Section A -Research paper

Rheumatoid arthritis: Etiology, Diagnosis and Management: Review Article

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Abstract:

Rheumatoid arthritis (RA) is a multifactorial autoimmune disease of unknown etiology, primarily affecting the joints, then extra-articular manifestations can occur. Due to its complexity, which is based on an incompletely elucidated pathophysiological mechanism, good RA management requires a multidisciplinary approach. The clinical status of RA patients has improved in recent years due to medical advances in diagnosis and treatment, that have made it possible to reduce disease activity and prevent systemic complications. The most promising results were obtained by developing disease-modifying anti-rheumatic drugs (DMARDs), the class to which conventional synthetic, biologic, and targeted synthetic drugs belong.

Keywords: Rheumatoid arthritis**,** Etiology

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Introduction:

Rheumatoid arthritis is an autoimmune inflammatory disease primarily characterized by synovitis. It commonly affects women in their 30s to 50s, with an incidence of 1 in 150. resulting in irreversible physical dysfunction and deformation of the affected joints. Thus, proper diagnosis and treatment are required in the early stages of the disease. If the disease is active for some time without adequate control, it can typically lead to chronic joint damage and subsequent disability with deformity, as you can see in figures 1 and 2 **(1).**

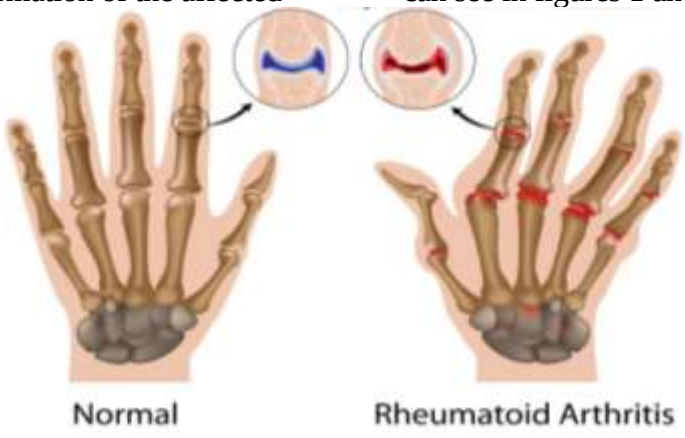

Figure 1: Difference between a healthy hand and a hand with joint damage and deformity due to rheumatoid arthritis (1).

Figure 2: RA patient with hand deformities (1)

Clinically, the symptoms of RA significantly differ between early-stage RA and later, insufficiently treated stages of the disease. Early-stage RA is characterized by generalized disease symptoms such as fatigue, a flu-like feeling, swollen and tender joints, and morning stiffness and is paralleled by elevated levels of C-reactive protein (CRP) and an increased erythrocyte sedimentation rate (ESR) **(2).**

Epidemiology

Although the prevalence of RA in some regions is unknown due to a lack of strong epidemiological studies, the reported rates seem fairly constant in many populations. Most epidemiological studies in RA have been done in Western countries, showing a prevalence of RA in the range of 0.5–1.0% in white individuals **(3).**

Aetiology

The aetiology of RA remains unknown. It is thought to result from the interaction between patients' genotype and environment. In a nationwide study of 91 monozygotic (MZ) and 112 dizygotic (DZ) twin pairs in the United Kingdom, the overall MZ concordance rate was 15% and 5% among dizygotic twins. The heritability of rheumatoid arthritis is approximately 40% to 65% for seropositive rheumatoid arthritis and 20% for seronegative rheumatoid arthritis.**(4).**

The risk of developing rheumatoid arthritis has been associated with three HLA-DRB1 alleles: HLA-DRB1*04, HLA-DRB1*01, and HLA-DRB1*10. These HLA-DRB1 alleles contain a stretch of conserved five amino acid sequences and the shared epitope (SE) in the third hypervariable region of their DRB1 chain, which has been associated with the risk of developing RA**(5).**

It has been suggested that polymorphisms in the signal transducers and activators of transcription (STAT)-4 and interleukin (IL)-10 genes also confer susceptibility to RA. Single nucleotide polymorphisms (SNPs) in PSORS1C1,

PTPN2, and MIR146A genes are associated with severe disease**(6).**

The human leukocyte antigen-shared epitope (HLA-SE) is the most well-known and strongest genetic risk factor for the development of rheumatoid arthritis (RA), especially for anti-citrullinated protein antibody (ACPA)-positive RA. Similarly, smoking is the strongest environmental risk factor for autoantibody-positive RA**(7).**

