SAMQUEST-Journal of Emerging Innovations
Vol.1,Issue1,pp.10-20,Jan-June2025
Available online at: www.samglobaluniversity.ac.in

Review

A Comprehensive Review On Health Challenges in Rheumatology and Musculoskeletal Disorders

Murtuza Zaki*, Zaid Shamshee
SchoolofPharmacy,SAMGlobalUniversity,Raisen-464551,MadhyaPradesh,India
*CorrespondingEmail:zakimurtuza5272@gmail.com
Received:10/Jun/2025;**Accepted**:15/Jun/2025;**Published**: 25/Jun/2025.

Abstract: Rheumatoid arthritis (RA) is a systemic poly-articular chronic autoimmune joint disease that mainly damages the hands and feet, and affects 0.5% to 1.0% of the population worldwide. The deformation of skeletal muscles is observed in an arthritic patient. The present review is a discussion on rheumatoid arthritis that includes etiology, pathology and pathogenesis, signs and symptoms, clinical complications, diagnosis, treatment, and therapy. The targets to treat rheumatoid arthritis are interleukins, tumor necrosis factor-alpha, sialoprotein I, and several other factors. Different biomarkers are used for diverse types of rheumatoid arthritis and the mechanism also varies. Recent trends in the management of rheumatoid arthritis are the main concern of this article.

Keywords: Autoimmune Disorder, Interleukins, Rheumatoid arthritis

Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disorder that causes inflammation in the joints and surrounding tissue. It is characterized by symmetrical joint involvement, meaning that if one joint is affected, the opposite joint is also usually affected. The inflammation caused by RA can lead to swelling, stiffness, and pain in the affected joints, and it can also cause fatigue and overall weakness. RA is a progressive disease, which means that it can get worseovertime.RAaffectsapproximately1%oft he global population and is two to three times more common in women than in men. It can occur at any age, but it most commonly developsinpeoplebetweentheagesof40and 60. RA is a systemic disease, meaning that it can affect the whole body, not just the joints. It can cause inflammation in other organs, such as the eyes, lungs, and heart, and it can also cause vasculitis, which is inflammation of the blood vessels. The cause of RA is not fully understood, but it is thought to be the result of a combination of genetic and environmental factors. People with a family history of RA are more likely to develop the disease, and certain genetic markers have been identified as being associated with an increased risk of developing RA. Environmental factors that may contribute to the development of RA include infections, smoking, and exposure to certain toxins.

The diagnosis of RA is typically made based on a combination of clinical symptoms, laboratory tests, and imaging studies. The most common symptoms of RA are joint pain, stiffness, and swelling, but RA can also cause fever, weight loss, and fatigue. Laboratory tests that may be used to help diagnose RA include blood tests to measure inflammation, such as the erythrocyte sedimentation rate (ESR) and the C-reactive protein (CRP) level, and tests to measure autoanti bodies, such as rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) antibodies. Imaging studies, such as X-rays and magnetic resonance imaging(MRI), may also be used to help diagnose RA and to monitor the progression of the disease.

The goals of treatment for RA are to reduce inflammation, improve physical function, and prevent joint damage. The mainstay of treatment for RA is pharmacotherapy, which includes non-steroidal anti-inflammatory drugs (NSAIDs),disease-modifying anti-rheumatic

drugs (DMARDs), and biologic. In addition to pharmacotherapy, other treatment options for RA include lifestyle modifications, such as getting enough rest, exercising regularly, and managing stress, and physical therapy, which can help improve physical function and reduce pain. Surgery may also be an option for people with RA who have severe joint damage or deformity. RA is a chronic disease that can significantly impact the quality of life of people who have it. RA can be a challenging disease to manage, but with appropriate treatment and self-management, people with RA can lead full and active lives.

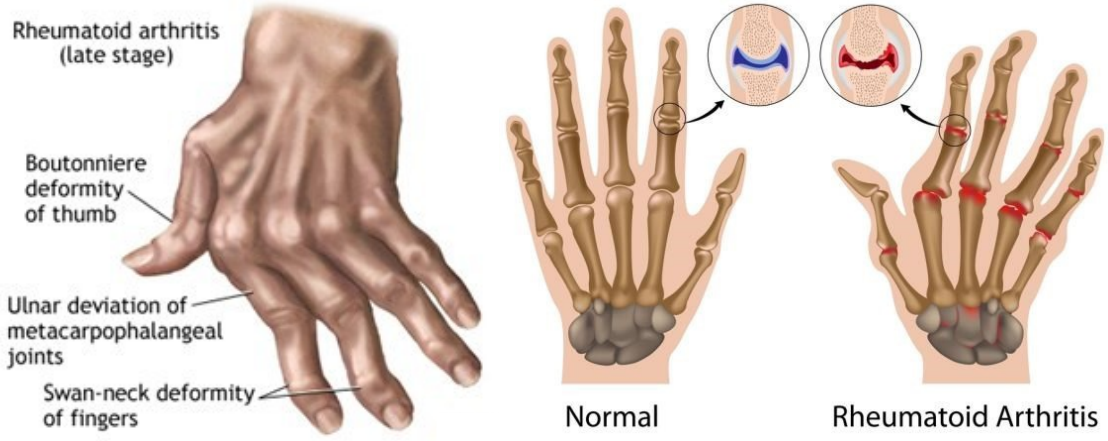

Fig.1. Symptoms of Rheumatoid arthritis.

