].

5.2 Host Factors: Comorbid host variables, as well as genetic, epigenetic, hormonal, reproductive, and neuroendocrine host factors, have also been linked to the development of RA. Environmental risk factors encompass numerous variables such as food, socioeconomic status, microbiota and infectious agents, smoking, and other airborne exposures, and so on [30]. The host has a direct bearing on the likelihood of getting RA, just like in many other immune-mediated disorders (Figure 5). First and foremost, genetic factors are included in this, as they contribute significantly to the risk of disease. More recently,

epigenetic pathways have been revealed to be directly involved in RA pathogenesis, modifying the risk of disease progression. Interestingly, they are environment-dependent, so tying extrinsic and intrinsic elements together [34].

6. Symptoms of rheumatoid arthritis include: [3,4,24]

Smaller joints, especially those that connect your fingers to your hands and your toes to your feet, are typically the first to be affected by early rheumatoid arthritis. Symptoms frequently expand to the wrists, knees, ankles, elbows, hips, and shoulders as the illness worsens.

- Pain, swelling, stiffness and tenderness in more than one joint.
- Stiffness, especially in the morning or after sitting for long periods.
- Pain and stiffness in the same joints on both sides of your body.
- Fatigue (extreme tiredness).
- Weaknesses.
- Painful, stiff, swollen, and deformed joints
- Reduced movement and function
- Fever, fatigue, weight loss, eye inflammation and anemia may also be seen.
- Symmetric synovial inflammation, morning stiffness lasting more than 30 minutes, and numerous extra-articular symptoms such as rheumatoid nodules, amyloidosis, and systemic vasculitis.

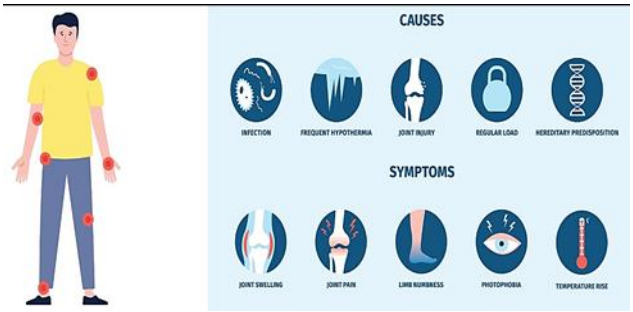

Figure 6: Causes and symptoms of Rheumatoid Arthritis [24]

7. Diagnosis

DMARDs are started after rheumatoid arthritis is fully diagnosed according to the diagnostic criteria. Potentially, this diagnostic procedure enables therapeutic intervention before joint damage. First, several illnesses are ruled out, including osteoarthritis, spondyloarthritis, connective tissue disease with arthritis in one or more joints, and arthritis brought on by crystals [35]. An early identification of RA is a crucial first step towards improving the long-term prognosis. Joint swelling is the hallmark symptom of RA, and any other potential reasons of this swelling need to be ruled out [36]. If symptoms appear before six weeks, a viral process, such parvovirus, may be to blame. Repeated self-limited bouts of sudden swelling of the joints indicate crystal arthropathy; arthrocentesis should be done to check for crystals of calcium pyrophosphate dihydrate or monosodium urate monohydrate [37].

To shift the emphasis from late-stage phase management to early detection of RA, the 2010 American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) classification criteria for RA assess several variables, including risk factors, the number and type of joints involved, and the duration of symptoms [35]. It is now possible to detect and treat people with early inflammatory arthritis who advance to later RA by using newly developed diagnostic criteria. By using these criteria, inflammatory arthritis patients who meet the 1987 ACR criteria in the future can be distinguished from non-RA patients [36].

7.1 Diagnostic Tests

A common feature of autoimmune illnesses like RA is the presence of autoantibodies. Rheumatoid factor is not exclusive to RA; it can also be seen in healthy older people and patients with other illnesses, like hepatitis C. More particular to RA, anti-citrullinated protein antibodies may contribute to the pathophysiology of the disease. Between 50 and 80 percent of people with RA have an antibody to rheumatoid factor and anti-citrullinated protein [37].