Changes in the composition and function of the intestinal microbiome have been related to rheumatoid arthritis as well. The composition of the gut microbiome becomes altered in patients with rheumatoid arthritis (dysbiosis), and rheumatoid arthritis patients have decreased gut microbiome diversity compared with healthy individuals. There is an increase in these genera: *Actinobacteria, Collinsella, Eggerthalla, and Faecalibacterium. Collinsella* alters gut mucosal permeability and has been related to increased rheumatoid arthritis disease severity**(8).**

Pathophysiology of Rheumatoid Arthritis

Although the pathophysiological mechanisms for RA are not fully explained, several hypotheses have been postulated. It has been reported that immunological processes can occur many years before symptoms of joint inflammation are noticed, the so-called pre-RA phase **(9).**

The interactions between epigenetic modifications on the genomic structure and environmental factors can lead to modified self-antigens, as in the case of immunoglobulin G (IgG), type 2 collagen, and vimentin. These proteins with arginine residues can be converted to citrulline by peptidyl arginine deiminases in a post-translational modification called citrullination**(10).**

Moreover, joint disorders like synovial hyperplasia or synovial infections can trigger cytokine release that may cause joint inflammation, as well as modified self-antigens. **(11).**

Due to the susceptibility genes HLA-DR1 and HLA-DR4, the immune system is no longer able to recognize citrullinated proteins (vimentin, type II collagen, histones, fibrin, fibronectin, Epstein-Barr nuclear antigen 1, _-enolase) as self-structures. Antigens are taken up by antigen-presenting cells (APC), which are dendritic cells that are activated to initiate an immune response. The whole complex migrates to the lymph node, where the activation of CD4+ helper T cells takes place. Furthermore, the germinal center of the lymph node contains B cells that get activated by reciprocal and sequential signals with T cells, an immunological process called costimulation**(12).**

An example of costimulation is the interaction between CD28 and CD80/86. At this level, B cells undergo somatic hypermutation or class-switch recombination and start to proliferate and differentiate into plasma cells that produce autoantibodies depending on the receptors of the precursor cells. Autoantibodies are proteins produced by an immune system that no longer discriminates self from non-self structures, so self-tissues and organs are accidentally targeted**(13).**

RF and ACPA are the most studied autoantibodies involved in RA. RF is an IgM antibody with a testing specificity of 85% in RA patients that targets the Fc portion of IgG, also called the constant region. It also forms an immune complex with IgG and complement proteins, a complex that can migrate in the synovial fluid. However, ACPA is more specific for RA and targets citrullinated proteins, and after their binding interactions, immune complexes are formed with an accumulation in the synovial fluid. **(14).**

All the features of an immune response in the pre-RA phase are summarized in **Figure 3.**