Pharmacology

Rheumatoid arthritis (RA) can progress if left untreated, and remission is rare. Therefore, medication is essential in managing RA symptoms and progression. Once diagnosed, it is recommended to begin therapy promptly. Optimal RA management typically involves a combination of medications and other therapies. Currently, there are five main categories of medications: analgesics, non steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, and biologic and non-biologic disease-modifying anti-rheumatic drugs (DMARDs). Biologic medications are recommended if DMARDs are ineffective. Abatacept is the second most commonly used biologic medication and is often combined with methotrexate (MTX). According to some studies, tocilizumab is the most effective biologic medication when used alone. Although rituximab is equally as effective as anti-TNF,it is rarely used as the first biological therapy due to safety concerns. Combination therapies are frequently used. Specific components of the immune system, such as cytokines, B-cells, T-cell activating agents, and antigen-presenting cells (APCs), can now be targeted for RA treatment (Sarkar 2022, Radu and Bungau, 2021).

Causes

The exact cause of rheumatoid arthritis (RA)is not fully understood, but it is thought to be the result of a combination of genetic and environmental factors. RA is an autoimmune disorder, which means that the immune system mistakenly attacks the body's own tissues. In the case of RA, the immune system attacks the synovium, the lining of the joints, leading to inflammation and the characteristic symptoms of RA, such as joint pain, stiffness, and swelling. Some of the factors that are thought to be involved in the development of RA include (Sailaja 2014).

Genetic Susceptibility

There is a strong genetic component to the development of rheumatoid arthritis (RA). Studies have shown that certain genetic variations or mutations are associated with an increased risk of developing RA. One of the most significant genetic factors in RA is the human leukocyte antigen (HLA) system. HLA genes code for proteins that help the immune system recognize foreign substances and distinguish them from the body's own tissues. In people with RA, certain HLA genes, such as HLA-DRB1, have been linked to an increased risk of developing the disease. Other genes that have been associated with RA includethePTPN22gene,which plays a role

in regulating the immune system, and the STAT4 gene, which is involved in the signaling pathways that control inflammation. However, having a genetic predisposition to RA does not necessarily mean that a person will develop the disease. Environmental factors,such as smoking or exposure to certain chemicals, may interact with genetic factors to trigger the development of RA. Furthermore, some people may develop RA without any known genetic risk factors (Bullock et al. 2019).

Environmental Factors

Smoking: It is correct that smoking is the strongest known environmental risk factor for RA. This association has been known for over a decade and has been further characterized in recent studies. The risk of RA increases with the amount and duration of cigarette use, with the heaviest smokers having a two-fold increase in risk compared to those who have never smoked. Additionally, an individual remains at increased risk even after cessation for 20 years or more. The risk of RA from smoking is further modified by the number of shared epitope copies, suggesting gene-environment interaction. The shared epitope, a specific sequence of amino acids on the HLA-DRB1 allele, is the strongest known genetic risk factor for RA. Smokers who carry two copies of the shared epitope have a 21-fold higher risk of developing ACPA-positive RA compared to non-smokers who do not carry the shared epitope. This greatly elevated risk is attributed to the gene-environment interaction between smoking and the shared epitope. Smokers may induce citrullination, and carriers of the shared epitope may be genetically predisposed to developing antibodies against citrulline. It is important to note that the risk of RA from smoking is specifically associated with an increased riskof ACPA-positive and not ACPA-negative RA. Furthermore, the gene-environment interaction between smoking and the shared epitope has been observed in several European cohorts, but not in North American cohorts (Bullock et al. 2019).

Immunity: The pathogenesis of RA is complex and involves multiple immune cells, including B-cells, T-cells, and macrophages. B-cells are essential in the development of RA as they produce antibodies against self-antigens such as rheumatoid factors (RFs) and anti-citrullinated protein antibodies (ACPA), which are found in the synovial fluid and serum of RA patients. These antibodies are believed to play a role in the destruction of joint tissue by activating complement and recruiting inflammatory cells to the synovium. In addition, B-cells also secrete pro-inflammatory cytokines such as interleukin-6 (IL-6), which promote the survival and activation of T-cells and macrophages. T-cells are also crucial in RA pathogenesis as they activate macrophages and fibroblasts, leading to the production of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-1 (IL-1), which contribute to the destruction of joint tissue. CD4+ T-cells, particularly Th1 and Th17 subsets, are the main T-cell populations involved in RA pathogenesis. Th1 cells produce interferon-gamma (IFN-γ), which activates macrophages, while Th17 cells produce IL-17, which stimulates the production of pro-inflammatory cytokines and chemokines.

