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Recent Advances in Clinical Investigations and Novel Therapeutic Approaches in the Management of Rheumatoid Arthritis

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A B S T R A C T

Rheumatoid arthritis (RA) causes joint inflammation and pain. It happens when the immune system doesn't work properly and attacks the lining of the joints, called the synovium. The disease commonly affects the hands, knees or ankles, and usually the same joint on both sides of the body, such as both hands or both knees. But sometimes RA causes problems in other parts of the body as well, such as the eyes, heart and circulatory system and/or the lungs. In a healthy person, the immune system fights invaders, such as bacteria and viruses. With an autoimmune disease like RA, the immune system mistakes the body's cells for foreign invaders and releases inflammatory chemicals that attack those cells. Tn RA, it attacks the synovium, the tissue lining around a joint that produces a fluid to help the joint move smoothly. The inflamed synovium gets thicker and makes the joint area feel painful and tender and look red and swollen, and moving the joint may be difficult. In the early stages, people with RA may not see redness or swelling in the joints, but they may experience tenderness and pain. RA can cause the ends of the bones within a joint to wear down (erosions). An X-ray, ultrasound, or MRI (magnetic resonance imaging) scan can look for erosions. Imaging results can also show how well treatment is working. RA with a symptom duration of fewer than six months is defined as early RA, and when the symptoms have been present for more than six months, it is defined as established RA. RA, if untreated, is a progressive disease with morbidity and increased mortality. This activity describes the evaluation and management of rheumatoid arthritis and reviews the role of the interprofessional team in improving care for patients with this condition.

Keywords: Rheumatoid arthritis, immune system, autoimmune disease, erosions, management.

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1. Introduction

Rheumatoid arthritis (RA) is a systemic autoimmune disease characterized by inflammatory arthritis and extra-articular involvement. It is a chronic inflammatory disorder caused in many cases by the interaction between genes and environmental factors, including tobacco, that primarily involves synovial joints. It typically starts in small

peripheral joints, is usually symmetric, and progresses to involve proximal joints if left untreated. Joint inflammation over time leads to the destruction of the joint with loss of cartilage and bone erosions. RA with symptom duration of fewer than six months is defined as early RA, and when the symptoms have been present for more than six months, it is defined as established RA.RA, if untreated, is a progressive disease with morbidity and increased mortality.

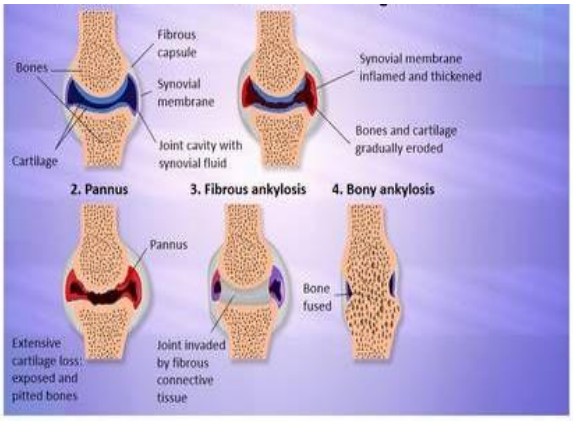

Fig 1: Stages of RA

History of rheumatoid arthritis

Eith descriptions in the Ebers Papyrus around 1500 BC and evidence of the disease in Egyptian mummies. While ancient texts mentioned similar conditions, the modern medical understanding of RA began with Augustin Jacob Landré-Beauvais's 1800 dissertation. The term "rheumatoid arthritis" was coined in 1890, and treatments have evolved from simple rest to modern disease-modifying drugs1-6.

Ancient and classical history

1500 BC: The Ebers Papyrus describes a condition similar to RA.

400 BC: Hippocrates notes an arthritic condition that begins in the hands and feet, although he doesn't specify RA.

300–200 BC: Ancient Indian medical texts like the Charak Samhita describe joint pain, swelling, and loss of mobility.

Ancient Egypt: Skeletal remains of mummies show deformities consistent with RA.

Galen (129–216 AD): Introduced the term "rheumatismus".

Modern history

1800: Augustin Jacob Landré-Beauvais gives the first modern medical description of the disease in Paris. He noted it primarily affected the poor and women more frequently than men.

1890: The term "rheumatoid arthritis" is officially adopted, replacing older terms like arthritis deformans.