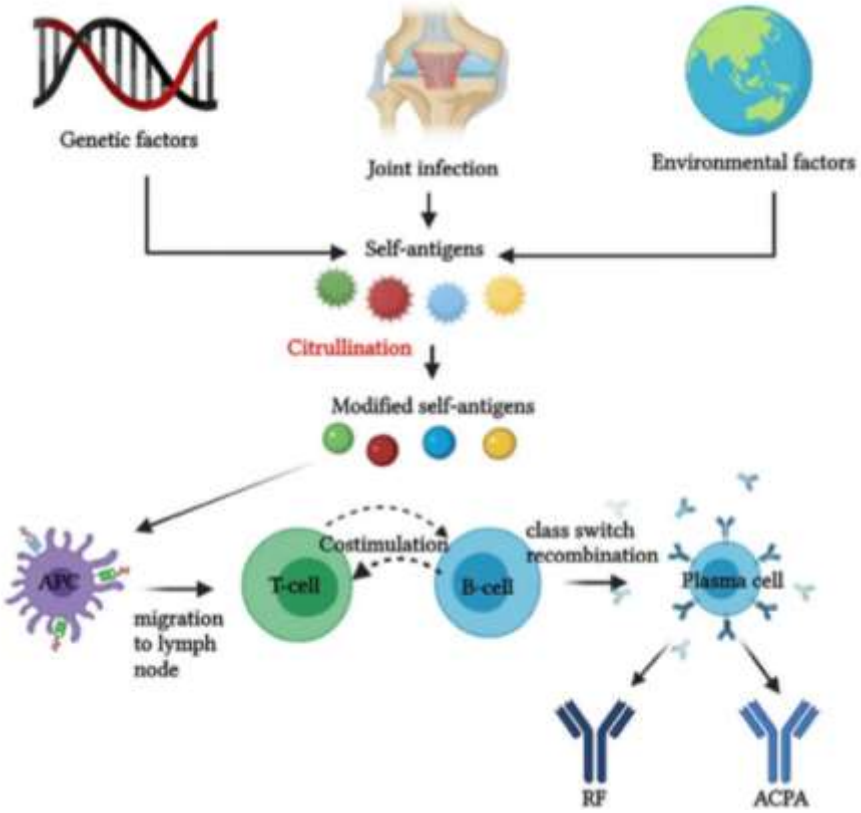

Figure 3. Immunological processes in the pre-RA phase. ACPA, anti-citrullinated protein antibodies; APC, antigenpresenting cells; RF, rheumatoid factor (13).

Risk factors

Risk factors for developing RA can be generically divided into host- and environment-related categories. Host factors that have been associated with RA development may be further grouped into genetic, epigenetic, hormonal, reproductive, neuroendocrine, and comorbid host factors. In turn, environmental risk factors include smoking and other airborne exposures; microbiota and infectious agents; diet; and socioeconomic factors. Herein, we provide a state-of-the-art overview of the current knowledge on this topic, aimed at clinicians and researchers in the field of RA **(15).**

Host Factors

As with many other immune-mediated diseases, the host is closely linked to the risk of developing RA. This includes, first and foremost, genetic factors, which account for a major proportion of disease risk. More recently, epigenetic mechanisms have been identified as being directly involved in RA pathogenesis, modulating the risk of disease development. Notably, they can be influenced by the environment, linking extrinsic and intrinsic factors. Hormonal, reproductive, and neuroendocrine factors have long been proposed as contributing to RA, given the observed female preponderance of the disease. Finally, a number of concomitant pre-existing conditions have been proposed to increase the risk of an RA incident. **(15).**

Genetic Factors

Data supporting a genetic component in RA first arose from familial and twin studies. In fact, the risk of a monozygotic twin of an RA patient for developing RA is 9–15%, which is up to 4-fold that seen for dizygotic twins, and much higher than the general **(16).** Likewise, first-degree relatives have a relative risk of RA that varies from 2 to 5 and is similar in men and women **(17).**

Epigenetic Factors

In the last decade, the role of epigenetics in RA development has started to be unraveled. Epigenetic mechanisms induce heritable variations in gene expression without actual changes in the deoxyribonucleic acid (DNA) sequence **(18).** In this way, they may help to explain the low concordance rate observed between monozygotic twins (9–15%) (8–10) and the incomplete contribution of genetic factors to the disease. Indeed, a recent large epigenome-wide association study found differentially variable methylation signatures in monozygotic twin pairs discordant for RA. Additionally, because epigenetic modifications can be induced by external stimuli (e.g., drugs, smoke, diet), they might provide the link between genome and environment interactions. The major epigenetic changes include DNA methylation, post-translational histone modifications, and non-coding RNAs, all of which have been shown to contribute to RA susceptibility**(19).**

Hormonal, Reproductive and Neuroendocrine Factors

Considering the female preponderance in the distribution of RA**,** hormonal and sex-related factors have long been investigated as predisposing to the disease. The sex imbalance is commonly attributed to estrogens, which are generally described as being pro-inflammatory, in opposition to the anti-inflammatory effects of progesterone and androgens, which are decreased in both male and female RA patients. However, their actions are far more complex, and in fact, estrogens also possess anti-inflammatory properties in a number of cells and tissues. **(20).**

The global net effect is likely dependent on other factors such as serum and tissue concentrations, predominant cell types, and oestrogen receptors involved, as well as the reproductive stage **(15).**

These mechanistic aspects are important to understand the conflicting findings reported for a number of hormonal and reproductive factors in the risk of RA. Parity, breastfeeding, pregnancy loss, early menarche, age at first pregnancy, Oral contraceptives (OCs), and hormone replacement therapy have all been associated with increased, unchanged, or decreased likelihood of development of RA **(20).**