Macrophages are critical effector cells in RA pathogenesis as they produce pro-inflammatory cytokines and chemokines that contribute to joint inflammation and destruction. In the early stages of RA, macrophages are present in the synovium and produce pro-inflammatory cytokines such as TNF-α, IL-1, and IL-6, which promote the recruitment and activation of other immune cells. Activated macrophages also produce matrix metallo proteinases (MMPs), which degrade the extracellular matrix and lead to cartilage and bone destruction. In summary, immune cells, particularly B-cells,T-cells, and macrophages, play critical roles in RA pathogenesis by producing pro-inflammatory cytokines and antibodies against self-antigens. Understanding the complex interactions between these cells is essential for developing effective therapies to treat RA.

B-Lymphocytes: In RA patients, both checkpoints are usually defective, leading to the large production of auto reactive mature naïve B-cells. As shown in a previous study, untreated RA patients show a 3.4-fold increase in auto reactive B-cells in the peripheral blood compared to non-RA patients. Such a defect can be caused by a mutation in the PTPN22 gene that disrupts the BCR signaling pathway

in the central B-cell tolerance checkpoint (Armitage et al. 2021). The impairment of such tolerance checkpoints in RA patients cannot be effectively treated with drugs that reduce inflammation and alleviate other clinical presentations due to the irreversible genetic defect. The impaired peripheral tolerance checkpoint is also evident as shown by the elevated levels of mature naive B-cells that express both polyreactive and human epithelial (HEP-2)-reactive antibodies in RA patients (Yap et al. 2018). The peripheral checkpoint dysfunction results in defects in Treg as well as B-cell resistance to suppression and apoptosis (Kinnunen et al. 2013). BAFF is increased in the presence of cytokines and chemokines, as well as through TLR activation in RA patients. Such an increase in BAFF expression further prolongs the survival and maturation of auto reactive B-cells, hence sustaining the inflammation and exacerbating the autoimmune conditions (Yap et al. 2018).

Macrophages: Macrophages play a crucial role in the pathogenesis of RA and are a promising target for therapeutic intervention. While macrophages normally reside in tissues in a resting state, they become activated in an inflamed joint and secrete pro-inflammatory cytokines and enzymes that contribute to joint destruction. Additionally, macrophages act as antigen-presenting cells and are involved in T-cell activation, leading to the production of pro-inflammatory mediators. Targeting macrophages is effective in treating RA by inhibiting inflammation and bone erosion. One approach is to switch the macrophage phenotype from pro-inflammatory (M1) to anti-inflammatory (M2) using various agents. Other therapeutic strategies include using si RNA, anti-TNF, and nano systems. These approaches have the potential to be developed into effective anti-rheumatic drugs.

Hormonal Factors

Hormonal changes, such as those that occur during menopause, have been linked to an increased risk of developing RA.

Estrogen: In summary, estrogens have complex interactions with the immune system that can be pro- or anti-inflammatory depending on the cell type and concentrations involved. Estrogens support immunoglobulin class switching in B cells and would be expected to have a deleterious effect on autoimmune diseases characterized by autoantibody production. Estrogens generally exert inhibitory effects on pro-inflammatory TH1 cells, while they may inhibit pro-inflammatory TH17 cells via ERα or have the opposite effect via ERβ. At high concentrations such as seen in pregnancy, estrogens induce the secretion of IL-10 and suppress TNFα production in T cells, supporting an anti-inflammatory cytokine milieu. Estrogens have also been found to have a range of direct anti-inflammatory actions on T cells, including the stimulation of apoptosis of human RA synoviocytes and the reduction of the production of inflammatory cytokines in rats with collagen-induced arthritis. The FOXP3 locus possesses sex steroid response elements enabling direct binding of hormones and subsequent modulation of FOXP3 activation. In mouse models of RA, exogenous estrogen administration has been shown to ameliorate postpartum flare and retard disease development in collagen-induced arthritis.

Menopause: A consistent finding is the increased risk of RA in early menopause. In the large Nurses' Health Study cohort, menopause at <44 years increased the risk of sero negative RA [hazard ratio (HR) 2.4, 95% CI 1.5–4.0]. Menopause has also been associated with the development of ACPA in first-degree relatives of patients with RA.

Androgen: In men with RA, low serum levels oftestosteronewerefoundtobestronglypredictive ofseronegativedisease(OR0.31, 95%CI0.12–0.85)butnotsignificantlypredictive ofseropositivedisease.Men with untreated hypogonadism have been found to be at increased risk of a range of autoimmune diseases, including RA(HR1.31,95%CI1.22–1.44),as are men with Klinefelter syndrome (RR 3.3, 95% CI 2.0–5.2).