19th Century: Artists like Rembrandt and Rubens depicted the hand deformities of RA, and Thomas Sydenham wrote about its chronic and progressive nature.

1948:Glucocorticoid treatment becomes available, reducing symptoms.

Late 20th Century: Disease-modifying antirheumatic drugs (DMARDs) are introduced, which can slow the progression of the disease7-11.

Etiology

The etiology of RA has a significant basis in genetics. It is thought to result from the interaction between patients' genotypes and environmental factors. 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 in dizygotic twins, 5%. The heritability of rheumatoid arthritis is approximately 40% to 65% for seropositive rheumatoid arthritis and 20% for seronegative rheumatoid arthritis. The risk of developing rheumatoid arthritis has been associated with HLA-DRB1 alleles: HLA-DRB1*04, HLA-DRB1*01, and HLA-DRB1*10. These HLA-DRB1 alleles contain a stretch of a conserved sequence of 5 amino acids referred to as the "shared epitope" (SE) in the third hypervariable region of their DRB1 chain, which has been associated with the risk of developing RA.

Polymorphisms in other genes are associated with RA, including PAD14, PTPN22, CTLA4, IL-2RA, STAT4, TRAF1, CCR6, and IRF5. Single nucleotide polymorphism (SNP) in PSORS1C1, PTPN22, and MIR146A genes are associated with severe disease. The term epigenetics refers to heritable changes without altering the DNA sequence. These changes may be present in chromatin or the DNA. These include DNA methylation, histone modification, and non-coding RNA-mediated regulation. RA-FLS (fibroblast-like synoviocytes) overexpress tyrosine phosphatase SHP-2, coded by gene PTPN11, compared to synoviocytes from osteoarthritis (OA) patients, promoting the invasive nature of RA-FLS. The enhancer region of the PTPN11 intron contained two hypermethylated sites, resulting in abnormal epigenetic regulation of the gene and alteration of the function of RA-FLS.

2. Epidemiology

The worldwide prevalence of RA in the Global Burden of Disease 2010 Study is about 0.24%. The prevalence of RA is higher in Western and Northern Europe, North America, and other regions with people of European descent, such as Australia. The prevalence is lower in Central and South America and even lower in East Asia and Africa. The annual incidence of RA in the United States and other western nations of northern Europe is about 40 per 100,000 persons. According to epidemiologic data, RA is more prevalent in women compared to men, with a lifetime risk of RA of 3.6% in women compared to 1.7% in men. RA risk also increases with age, with a peak incidence between age 65 to 80 years of age[12-17].

The period prevalence of RA was more in urban areas (0.69%) than in rural areas (0.54%). The period prevalence of RA was higher in high-income countries (0.49%) compared to low-income countries (0.35.%). RA prevalence was higher in North America and Europe and lower in Asia and South America (See Table below). Data from Africa is limited and varies significantly by country, with RA being more common in North Africa and lower in sub-Saharan Africa. As outlined above, there is a genetic disposition towards RA, which was demonstrated to be about 40% in a large study from Sweden in 2013. The study also reported a higher heritability for seropositive RA and early-onset RA. According to their report, the risk of RA

with a first-degree relative positive for RA is three-fold higher than a second-degree relative with RA giving a two-fold higher risk. Multiple different genetic predispositions to explain this finding have now been identified. The strongest genetic predisposition for RA is from the HLA-DRB1 region (shared epitope). Among modifiable risk factors, cigarette smoking has the strongest association with RA. Diet and nutrition have been shown to play a significant role as environmental triggers for RA. The typical 'western' diet that is rich, high in caloric content, and low in fiber increases the risk of RA.

3. Pathophysiology

RA, in some patients, is triggered by some sort of environmental factor in a genetically predisposed host. The best example is tobacco use in a patient with the HLA-DRB1 "shared epitope" gene and the development of ACPA-positive RA. RF and ACPA antibodies are the best-known autoantibodies in RA, but several other autoantibodies are relatively specific for RA. The presence of antibodies in rheumatoid arthritis is referred to as seropositive RA. RF is an antibody of any isotype that binds to the Fc portion of IgG.