Environmental Factors

Although the data above support a large impact of the host on the development of RA, the environment also plays a fundamental role in determining the ultimate risk of the disease. In fact, extrinsic factors have been identified that interact with at-risk subjects and confer a multiplicative increase in the likelihood of developing RA. Environmental factors can be roughly grouped into four categories: airborne exposures, notably including smoking; microbiota and infectious agents; diet; and socioeconomic factors, including occupational and recreational exposures. Extensive data are available directly implicating these numerous aspects in the aetiology of RA **(15).**

Smoking and other airborne exposures

The recognition of the lung as a major site of early pathogenic events has been one of the great breakthroughs in the understanding of the disease and is well-exemplified by the strong association of several airborne noxious agents with RA**(21).**

Smoking is the most important of such exposures and has been established as one of the main risk factors for the development of RA. Its association with RA has been extensively replicated since the first description more than three decades ago, and smoking is currently thought to explain 20–25% of overall RA risk and up to 35% of ACPA-positive RA **(15).**

Several other inhaled agents are thought to exert similar harmful effects and increase the risk of RA. The first to be recognised and best studied is silica, a common occupational exposure (e.g., in mining, construction, or ceramic industries) that is independently associated with RA**(22).**

it is specifically associated with ACPA. positive RA, and both exposures have an additive effect, which increases with pack-years of smoking**(23).**

Diet

The epidemiological association of dietary factors with RA has been extensively studied. In spite of the difficulties in accurately assessing patient nutritional behaviour before RA onset and isolating the effect of a given food, drink, or nutrient, some findings are consistent. Importantly, they also provide clues on RA aetiology and pathogenesis, as shown by the influence of the modulation of the intestinal microbiome by diet on the risk of developing RA**(24).**

Socioeconomic and Other Environmental Factors

A lower socioeconomic status seems to increase RA risk, although it probably has a stronger link with poor disease outcomes. A lower level of education is independently

associated with RA, particularly with seropositive disease. Although earlier reports did not find a significant effect of education or other socioeconomic factors on RA risk, the associations observed in the positive studies could not be attributed to smoking or other known socioeconomic or lifestyle factors. Moreover, low childhood (i.e., parental) household education and other poor early life socioeconomic status (food insecurity, young maternal age) have also been linked to greater development of adult RA, further supporting the positive epidemiologic observations **(15).**

Clinical features of rheumatoid arthritis

The clinical manifestations of RA are highly varied. In some patients, the disease starts quietly and with fatigue, anorexia, general malaise, and vague musculoskeletal symptoms until later synovitis. These early symptoms may persist for weeks or months, making it difficult to diagnose. RA is a symmetric polyarthritis that primarily involves the small joints of the foot, wrist, and ankle. Other joints that are most commonly involved are the cervical spine, shoulders, elbows, hips, and knees. In about 10% of the patients, the onset is more acute, and polyarthritis develops rapidly, accompanied by symptoms like fever, lymphadenopathy, and splenomegaly. In 1.3% of the patients, the symptoms are initially confined to one or more joints. Although it may be possible for some patients to have unsymmetrical joint involvement, the symmetrical involvement of the joints is typical. Long morning stiffness usually lasts more than an hour and often several hours, which is a classic feature of RA and other inflammatory arthropathies. Likewise, after prolonged inactivity, joint stiffness increases and symptoms generally improve with moderate activity**.**

RA is a systemic disease and has various extra-articular symptoms. Easily palpable subcutaneous rheumatoid nodules are usually found in the elbow area and, to a lesser extent, in the lungs and elsewhere, and rarely in the heart. The incidence of multiple pulmonary nodules in a patient with RA is called Caplan's syndrome. Pleuritis, pericarditis, and interstitial lung disease (ILD) are seen in a small number of patients. Felty's syndrome is a rare complication and is usually seen with vasculitis **(25).**