Other Factors

Other factors that may contribute to the development of RA include obesity, stress, and certain medications. It is likely that different mechanisms contribute to the development of RA in different people, and further research is needed to fully understand the causes of this complex disease.

Types

There are several different types of rheumatoid arthritis (RA), including

Classic RA: This is the most common type of RA, characterized by symmetrical joint involvement (affecting the same joints on both sides of the body), morning stiffness, and fatigue.

Sero positive RA: "Sero positive RA is the most common type of RA," says Beth Wallace, M.D., assistant professor in internal medicine at the University of Michiganin Ann Arbor and a staff rheumatologist at the VA Ann Arbor Healthcare Center. According to the Hospital for Special Surgery, approximately 80% of people with RA are sero positive. Both types of RA result in very similar joint symptoms and distribution, and the exact level of anti-CCP and RF antibodies isn't all that important when determining how RA affects joints, says Jon Tyler Giles, M.D., associate professor of medicine in the division of rheumatology at Columbia University Vagelos College of Physicians and Surgeons in New York City. "It doesn't tell us how much inflammation you have, or how swollen the joints are going to be," he explains. Some people can have high levels of these antibodies but feel better than someone with very low levels. However, the presence of anti-CCP and RF antibodies can help doctors get a better idea of a patient's prognosis and how to approach treatment, Dr. Giles says. "People who are sero positive are more likely to not have the disease remit[or improve]on its own, especially if you have a high level of those antibodies," Dr. Giles says. "You are also more likely to have more damage to your joints over time" (Wragg 2011). People with sero positive RA also tend to not respond as well to treatment, says Dr. Wallace. The same medications are used to treat both types of RA, but sero positive RA may not respond as quickly and may ultimately require more aggressive treatment. Dr. Wallace also notes that sero positive RA is more often associated with extra-articular complications, meaning that systemic inflammation can cause problems beyond just the joints. Research has linked sero positive RA to complications such as cardiovascular disease, lung disease, and eye inflammation.

Sero negative RA: The absence of anti-CCP and RF antibodies in the blood means Some one has sero negative RA, which is associated with less joint symptoms beyond the joints and a higher likelihood of being responsive to treatment, as well as less progression of bone erosion. However, a proper diagnosis and appropriate treatment are still necessary to prevent long-term joint damage. While the absence of these antibodies can make an RA diagnosis less certain, other information such as symptoms, joint exams, imaging tests, and other blood test scan still be used to diagnose sero negative RA. There may also be other distinct antibodies in people with RA that can help with diagnosis and treatment, although they have not yet been identified.

Juvenile RA: JIA, or juvenile idiopathic arthritis, describes multiple types of autoimmune, inflammatory arthritis in children. There are six types, some of which look very much like RA. The pattern of joint involvement and course of disease is very similar to RA, and similarly to RA, JIA shows up in patterns of flares and remission. It also has systemic effects on the body.

Oligoarticular JIA affects four or fewer joints, typically the large ones, while poly articular (also known as poly arthritis) JIA affects five or more joints, often on both sides of the body, and may affect both large and small joints. Both are similar to RA, but poly articular JIA is most similar and is the equivalent of childhood-onset RA, according to Dr. Giles. Blood testing for RF factor is done when a child has poly articular RA.

While treatments for poly articular JIA may involve the same immune-modulating medications as adult RA, and long-term joint damage can occur if it's not treated, it's common to grow out of JIA. However, it is possible to be diagnosed with true RA when you're young, but it's quite rare, and most of these cases involve diagnosis in adolescence, not younger than that.

This type of RA affects children and adolescentsundertheageof16.Ithasmanyof the same features as adult RA, but the course of the disease may be different.

Symptoms

The symptoms of rheumatoid arthritis (RA) vary widely from person to person, and the severity of the disease can also vary widely. Some people with RA may experience only mild symptoms, while others may have severe

and disabling symptoms. The most common symptoms of RA are joint pain, stiffness, and swelling.

Joint pain and stiffness are often worse in the morning or after a period of inactivity, and they may improve with movement. The joints most commonly affected by RA are the small joints in the hands and feet, but RA can also affect other joints, such as the wrists, elbows, shoulders, knees, and ankles. RA is a symmetrical disorder, meaning that if one joint is affected, the opposite joint is also usually affected.