- Differential rheumatoid factor and the sedimentation rate of erythrocytes or C-reactive proteins are among the first laboratory tests.
- In certain cases, suction of the joint may be necessary to overcome viral or crystal-induced arthritis (in the event of monoarticular presentations).
- Hepatic and renal baseline function tests (for the selection of drugs) [38].

7.2 Vaccination

Every patient should get a pneumococcal vaccination and an annual influenza vaccination due to the infection risks linked to both RA and immunosuppressive treatment.

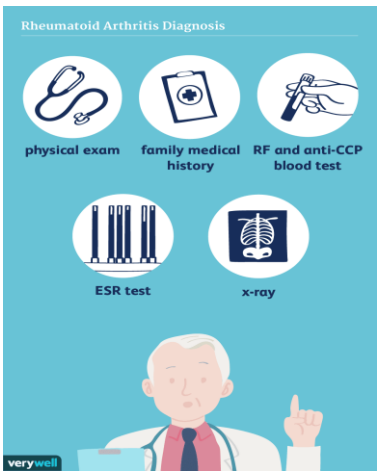

Figure 7: Various Diagnostic tests of Rheumatoid Arthritis[40]

Patients receiving biological therapy or those who have received high-dose steroids (>20 mg prednisolone daily for one week) during the last three months should not get live attenuated vaccinations, including herpes zoster [39].

7.3 Therapy:

Two contemporary management techniques for RA treatment are "Windows of opportunity" and "Treat to Target." To obtain a long-term remission, it means early therapeutic intervention with the goal of changing a pathologic process in the early stages of the disease [41]. Over the past ten years, new drugs that can cause this condition to go into remission have entered clinical use. These include kinase inhibitors, anti-IL1 and anti-IL6 medicines, TNFa blockers, B cell depletion regulators, and lymphocyte co-stimulators, among other disease-modifying antirheumatic medications (DMARDs), both biologic and nonbiologic [42].

7.4 X-rays: When diagnosing rheumatoid arthritis, X-rays are frequently taken. Since the hands and feet are the areas most afflicted by RA, X-rays of these areas are frequently taken. X-rays may be normal in the early stages of RA. As the condition worsens, x-rays may show RA-specific features such as erosions surrounding the joint, subluxation and deformity of the joint, and thinning of the bone surrounding the joint. Rheumatoid arthritis is also treated with X-rays to monitor response to therapy and make sure the condition is not getting worse [43].

7.5 MRI: When rheumatoid arthritis is highly suspected, but the x-rays and antibodies are normal, MRI may be utilized to make the diagnosis. The diagnosis is supported by the presence of synovitis, an inflammation of the joint, or the bone erosion characteristic of RA [44].

7.6 Ultrasound: Since ultrasound is a simple, non-invasive, and reasonably priced technology that can be quickly completed in the office, its use in the diagnosis and follow-up of RA is growing in popularity. According to studies, ultrasonography may detect joint degradation and inflammation just as well as MRI. The proficiency of the individual doing the ultrasound determines how accurate the results will be [45].

8. Advance Treatment of RA

The main goal of treating rheumatoid arthritis is to suppress the disease and induce remission as soon as possible after diagnosis before joint deterioration begins. A thorough evaluation of the disease's activity, imaging results (such as radiography findings), complications, and comorbidities should be used to inform therapeutic strategy decisions [46]. B-cell therapy, TNF-α blocking, angiogenesis-inhibiting drugs, IL-1 and IL-6 inhibitors, and other therapeutic strategies are now being used to treat RA. Commonly used synthetic medications for the treatment of RA include nonsteroidal anti-inflammatory drugs (NSAIDs) and disease-modifying anti-rheumatic drugs (DMARDs), such as methotrexate, cyclophosphamide, sulfasalazine, and intramuscular gold [47]. Studies on the long-term safety and effectiveness of DMARDs are becoming more and more significant as they are used more frequently and for longer periods of time. One such trial involved 1272 RA patients in North America who were given 25 mg of etanercept twice a week for ten years to evaluate the safety and efficacy profile of the drug after ten years of therapy [48].