RA patients often have antibodies to citrullinated proteins. These antibodies have been identified in patients with RA since 1964 (antiperinuclear factor) and were also described in 1979 (anti-keratin antibodies) by different assays. In the 1990s, these antibodies were determined to be the same antibodies with high specificity for RA. The antibodies were found to have specificity for filaggrin, a citrullinated peptide. The epitope for these antibodies is citrullinated peptides. A cyclic citrullinated peptide (CCP) was synthesized, which could be used in an ELISA to test for these antibodies in patients in a clinical situation. These antibodies are called anti-cyclic citrullinated peptide antibodies (ACPA). Citrulline is derived from the post-transcriptional modification of arginine by peptidyl arginine deiminase (PAD). This reaction occurs at sites of tissue damage and inflammation, such as the lungs in smokers. HLA-DRB1 shared epitope preferentially presents epitopes containing citrulline. ACPA can be IgG, IgM, or IgA isotypes. ACPA can bind citrullinated residues on self-proteins like vimentin, fibronectin, fibrinogen, histones, and type 2 collagen[18-25].

Anti-carbamylated protein antibodies (anti-CarP antibodies) are also found in patients with RA. Carbamlyation is the conversion of lysine to homocitrulline in the presence of urea and cyanate. Myeloperoxidase converts thiocyanate to cyanate. The molecular structure of homocitrulline is similar to citrulline; however, anti-CarP antibodies are distinct antibodies that have been associated with RA in both ACPA-positive and ACPA-negative patients. There are other autoantibodies that have been described in RA patients, including those directed against fibrinogen, enolase, and vimentin.

The immune response in RA starts at sites distant from the synovial joints, such as the lung, gums, and GI tract. In these tissues, modified proteins are produced by biochemical reactions such citrullination. The mechanism behind environment-triggered RA is thought to be due to the repeated activation of innate immunity. Using the lungs as an example, cigarette smoking induces peptidyl arginine deiminase (PAD) expression in alveolar macrophages, which leads to the conversion of arginine to citrulline in the airway. This process creates a "neoantigen" that activates an immune response and leads to the formation of anti-citrullinated protein antibodies (ACPAs).

Patients are genetically predisposed to develop an immune response to the modified proteins, anti-modified protein antibodies (AMPA). Citrullination is produced by the action of PAD on arginine. Isoforms PAD2 and PAD4 are most strongly implicated in RA. Anti-PAD4 antibodies are found in patients with RA, are highly specific for RA, and are associated with ACPA positivity in other mucosal areas, the inflammatory response in gingivitis is associated with the presence of *Porphyromonasgingivalis*, which causes an inflammatory reaction. There is an influx of leukocytes that produce PAD4. *P gingivalis* also produces a PAD-like enzyme. These enzymes can citrullinate resident proteins, which then can act as autoantigens. Anti-acetylated protein antibodies have recently been associated with RA (in approximately 40% of RA patients), predominately in seropositive patients. Acetylation is an enzymatic process converting lysine to acetyllysine, thought to be mediated by bacteria, which may provide a link to RA and microbiome dysbiosis. The exact mechanism at this time remains unclear. So there are several types of modified proteins that can be the target of autoantibodies produced by citrullination, carbamylation, and acetylation[26-33].

Autoantibodies appear before the onset of clinical arthritis. Autoimmunity starts at the molecular and cellular level long before the clinical phase of RA, often referred to as pre-symptomatic or pre-clinical RA. During this phase, certain immunologic and biochemical abnormalities have been found, but the patients are asymptomatic. RF and ACPA can be present in the serum up to 10 years before the onset of clinical symptoms. With time the concentration of ACPA and serum cytokine levels increase. Many patients develop autoantibodies but do not develop the overt disease. Some patients will eventually transition from autoimmunity to immune-mediated inflammation primarily focused in the synovium. These autoantibodies are produced by plasma cells in the synovium. The synovium in RA is infiltrated by immune cells, which include innate immune cells (monocytes, dendritic cells, mast cells) and adaptive immune cells (T-helper 1, Th1); T-helper 17, Th17), B cells, and plasma cells). Synovial fibroblast-like synovial cells (FSC) are activated. Neutrophils are not present in the synovium but egress from the blood to the synovial fluid.

Cytokines and chemokines such as tumor necrosis factor (TNF), interleukin-6 (IL-6), and granulocyte-monocyte colony-stimulating factor (GM-CSF) activate endothelial cells and attract immune cells within the synovial compartment. The FSC in the rheumatoid synovium

changes to an invasive phenotype. FSC and inflammatory cells produce RANKL leads to osteoclast generation resulting in bone erosions, the hallmark feature of rheumatoid arthritis. It is important to note that synovial biopsies in seropositive patients with arthralgia were essentially unremarkable. It is theorized that a second environmental trigger is needed to cause clinically apparent disease. When this is established, a destructive inflammatory process begins. Fibroblast-like synoviocytes (FLS) migrate from joint to joint, leading to progressive joint damage.