- Pain or aching in more than one joint.
- Stiffness in more than one joint.
- Tenderness and swelling in more than one joint.
- The same symptoms on both sides of the body (such as in both hands or both knees)
- Weightloss.
- Fever.
- Fatigueor tiredness.
- Weakness

Epidemiology

Rheumatoid arthritis (RA) affects approximately 1% of the global population. It is more common in women than in men, with a female-to-male ratio of 2:1. RA can occur at any age, but it most commonly develops in people between the ages of 40 and 60. RA is more common in certain ethnic groups, with higher rates of the disease observed in people of European descent compared to people of African or Asian descent. RA is also more common in people who smoke and in people who have a family history of the disease.

RA is a leading cause of disability worldwide, with the severity of the disease varying widely from person to person. Some people with RA may experience only mild symptoms, while others may have severe and disabling symptoms. RA can also cause inflammation in other organs, such as the eyes, lungs, and heart, and it can also cause vasculitis, which is inflammation of the blood vessels.

Effective treatment for RA can improve symptoms and prevent joint damage, but the disease is not curable. RA is a progressive disease, which means that it can get worseover time, and it is important for people with RAto receive on going medical care to manage Their symptoms and prevent complications (Radu and Bungau 2021).

Pathogenesis

There are two major subtypes of rheumatoid arthritis (RA) based on the presence or absence of anti-citrullinated protein antibodies (ACPAs), which are detectable in approximately 67% of RA patients and serve as a valuable diagnostic tool for early, undifferentiated arthritis and predicting disease progression. Citrullination, which is catalyzed by the enzyme peptidyl-arginine- deiminase (PAD), converts arginine to citrulline through post-translational modification. The ACPA-positive subset of RA has a more aggressive clinical phenotype compared to the ACPA-negative subset, which has different genetic associations and immune cell responses to citrullinated antigens. Additionally, the ACPA-negative subset may have a less effective treatment response to methotrexate (MTX) or rituximab, highlighting the need for further research into potential pathophysiological differences between the two subsets. This review will focus on the ACPA-positive subset of RA and categorize the progression of RA into distinct stages, although it is important to note that these stages may occur sequentially or simultaneously.

RA pathophysiology is not yet fully understood, but several hypotheses have been proposed. The pre-RA phase suggests that immunological processes may occur many years before joint inflammation symptoms are noticed. Epigenetic modifications and environmental factors may lead to modified self-antigens such as IgG, type 2 collagen, and viment in, which can be converted to citrulline by peptidyl arginine deiminases. Jointdisorders such as synovial hyperplasia or synovial infections can also trigger cytokine release that may cause joint inflammation and modified self-antigens. Due to the HLA-DR1 and HLA-DR4 susceptibility genes, the immune system may no longer recognize citrullinated proteins as self-structures, and antigens are taken up by APCs to initiate an immune response. $CD4_{+}$helper T cells are activated in the lymph node, and B cells get activated through costimulation. B cells undergo somatic hyper mutation or class- switch recombination and differentiate into

plasma cells that produce autoanti bodies. RF and ACPA are the most studied auto antibodies involved in RA, with ACPA being more specific for RA and forming immune complexes with citrullinated proteins that accumulate in the synovial fluid (Wragg 2011, Radu and Bungau 2021).

Diagnosis

Laboratory Technique

Rheumatoid factor (RF) and anti-citrullinated peptide antibodies(ACPA)are both laboratory tests used in the diagnosis of rheumatoid arthritis (RA). A positive result for either test can support a diagnosis of RA, and having both tests positive increases the specificity of the diagnosis. However, as you mentioned, up to50% of patients with RA may have negative results on both tests when initially evaluated, and up to 20% of patients may remain negative during follow-up. This is why a diagnosis of RA is not solely based on laboratory testing, and a thorough clinical evaluation by a rheumatologist is important. Once a diagnosis of RA is established, there is generally no need for serial testing of these serologies for disease prognosis. However, these tests may be repeated periodically to monitor disease activity and response to treatment. It's important to note that a diagnosis of RA should not be based solely on serologic testing, and a thorough clinical evaluation by a rheumatologist is necessary to confirm the diagnosis and determine the most appropriate treatment plan.

Erythrocyte sedimentation rate (ESR) and serum C-reactive protein (CRP) are both markers of systemic inflammation and are commonly elevated in patients with RA. These tests may be repeated after the initial evaluation and diagnosis to assess and monitor disease activity and inflammation throughout the disease. In general, both ESR and CRP levels correlate with disease activity in RA, with higher levels indicating more active disease. However, it’s important to note that these tests are not specific to RA and can be elevated in a variety of other inflammatory conditions. Therefore, while ESR and CRP testing can be helpful in the diagnosis and management of RA, they should be used in conjunction with other clinical and laboratory assessments to determine disease activity and response to treatment.