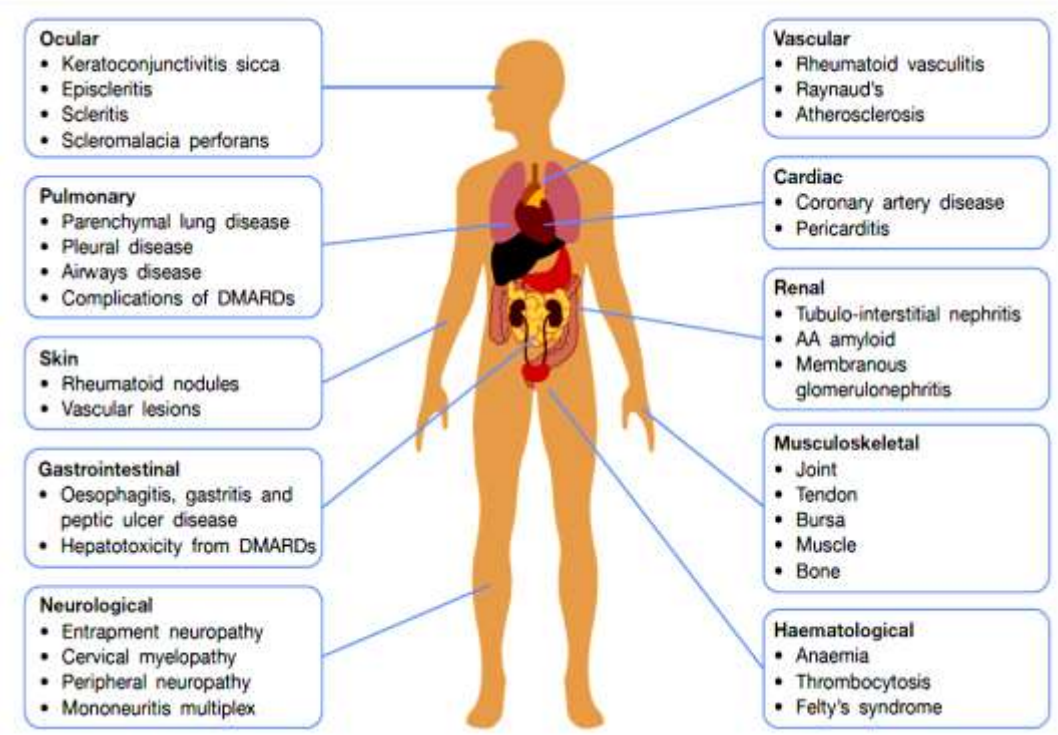

Figure 4: Clinical manifestation of RA (26).

Diagnosis

RA is a clinical diagnosis. It is easy to diagnose RA in the presence of a typical, stabilized disease. In most of the patients, the disease shows its typical clinical symptoms within 1 to 2 years after onset. Symmetrical synovitis of the small joints is a classic sign for the patient during admission. About 20–30% of the patients are admitted with one joint involvement (usually in the knee joint). The temperamental symptoms that show the inflammatory nature of the disease, like morning stiffness, reinforce the diagnosis of RA. Subcutaneous nodules are a good diagnostic mark **(27)**

Patients with RA typically present with pain and stiffness in multiple joints. The wrists, proximal interphalangeal joints, and metacarpophalangeal joints are most commonly involved. Morning stiffness lasting more than one hour suggests an inflammatory etiology. Boggy swelling due to synovitis may be visible or subtle synovial thickening may be palpable on joint examination. Patients may also present with more indolent arthralgias before the onset of clinically apparent joint swelling. Systemic symptoms of fatigue, weight loss, and low-grade fever may occur with active disease **(28).**

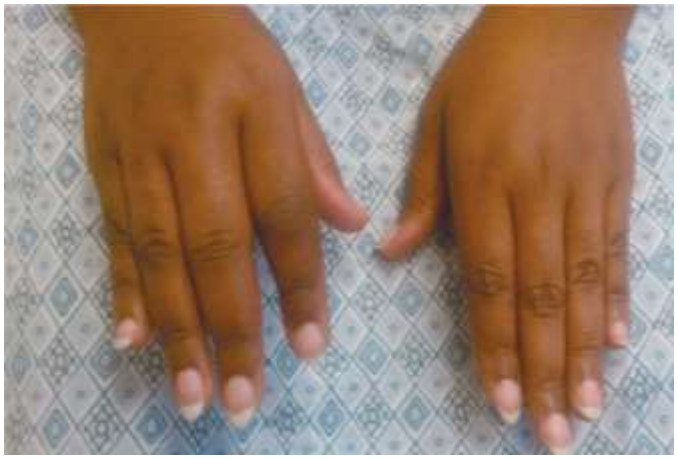

Figure 5: Boggy swelling in proximal interphalangeal and metacarpophalangeal joints (more prominent on patient's right hand) in a patient with new-onset rheumatoid arthritis. Note that with joint swelling, the skin creases over the proximal interphalangeal joints become less apparent (28).