All elements of the immune system are involved, including innate immunity and adaptive immunity, which includes the cellular (T cell) immune response and the humeral (B cell) immune response.The innate immune response includes macrophages which produce TNF, IL-6, IL-1, GM-CSF, IL-15, IL-18, IL-32, and chemokines which promote tissue inflammation. Other elements of innate immunity include cells such as endothelial cells, which allow the egress of immune and inflammatory cells such as neutrophils which migrate to the synovial fluid and produce prostaglandins, proteases, and reactive oxygen intermediates, all of which are pro-inflammatory and cause destruction to the cartilage.

Resident fibroblasts-like synoviocytes (FLS) are activated by proinflammatory cytokines, PGDF, and chemokines to proliferate with invasive characteristics and produce matrix metalloproteinases (MMP) and ADAMTS. Chondrocytes are activated by TNF, IL-1, and IL-17, producing matric enzymes resulting in cartilage damage. Resident mast cells produce vasoactive amines, leukotrienes, proteases, and TNF. Osteoclasts are activated by RANKL, which plays a vital role in producing bone erosions. Another element of innate immunity is the complement system which is activated by RF and ACPA-containing immune complexes producing C3a and C5a, which are pro-inflammatory, attracting and activating neutrophils and also activating macrophages and mast cells.[34-44]

Adaptive immunity includes T cells and B cells which respond to antigenic stimuli. In RA, one of the main antigens triggering autoimmunity is modified proteins such as citrullinated proteins. At mucosal sites, T cells are activated by these modified proteins, which trigger B cells to produce AMPA, including ACPA. In some patients, this immune response develops into an immune-mediated inflammation in the synovium. T cells and B cells take up residence in the synovium populating the subsynovial region. The mononuclear cell infiltrate appears histologically like a lymphoid organ. Dendritic cells serve as a bridge between innate and adaptive immunity by presenting antigens to antigen-specific T cells.

T cells interact with B cells, activating antigen-specific B cells to differentiate into plasma cells that produce RF and ACPA. These autoantibodies bind to their antigens forming immune complexes that can further the inflammatory response by activating the complement system. Some activated T cells become type 1 helper T cells (Th1) and type 17 helper T cells (Th17). Th17 cells produce IL-17, a proinflammatory cytokine that attracts other T cells and neutrophils.

Cytokines are produced in large amounts in the synovium and play an important role in propagating an intense inflammatory response resulting in bone erosions and cartilage loss. Chronic inflammation also plays a role in associated comorbidities, such as the increased risk of cardiovascular disease. The following table outlines the most important cytokine involved in the pathogenesis of RA.

Diagnostic Lab Tests

Evidence of RA may be seen in the blood, so blood tests play an important role in making a diagnosis.

- **Erythrocyte sedimentation rate (ESR or SED rate):**The ESR can gauge how much inflammation is in your body by measuring how quickly red blood cells (erythrocytes) separate from other cells in the blood and collect as sediment in the bottom of a test tube. Because inflammation can be caused by conditions other than RA, the results must be considered along with those of other tests when making an RA diagnosis.
- **C-Reactive Protein (CRP):** This measures levels of CRP, a protein produced by the liver that signals inflammation. High CRP levels are common in RA and other inflammatory forms of arthritis. Because a high CRP may be present with many diseases and conditions, a high CRP in itself does not mean you have arthritis or identify which form you may have. The results must be interpreted in the context of your symptoms as well as the results of other tests.
- **Rheumatoid factor (RF):** Rheumatoid factor is a protein made by the immune system which may attack healthy tissues. High levels of rheumatoid factor could help your doctor make a diagnosis of RA. However, RF levels may also be high in other autoimmune diseases, so an RF test alone cannot be used to diagnose RA.
- **Anti-CCP antibody test** (**ACCP or CCP**). This test is for a type of autoantibody called cyclic citrullinated peptide (CCP) antibodies, which can be found in the blood of 60% to 80% of people with rheumatoid arthritis. The test is often conducted along with an RF test.
- **Antinuclear antibody test (ANA).** Antinuclear antibodies (ANA) are a type of autoantibody, a protein that attacks your body's own tissues. The presence of ANAs can indicate an autoimmune condition, including RA[45].