Tests

Antinuclear antibody (ANA) testing is a laboratory test that is often used to help diagnose autoimmune diseases, including systemic lupus erythematosus (SLE) and other systemic rheumatic diseases. A negative ANA result can help exclude SLE and other autoimmune conditions, although a negative result does not rule out RA. On the other hand, a positive ANA test is not specific to any one disease and can be seen in a variety of conditions, including RA. Therefore, a positive ANA test alone is not sufficient to make a diagnosis of SLE or other autoimmune diseases. If a patient has a positive ANA test, further testing for specific auto antibodies, such as anti-double-stranded DNA and anti-Smith antibodies, may be performed to help differentiate between SLE and other rheumatic diseases. These autoantibodies are more specific for SLE than ANA, but they can also be seen in other conditions. It's important to note that the diagnosis of RA is primarily based on clinical features, and ANA testing is not routinely performed in patients with suspected RA unless there is a concern for overlap with another autoimmune disease.

A complete blood count (CBC) with differential and platelet count, as well as tests of liver and kidney function, serum uric acid, and a urinalysis, are commonly performed as part of the initial evaluation of a patient with suspected RA. The CBC may show anemia and thrombocytosis, which can be consistent with chronic inflammation in RA. Abnormalities in liver and kidney function tests could indicate the presence of comorbid conditions that may impact therapeutic choices or drug dosing. Elevated serumuric acid levels may prompt additional investigations to exclude gout, another form of arthritis that can cause joint pain and inflammation. In rare cases, poly articular gout can be mistaken for RA, so it's important to consider this possibility in patients with hyperuricemia and joint symptoms.

Overall, these laboratory tests can provide important information to help diagnose and manage RA, as well as identify potential comorbidities that may impact treatment decisions. However, it's important to interpret these tests in the context of the patient's overall clinical presentation and to consider other factors that may contribute to abnormal

results. Radiographs of the hands, wrists, and feet are often obtained during the initial evaluation of a patient with suspected RA primarily to establish a base line for monitoring disease progression. However, characteristic joint erosions may be observed on radiographs in some patients presenting with symptoms for the first time, which can aid in diagnosis and provide prognostic information. Radiographs can also help differentiate RA from other disorders that may present with similar symptoms, such as psoriatic arthritis, spondyl oarthro pathy,gout,or chondrocalcinosis. In these cases, radiographic changes that are more characteristic of these conditions may point to an alternative diagnosis. It's important to note that radio graphic changes may not be present in the early stages of RA and that joint erosions can develop over time. Therefore, radio graphs may not be sufficient to establish a definitive diagnosis of RA, and other clinical and laboratory findings should also be considered. Overall, radiographs can provide valuable information for monitoring disease progression and identifying alternative diagnoses, but their interpretation should be considered in the context of the patient's overall clinical presentation.

Studies

It is important to note that these serologic studies for infection are only necessary in patients with a very short duration of symptoms and who are sero negative forACPA and RF. In most cases of RA, these tests are not necessary and would not be informative for the diagnosis or management of the disease. The decision to perform these tests should be based on the individual patient's clinical presentation and risk factors for these infections. Synovial fluid analysis is an important diagnostic tool that can help distinguish between different types of arthritis and guide appropriate treatment. It involves withdrawing synovial fluid from a joint using a needle and analyzing it in a laboratory. The results of synovial fluid analysis, including cell count, differential, crystal search, and Gram stain and culture, can help identify the cause of joint inflammation, such as infection, gout, or pseudo gout. That is correct. MRI and ultrasound may be useful in establishing the presence of synovitis in patients with normal radiographs and uncertainty regarding either the diagnosis or the presence of inflammatory changes. MRI and ultrasound are more sensitive than radiography at detecting changes resulting from synovitis. However, they do not have an established role in the routine evaluation of patients with polyarthritis. Abnormalities observed in imaging studies should be considered consistent with, but not diagnostic of, RA as each can be observed in other conditions.

Treatment

Biological Targeted Therapy

TNF Inhibitor: Indeed, TNF inhibitors are effective in the treatment of several inflammatory conditions, including RA, Crohn's disease, psoriatic arthritis, ankylosing spondylitis, and others. However, the use of TNF inhibitors is associated with an increased risk of infections, including serious and sometimes life-threatening infections, such as tuberculosis and sepsis. Therefore, patients receiving anti-TNF therapy should be carefully monitored for signs of infection and treated promptly if an infection is suspected. In addition, TNF inhibitors should be avoided in patients with active infections, including chronic hepatitis B or C, and in patients with a history of malignancy or congestive heart failure. Close communication and collaboration between the patient and their health care provider is crucial to ensure the safe and effective use of TNF inhibitors.

IL-1 Inhibition: Anakinra is an alternative treatment option for RA that targets the pro-inflammatory activity of IL-1, and it has been shown to reduce symptoms and slow the progression of structural damage in people with moderate to severe RA in clinical trials. However, it has a short half-life and needs to be given subcutaneously every day, which may be inconvenient for some patients. Additionally, it has lower response rates than TNF inhibitors and is therefore typically only provided to individuals who are intolerant to TNF inhibitors.