Diagnostic criteria

In 2010, the American College of Rheumatology and European League Against Rheumatism collaborated to create new classification criteria for

The new criteria are an effort to diagnose RA earlier in patients who may not meet the 1987 American College of Rheumatology classification criteria. The 2010 criteria do not include presence of rheumatoid nodules or radiographic **(28).**

Imaging diagnosis of RA

Accurate diagnosis involves the association between the detection and quantification of biomarkers with imaging tools. The ACR-EULAR 2010 classification includes ultrasonography, computed tomography (CT), and magnetic resonance imaging (MRI) as imaging tools for establishing an early diagnosis, due to their much higher accuracy than in the case of conventional radiographs (**29).**

X-ray examinations of joints cannot reveal the early presence of degradation and erosion **(30).**

Even though X-rays are still used as a diagnosis technique for late changes in the joints. Moreover, a few radiographic hallmarks of RA have been identified, including symmetrical abnormalities, periarticular osteopenia, narrowing of the joint spaces, and marginal degradation. swelling of the soft tissue and synovial cysts and nodules **(31).**

Ultrasonography is a diagnostic technique. It can detect small bone and cartilage erosions and explore the structures in great detail. Doppler ultrasound may differentiate active from inactive inflammatory tissues. Ultrasonography detectes more erosions, especially in early RA **(32).**

CT is a rarely used imaging technique that, due to its ionizing radiation, can damage the deoxyribonucleic acid (DNA) of human cells and has limited soft tissue contrast **(31).**

However, it can be successfully used in medical cases where 3D imaging is required. Clinical trials conducted over time have demonstrated similarities between CT and MRI **(33).**

However, MRI is the most accurate imaging tool for the detection of early RA. Contrast-enhanced MRI can generate a differential diagnosis between joint effusion and synovitis. Furthermore, it can detect early erosions and hypertrophies, and it is the gold standard for bone marrow edema detection. A recent longitudinal study evaluated the role of MRI in predicting RA progression in patients with clinical symptoms but showed no correlation between them, even though the detection accuracy was high **(34).**

Treatment of Rheumatoid arthritis

The goals of treatment for RA are to reduce joint inflammation and pain, maximize joint function, and prevent joint destruction and deformity. Treatment regimens consist of combinations of pharmaceuticals, weight bearing exercise, educating patients about the disease, and rest. Treatments are generally customized to a patient's needs and depend on their overall health. This includes factors such as disease progression, the joints involved, age, overall health, occupation, compliance, and education about the disease **(35).**

First-Line Management: NSAIDS and Corticosteroids

The overall goal of first-line treatment is to relieve pain and decrease inflammation. Medications, considered to be fast-acting, are:

Nonsteroidal anti-inflammatory drugs (NSAIDs) include non-selective acetylsalicylate, naproxen, ibuprofen, and etodolac. Aspirin is an effective anti-inflammatory for RA when used at high doses, It is one of the oldest NSAIDs used for joint pain. NSAIDs work by inhibiting cyclo-oxygenase to prevent the synthesis of prostaglandins, prostacyclin, and thromboxanes. Common side effects are nausea, abdominal pain, ulcers, and gastrointestinal (GI) bleeding.

An even newer NSAID called celecoxib (Celebrex) is a selective Cox-2 inhibitor that has less risk of GI side effects [**(35).**

Corticosteroids are a more potent anti-inflammatory medication than NSAIDs, but they come with greater side effects. For this reason, they are only indicated for a short period of time at low doses as abridge therapy, during exacerbations or flares of RA. Intra-articular injections of corticosteroids can be used for the local symptoms of inflammation. They work by preventing the release of phospholipids and decreasing the actions of eosinophils, thereby decreasing inflammation. Their side effects include bone-thinning, weight gain, diabetes, and immunosuppression. Advising the patient to take calcium and vitamin D supplementation can prevent thinning of the bone. **(36).**

Second-Line Management: Disease-Modifying

Anti-rheumatic Drugs

The overall goal of second-line treatment is to promote remission by slowing or stopping the progression of joint destruction and deformity. Medications are considered to be slow-acting because they take from weeks to months to be effective. **(37).**