Diagnostic Imaging Tests

Imaging tests, along with the physical exam and laboratory tests, can help identify RA. These imaging tests may be used to diagnose RA.

- **X-ray.** X-rays can show bone damage, characteristic of RA, where they meet at joints. They are a common tool in diagnosis; however,

because it damage from inflammation develops over time and may not be visible via X-ray early on, it may not be useful for diagnosing early RA.

- **Magnetic resonance imaging (MRI).** MRI is procedure in which radio waves and a powerful magnet linked to a computer are used to create 3D images of structures inside the body. MRI can show changes in cartilage and bone that are indicative of RA.
- **Ultrasound.** Ultrasound, or sonography, uses sound waves to create pictures of structures inside the body. THis may be used to view changes in bones and cartilage suggestive of RA before any changes show up on X-ray. Other benefits of ultrasound include its relatively low cost and the fact it doesn't expose the body to radiation, like X-ray.
- **Computed tomagraphy (CT) scan.** A CT scan is an imaging procedure that combines a series of X-ray images to create cross-sectional images of parts of the body. Studies show CT scans may be effective for viewing early bone erosions that occur with RA.

Monitoring Lab Tests

Some of the same lab and imaging tests used in diagnosing RA are also used to monitor disease progression and response to treatment.

- **Erythrocyte sedimentation rate (ESR or sed rate):** A reduced sed rate is an indication that inflammation is being controlled.
- **C-Reactive Protein (CRP):** As with sed rate, lower levels of CRP indicate that inflammation is being controlled.
- **The MBDA test (Vec*tra DA*).** This blood test checks for 12 proteins, hormones and growth factors. It gives your doctor a single disease activity score that can indicate how aggressive your disease is, how likely you are to have a flare when stopping medications and what drug combinations may work best for you.
- **Complete Blood Count (CBC):** While the CBC won't necessarily tell your doctor how active your disease it is, components of the test can help if you have complications from RA or its treatment. For example, low red blood cell levels indicate anemia, which is common in people with RA. Low white blood cells, which are needed to fight infection, and low platelets, which are needed to make blood clot, can sometimes occur in people taking biologics.
- **Liver enzyme (SGOT, SGPT, bilirubin, alkaline phosphatase).** Measuring levels of enzymes in the blood can help your doctor determine if you have liver damage, which may be related to RA treatment, an associated autoimmune condition or RA itself.
- **Hematocrit (HCT)& hemoglobin (Hgb):** These tests measure your number and quality of red blood cells. Lower red blood cell counts may mean medications, such as NSAIDs or corticosteroids, are causing gastrointestinal bleeding.
- **Lipid panel.** Because some medications for RA, such as interleukin inhibitors and JAK inhibitors, may cause increases in your triglyceride and cholesterol levels, your doctor may check those levels during RA treatment and prescribe medication to lower lipid levels if necessary.
- **Kidney function tests.** Lab tests performed on your blood and urine can tell your doctor how well your kidneys are removing waste products from the body. Kidney damage may occur due to RA itself or medications used to treat it, including nonsteroidal anti-inflammatory drugs (NSAIDs), disease-modifying antirheumatic drugs (DMARDs), corticosteroids and biologics.

Monitoring Imaging Tests

A variety of imaging tests may be used to monitor joint damage resulting from inflammation. They may be the same as those used in diagnosing RA, including