Table 1: List of some drugs used for the treatment of Rheumatoid Arthritis [56-59]

Drugs	Dosage	Frequent Adverse Effects
Adalimumab	40 mg/2 weeks	Decreased hemoglobin concentration, hypertension, headache, dizziness, drowsiness, upper airway infections, rhinitis, sinusitis, bronchitis, increased coughing, pneumonia, nausea, diarrhea, sore throat
Azathioprine	2–3 mg/kg BW/day	Nausea, vomiting, diarrhea, leukopenia, anemia, infection, drug fever
Certolizumab	200 mg/ 2 weeks after induction phase	Urinary tract infection, herpes simplex, upper airway infections, headache, dizziness, skin rash
Cyclosporine	2.5–3.5 mg/kg BW/day	Lack of appetite, nausea and occasional vomiting, diarrhea, muscle twitching and cramp may indicate magnesium deficiency
Methotrexate	10–25 mg/week	Stomatitis, hair loss, nausea, vomiting, elevated transaminases
Sulfasalazine	2 g/day after initial phase	Exanthema, pruritus, nausea, abdominal pain, lack of appetite, oligospermia, reversible loss of fertility in men, headache, feeling of weakness,
Rituximab	Two doses of 1000 mg at a 2-week interval every 6–12 months	Airway infections, reactions to infusion, influenza-like symptoms, infections, transitory hyperuricemia (15%)

8.1 DMARDS (disease-modifying anti- rheumatic drugs)

Drugs classified as DMARDs target molecules or molecular pathways that are involved in the inflammatory processes associated with RA. It has been demonstrated that some DMARDs are clinically and radiologically effective in the treatment of RA. TNF-α-inhibiting drugs were the initial class of DMARDs with newer medicines targeting B lymphocyte antibodies CD-20, IL6, and CD28 [49]. All rheumatoid arthritis patients should be evaluated for DMARDs. Medication selection is influenced by comorbidities, medical experience, compliance, and the degree of discomfort. Methotrexate, hydroxychloroquine, sulfasalazine, leflunomide, infliximab (Remicade), and etanercept (Enbrel) are the most often used drugs [50].

Basic principles: begin early, have a target: NSARs and GCs can be used to rapidly alleviate symptoms, but we now know that the main objective should be to rapidly prevent the condition from worsening. Adequate and consistent usage of DMARDs 51 is necessary for this. [51]. When DMARDs start during the first six months of diagnosis, over 80% of patient's initial function loss can be restored and in 42% to 48% of instances, the disease can go into remission [52]. There is some evidence that people who are seronegative don't respond as well to DMARD rituximab [53].

8.2 NSAIDS and Corticosteroids: To manage pain and inflammation, NSAIDs and oral, intramuscular, or intraarticular corticosteroids may be prescribed as part of RA medication therapy. Corticosteroids and NSAIDs should ideally only be used for temporary treatment [54]. Aspirin, diclofenac, and ibuprofen are NSAIDs that successfully relieve pain and swelling and enhance joint function; but, because they do not stop further joint deterioration, they are not disease-modifying medications. Mechanistically, the anti-inflammatory actions of NSAIDs can be mainly related to the reduction of proteinoid production [55].

CONCLUSION

In this article we have concluded that rheumatoid arthritis is a complex autoimmune disorder. It is characterized by chronic inflammation of the joints, pain, stiffness, and joint damage. It also affects other organs, impacting a patient's quality of life. The understanding of how RA works has resulted in specific treatments, like DMARDs, NSAIDs, and corticosteroids, that can help manage symptoms effectively. Through various test and examinations, we are able to recognise cause of disease and can customised treatment according to it for individual patients. Early diagnosis and timely intervention can improve a patient's life and prevent disease. Continued research into the immunological mechanism of RA holds promise for more personalized and effective strategies in the future.

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