T Cell Co-stimulation: Abatacept is a chimeric human protein that targets T cell activation by binding to antigen-presenting cells and preventing them from engaging with the T cell receptor. It is given intravenously once a month after a loading regimen of three administrations separated by two weeks.

Clinical trials have shown that it can improve the signs and symptoms of RA, and it was approved by the FDA for use in adult patients with RA in 2005 and in children aged 6 and above in 2008. Abatacept can be used alone or in combination with other DMARDs. While T cell activation is viewed as a critical event in the onset and course of RA, T cell-directed biological therapies for RA have been disappointing due to their lack of efficacy and high toxicity. Never the less, a variety of T cell- targeted therapeutic options, including biological therapies that target specific populations of activated T cells and pharmacological drugs that modify T cells precisely, have emerged as potential treatments for RA(Sarkar 2022, Wragg2011).

B-Cell Directed Therapy: Rituximab is a B-cell-targeted therapy that has been studied due to a better understanding of the role of B cells in the inflammatory process of RA. It depletes peripheral B cells quickly and specifically without harming plasma cells and has been shown to improve clinical signs and symptoms while reducing the progression of radio graphic disease in multiple clinical trials. It is administered intravenously as part of a treatment regimen that includes several doses spaced weeks apart, and retreatment is usually given every 6-9 months. The most commonly reported adverse events in clinical studies are infusion-related symptoms, such as rigors, fever, pruritus, chills, and urticarial rash, with or without accompanying hypotension. The FDA has approved rituximab for use in combination with methotrexate for adult patients who have had a poor response to anti-TNF therapy. Rituximab therapy has not been associated with an increased risk of infection when compared to placebo, and it has shown no detrimental effects on IgG levels.

Inhibitor of Janus-activated Kinase (JAK): JAK inhibitors have been shown to improve the signs and symptoms of RA and reduce radiographic progression in clinical trials. There are currently several JAK inhibitors approved by the FDA for the treatment of RA, including to facitinib, baricitinib, and upadacitinib. These drugs are taken orally and have been shown to be effective in reducing inflammation and improving physical function in patients with moderate to severe RA who have had an in adequate response to methotrexate or other conventional DMARDs. However, JAK inhibitors have also been associated with some adverse effects, such as an increased risk of infections, including serious infections, and an increased risk of blood clots. It is important for patients taking JAK inhibitors to be monitored closely for these potential adverse effects.

Biosimilar: Biosimilar have been shown to be as safe and effective as their reference products in numerous clinical trials for the treatment of RA. They have the potential to offer lower-cost alternatives to expensive biologic therapies, allowing more patients to access these treatments. However, it is important to note that biosimilars are not identical to their reference products and may have subtle differences that could impact their safety and efficacy. Therefore, rigorous regulatory and clinical testing is required to ensure their safety and efficacy before they are approved for use in patients. In addition, patients switching from reference products to biosimilars should be closely monitored to ensure that there are no adverse effects or changes in efficacy.

Combinational Therapy in RA

Combination therapy is an important approach in the management of RA, as it can improve disease activity and delay radiographic progression. Most combination therapies still include MTX as a key component, but alternative combinations have also been successfully used. Tripletherapy (MTX,HCQ, and SSZ) and COBRA therapy (MTX, SSZ, and prednisolone) are two well-established combination regimens. Biologic medications have also been shown to be effective when used in combination with MTX. A comprehensive study found that early combination therapy is most effective in achieving clinical remission and improving radiographic results in individuals with early, active RA. However, not all DMARD combinations have been properly examined, and there is a lack of data on head-to-head comparisons of different therapeutic combinations.

Epigenetic Therapy in RA

DNMT inhibitors (e.g. azacitidine, decitabine) inhibit DNA methyl transferases, which are enzymes responsible for adding methyl groups

to DNA, leading to gene silencing. HDAC inhibitors (e.g. vorinostat, romidepsin) block the activity of histone deacetylases, which are enzymes responsible for removing acetyl groups from histones, leading to gene silencing. By inhibiting these enzymes, epigenetic treatments can potentially reverse abnormal epigenetic changes that contribute to the development of RA. However, more research is needed to determine their effectiveness and safety in treating RA.

New Perspective in the Treatment of RA

Indeed, the ongoing research on RA promises to bring significant advancements to the field, including the development of new molecular targets and therapeutic drugs. Additionally, a personalized approach based on genetic studies combined with evidence-based therapy may improve the treatment out comes for RA patients, particularly those who are unresponsive to existing treatments. The use of MSCs as a potential therapeutic approach is also an exciting development in the field, offering a new way to manage the symptoms of RA. While there are still unmet needs in the treatment of RA, the advancements made over the past few decades provide hope for improved quality of life and better out comes for RA patients in the future.