- X-ray
- Magnetic resonance imaging (MRI)
- Ultrasound
- CT Scan

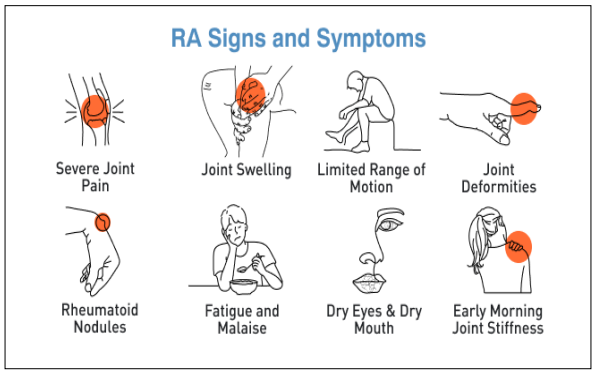

Fig.2: Clinical symptoms of RA

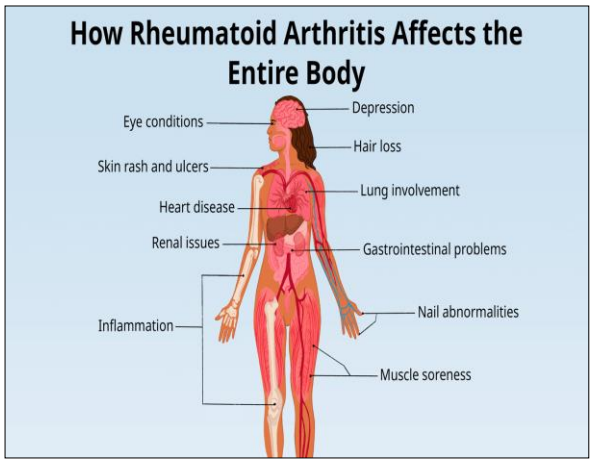

Fig 3: Rheumatoid arthritis complications

4. Treatment and Management

The goal of treatment in patients with RA is early diagnosis and early initiation of treatment to prevent irreversible damage to the joints. The International Task Force

Guidelines published in 2014 make the following recommendations regarding the treatment of RA[46-48]:

- The primary goal of treatment is to achieve long-term clinical remission and optimize quality of life with the absence of signs and symptoms associated with inflammatory disease activity.
- If clinical remission cannot be achieved, low disease activity is an acceptable alternative.
- Disease activity should be assessed every month in patients with moderate to severe disease activity.
- In patients with low disease activity or clinical remission, disease activity should be assessed every 3 to 6 months.

Multiple clinical assessment tools have been developed to assist clinicians in determining the disease activity of patients with RA. An updated recommendation from the American College of Rheumatology (ACR) in 2019 recommended using the following assessment tools because they met the minimum standard for evaluation per their recommendation. In clinical practice, the combination of the DAS28, CDAI, and RAPID3 is easy to use and includes patient input, provider input, and laboratory tests.

- Clinical Disease Activity Index (CDAI)
- Disease Activity Score (DAS)
- Disease Activity Score 28 Joints (DAS28-ESR/CRP)
- Patient-Derived DAS28
- Hospital Universitario La Princesa Index (HUPI)
- Multi-Biomarker Disease Activity Score (MBDA score, VECTRA DA)
- Rheumatoid Arthritis Disease Activity Index (RADAI)
- Rheumatoid Arthritis Disease Activity Index 5 (RADAI-5)
- Routine Assessment of Patient Index Data 3 (RAPID3)
- Routine Assessment of Patient Index Data 5 (RAPID5)
- Simplified Disease Activity Index (SDAI)

Disease-modifying antirheumatic drugs (DMARDs) typically used in treating RA include methotrexate, hydroxychloroquine, sulfasalazine, and leflunomide. Anti-TNF-alpha inhibitors include etanercept, infliximab, adalimumab, golimumab, and certolizumabpegol. Other biologic DMARDs include interleukin (IL) 6 inhibitors such as tocilizumab and sarilumab, T-cell costimulation inhibitors such as abatacept (CTLA4-Ig), and the anti-CD20 B-cell depleting monoclonal antibody such as rituximab. Targeted synthetic DMARDs include Janus kinases (JAK) inhibitors such as tofacitinib, baricitinib, and upadacitinib. DMARD therapy, including biologic agents and targeted synthetic agents (tofacitinib), should be temporarily held in patients with a serious active infection. They can be resumed after the infection has resolved and antimicrobial treatment has been completed. It is essential to remember that all patients starting treatment for RA should be screened for hepatitis B and C and tuberculosis. Methotrexate should be avoided in patients with liver disease. Patients with latent tuberculosis should complete treatment for at least one month before initiating biologic and targeted synthetic agents. If patients cannot take or complete treatment for latent tuberculosis, conventional DMARD therapy should be used. In patients with underlying skin cancer and lymphoproliferative disorders, biologic agents should be avoided except for rituximab in patients with lymphoproliferative disorders, as there is evidence of benefit from B-cell suppression in these cases.