Methotrexate (MTX) is the initial second-line drug (also considered an anchor drug). It is an analog to folic acid that competitively inhibits the binding of dihydrofolic acid (FH2) to the enzyme that is responsible for converting FH2 to folinic acid (FH4). Without FH4, the metabolism of purine and pyrimidine is impaired, and the

synthesis of amino acids and polyamine is inhibited. MTX is an immunosuppressive drug that requires regular blood tests due to its side effects, i.e., liver problems, cirrhosis, and bone marrow deterioration. Folic acid supplementation can reduce the risk of side effects. It is an effective DMARD, has a lower incidence of side effects than other DMARDs, and has dosage flexibility, meaning that doses can be adjusted as needed **(38).**

Antimalarial: **Hydroxychloroquine sulfate and chloroquine** is an antimalarial drug and can be used for long-term treatment of RA. This drug decreases the secretion of monocyte-derived proinflammatory cytokines. Common side effects include problems in the GI tract, skin, and central nervous system. The eyes, in particular, can be affected when this drug is taken at high doses. Patients on this medication require routine consultation with an ophthalmologist.

Leflunomide is an oral medication that is converted to malononitrilamide, which inhibits the synthesis of ribonucleotide uridine monophosphate pyrimidine. It relieves symptoms and retards the progression of RA. It is recommended to be used in combination with MTX but can constitute a monotherapy if patients do not respond to MTX. Side effects include hypertension, GI upset, liver damage, leukopenia, interstitial lung disease, neuropathy, rash, and bone marrow damage**(39)**.

Sulfasalazine is a DMARD typically used in the treatment of irritable bowel disease. Combined with anti-inflammatory medications, this DMARD can be used to treat RA. The mechanism of action of this drug in the treatment of RA has not been identified. It is thought that sulfapyridine, a reduced form of the medication after administration, may reduce secretions of interleukin (IL)-8 and monocyte chemoattractant protein (MCP). This drug has side effects of GI and central nervous system symptoms as well as rash. It is usually well-tolerated among patients, but should be avoided in patients with sulfa allergies since it contains sulfa and salicylate compounds **(35).**

Biologics

Also known as biological DMARDs, are rapidly effective in retarding the progression of the joint damage caused by RA. They are considered to be a more "direct, defined and targeted" method of treatment **(40).** Nonetheless, biologics pose the problem of serious side effects, such as increased risk of infections. Other common side effects include neurologic diseases like multiple sclerosis and lymphoma **(41).**

Tumor necrosis factor (TNF) is a messenger protein that promotes inflammation in joints. Biologic medications such as etanercept, infliximab, adalimumab, golimumab, and certolizumab pegol are all TNF inhibitors that prevent the recruitment of the cells that cause inflammation, bringing rapid symptom relief. They are recommended if other second-line medications are not effective. Unfortunately, these medications tend to be very expensive and their role in treating patients at various stages of RA and with various mechanisms of action is a matter of continuous investigation. They are often used in combination with other DMARDs, especially MTX. TNF inhibitors are contraindicated in patients with congestive heart failure of demyelinating diseases. Each biologic medication has a different mode of administration **(42).**

Anakinra is a drug that is injected subcutaneously daily. It works by binding to IL-1, a chemical messenger of inflammation. It can be used in combination with other DMARDs or as a monotherapy, but due its low response rate compared to other biologics, it is not used as frequently **(43).**

Rituximab is useful in RA because it depletes the B cells responsible for inflammation and the production of abnormal antibodies. Typically used in the treatment of lymphoma, this drug can be used in cases of RA where TNF inhibitors have failed. In addition, rituximab has shown benefits in treating the complications of RA, such as vasculitis and cryoglobulinemia. It is administered as an intravenous infusion in 2 doses, 2 weeks apart, every 6 months **(44).**

Abatacept is a biologic medication that works by blocking T cell activation. This is given as an intravenous infusion once a month or subcutaneously once a week. It is used in patients who have not been effectively treated with traditional DMARDs**(45).**

Tocilizumab is a biologic that works by blocking IL-6, a chemical messenger of inflammation. It is administered via intravenous infusion given monthly or via weekly subcutaneous injections. It is also used for patients who have not been effectively treated with traditional DMARDs **Lastly, tofacitinib** has a different mechanism of action and works by blocking Janus kinases within cells, which are enzymes of inflammation. For this reason, it is known as a JAK inhibitor. This medication is used for patients who have not been effectively treated with MTX. Tofacitinib is taken orally twice daily, alone or in combination with MTX. It should not be used in combination with traditional biologic medications or other potent immunosuppressants **(46).**

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