Complication

It is a progressive disease, which means that it can get worse over time. If left untreated, RA can cause several complications, including:

Joint Damage: The inflammation caused by RA can lead to joint damage, which can cause deformities and difficulty with movement.

Disability: RA can cause significant disability, especially in people with severe joint damage or deformities.

Extra-articular Manifestations: RA can cause inflammation in other organs, such as thee yes, lungs, and heart, and it canal so cause vasculitis, which is inflammation of the blood vessels.

Osteoporosis: RA can cause bone loss, leading to osteoporosis, which is a condition that makes bones weak and prone to fractures.

Infections: People with RA are at an increased risk of infections due to the use of immunosuppressive medications and the presence of underlying inflammation.

Cardiovascular Disease: RA has been linked to an increased risk of cardiovascular disease, including heart attack and stroke.

Conclusion

It is a leading cause of disability and can affect people of all ages, although it is most commonly diagnosed in middle-aged adults. RA can cause joint damage and other serious complications, including fatigue, anemia, and an increased risk of infections and cardiovascular disease. The exact cause of RA is unknown, but it is thought to be triggered by a combination of genetic, environmental, and hormonal factors. It is diagnosed through a combination of physical examination, laboratory tests, imaging studies, and referral to a rheumatologist. Treatment for RA typically involves a combination of medications and lifestyle changes to reduce inflammation, relieve pain, and prevent joint damage. The goal of treatment is to control the symptoms of RA and improve the patient's quality of life.

References

1. Ağce,Z.B.,Özkan,E.,Köse,B.(2016). Arthritis/Rheumatoid arthritis. In: Occupational Therapy - Occupation-focused holistic practice in rehabilitation (ed Meral Huri). DOI: 10.5772/intechopen.68477
2. Armitage, L.H., Wallet, M.A., Mathews, C.E. (2021). Influence of PTPN22 allotypes on innate and adaptive immune function in health and disease. Front.Immunol.,25;12,636618.doi: 10.3389/fimmu.2021.636618. PMID: 33717184; PMCID: PMC7946861.
3. Bullock,J.,Rizvi,S.A.,Saleh,A.M.,Ahmed,S.S., Do,D.P.,Ansari,R.A.,Ahmed,J.(2019). Rheumatoid arthritis: a brief overview of the treatment. Medical Principles and Practice, 27(6), 501-507.
4. Craig, K.D. (2010). Global year against musculoskeletal pain. Pain Research and Management, 15(5), 284-284.
5. Fonseca, L.J.S.D., Nunes-Souza, V., Goulart, M.O.F., Rabelo, L.A. (2019). Oxidative stress in rheumatoid arthritis: What the future might hold regarding novel biomarkers and add-on therapies. Oxidative Medicine and Cellular Longevity, 2019(1), 7536805.
6. Guo, Q., Wang, Y., Xu, D. et al. Rheumatoid arthritis: pathological mechanisms and modern pharmacologic therapies. Bone Res., 6, 15 (2018). https://doi.org/10.1038/s41413-018-0016-9
7. Handa, R., Rao, U.R.K., Lewis, J.F., Rambhad, G., Shiff, S., Ghia, C.J. (2016). Literature review of rheumatoid arthritis in India. International Journal of Rheumatic Diseases, 19(5), 440-451.
8. Iqbal,S.,Rattu,M.A.(2019).Review of rheumatoid arthritis. US Pharm, 44(1), 8-11.

9. Kinnunen, T., Chamberlain, N., Morbach, H., Choi, J., Kim, S., Craft, J., Mayer, L., Cancrini, C., Passerini, L., Bacchetta, R., Ochs, H.D., Torgerson, T.R., Meffre, E. (2013). Accumulation ofperipheral autoreactive B cells in the absence of functional human regulatory T cells. Blood. 28;121(9),1595-1603.doi:10.1182/blood-2012-09-457465.Epub 2012 Dec 5. PMID: 23223361; PMCID: PMC3587322.
10. Radu, A.F., Bungau, S.G. (2021). Management of rheumatoid arthritis: an overview. Cells,10(11), 2857.
11. Sailaja, A. K. (2014). An overall review on rheumatoid arthritis. Journal of Current Pharma Research, 4(2), 1138.
12. Sarkar, J.H. (2022). Rheumatoid arthritis: Modern therapeutic options for treatment. Technologies and Innovative Research, 9(9), no.e631-e634.
13. Wragg, K. (2011). Rheumatoid arthritis. Centre for Pharmacy Postgraduate Education, University of Manchester, pp. 40.
14. Yap,H.Y.,Tee,S.Z.,Wong,M.M.,Chow,S.K., Peh, S.C., Teow, S.Y. (2018). Pathogenic role of immune cells in rheumatoid arthritis: Implications in clinical treatment and biomarker development. Cells. 9;7(10),161. doi: 10.3390/cells7100161. PMID: 30304822; PMCID: PMC6211121.