Non-steroidal Anti-inflammatory Drugs (NSAIDs)

NSAIDs do not have any disease-modifying effects but are commonly used to relieve symptoms related to joint inflammation and pain. There are about 20 such drugs (depending on what country you are in) that are all effective at full doses. There is some variation in side effects and toxicities. There is a class Black Box warning for cardiovascular disease, although there is variation in the cardiovascular effects among NSAIDs. NSAIDs also have the potential for gastrointestinal, renal, and hematologic toxicity. The choice of a specific NSAID depends on the patient, their comorbidities, and the provider's familiarity with the specific drug. Non-acetylated salicylates (salsalate) have an excellent safety profile with little GI, renal, or hematologic effects but are not commonly used. There are recommendations for using NSAIDs with regard to a patient's cardiovascular and gastrointestinal comorbidities.

- Efficacy: indomethacin, piroxicam
- Convenience (1-2 doses per day): meloxicam, naproxen, celecoxib, nabumetone
- Overall safety: nabumetone
- GI safety: celecoxib, nabumetone
- Renal safety: possible nabumetone
- Hematologic safety (no antiplatelet effect): celecoxib, meloxicam, nabumetone

Corticosteroids

Corticosteroids are commonly used in patients with RA. There are several situations in which corticosteroids should be considered. In a new patient with very active RA, corticosteroids can be used as bridge therapy while DMARD therapy is instituted. Some studies show that using corticosteroids early in RA patients improves outcomes and has disease-modifying effects, including radiographic progression.

Nonbiologic DMARDs

This category includes methotrexate, hydroxychloroquine (HCQ), azathioprine (AZA), sulfasalazine, leflunomide, and cyclosporine. Methotrexate is the initial drug of choice for patients with RA. The recommended treatment plan recommends an initial dose of 10-15 mg/week of methotrexate with an escalation of 5 mg/month and a target dose of 20-25 mg/week.

TNF inhibitors

The TNF inhibitors include etanercept, infliximab, adalimumab, certolizumab, and golimumab. The ACR does not recommend using TNF inhibitors until a nonbiologic DMARD has been tried. However, studies have shown that adding TNF inhibitors in patients who have failed methotrexate therapy is better than adding another

nonbiologic DMARD. The most concerning adverse effect of these agents is opportunistic infections and reactivation of latent tuberculosis. There is some concern about the generation of antibodies against these agents, which may decrease their efficacy over time; however, using methotrexate in combination with these agents has been shown to decrease this complication.

Rituximab

Rituximab is a biologic DMARD that can be added for treating RA if patients have uncontrolled RA and who did not respond to TNF inhibitors. Rituximab is given as an intravenous infusion; it depletes CD20+ B-cells and decreases the immune response to vaccines in patients receiving rituximab. Responses to rituximab are better if the patients are seropositive and if the patients are also on methotrexate. As stated above, it is a preferred agent in patients with underlying lymphoproliferative disorders.

Abatacept

Abatacept inhibits T-cell activation by binding to CD80 and CD86. It is administered as a monthly intravenous infusion or as a weekly subcutaneous injection. Patients with uncontrolled RA, who have shown an inadequate response to methotrexate and TNF inhibitor therapy, benefit from abatacept therapy with proven efficacy from 6 months to 5 years of therapy.

Interleukin 6 Inhibitors

Tocilizumab, an IL-6 receptor inhibitor, is indicated for moderate-to-severe active RA in adults who have had an inadequate response to TNF inhibitor therapy. These patients develop clinically meaningful improvement with the use of tocilizumab[50-51].

Janus kinase (JAK) Inhibitors

JAK is a group of tyrosine kinases that participate in intracellular signal transduction for hematopoiesis and immune cell function. JAK inhibitors (such as tofacitinib) are oral agents that reduce the production of cytokines and are approved as second-line agents for the treatment of RA.

5. Conclusion

Rheumatoid arthritis is a tough condition that goes beyond just joint pain. It can mess with your whole body, leading to inflammation, stiffness, and disability if left unchecked. The earlier it is caught, the better the chances of managing it and avoiding long-term damage. People can still live a good life with the right treatment and lifestyle changes, even with RA. It is key to see a doctor if you notice any symptoms; catching it early can make a huge difference. RA might be challenging, but managing it and moving forward with the proper care is possible. A comprehensive clinical approach is required to make the diagnosis and prevent debilitating joint damage. The treatment of patients with rheumatoid arthritis requires both pharmacological and non-pharmacological therapy. The standard of care is early treatment with disease-modifying anti-rheumatic drugs[52-54].

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