WEST INDIAN JOURNAL OF IMMUNOLOGY
An official Journal of the West Indies Immunology Society
ISSN: 2958-6917

A compressive review on rheumatoid arthritis (RA)

Analisa Logie

Department of Para-clinical Sciences, University of the West Indies, St. Augustine, Trinidad and Tobago

Email address: analisa.logie@my.uwi.edu

Received: 01/02/2023 Revised: 04/04/2023 Published 10/06/2023

ABSTRACT

Rheumatoid arthritis (RA) is a systemic autoimmune disorder characterised by inflammatory arthritis. Genetic and environmental factors contribute to the development of RA. These include the presence of HLA DRB1 alleles, female sex, cigarette smoking, and infections. Inflammation in RA is mediated by autoreactive TH1/TH17 T cells produced in the lymph nodes or by activated antigen-presenting cells (APCs) that present autoantigen-derived peptides. This results in the production of proinflammatory cytokines and an influx of inflammatory cells into the synovium. RA usually affects the small joints of the hands and feet, characterised by morning stiffness that lasts for more than 1 h, painful, swollen, and tender joints. The other affected joints included the shoulder, elbow, and knee. As the disease progresses, extra-articular symptoms involving the heart, lungs, eyes, skin, musculoskeletal, and neurological systems can manifest. RA is diagnosed based on clinical, laboratory, and radiological findings. The goals of treatment for rheumatoid arthritis are to reduce joint inflammation and prevent disease progression and joint deformity. Pharmacological therapy includes disease-modifying anti-rheumatic drugs (DMARDs), glucocorticoids, TNF inhibitors, non-TNF inhibitors, and NSAIDs.

Keywords: Rheumatoid arthritis, Autoimmune diseases, Clinical signs and symptoms, Management

WEST INDIAN JOURNAL OF IMMUNOLOGY
An official Journal of the West Indies Immunology Society
ISSN: 2958-6917

1. INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disorder that can lead to irreversible joint damage. Initially, it affects the small joints of the hands and feet and then progresses to larger joints, characterised by inflammatory arthritis, and can result in extra-articular involvement. Symptoms of RA occurring less than 6 months were defined as early RA, whereas symptoms more than six months were defined as established. Diagnosis can be made using information obtained from clinical examinations, laboratory and radiological findings, and the standard treatment for the diagnosis of early RA is initiated with the use of disease-modifying anti-rheumatic drugs (DMARDs). Subsequent treatment options depend on the response to treatment, disease progression, and organ involvement [1].

2. ETIOLOGY

Genetic and environmental factors contribute to the development of RA. Rheumatoid arthritis has a concordance rate of 15% in identical twins, and its heritability is approximately 66%. Studies have shown that environmental factors contribute to the genetic risk of developing RA in twins. The risk of developing RA is associated with the presence of HLA DRB1 alleles, particularly HLA-DRB1*04 and HLA-DRB1*01, and single nucleotide polymorphisms in the PTPN22 gene. The HLA DRB1 alleles contain a five amino acid sequence (QKRAA, RRRAA, QRRAA) in positions 70-74 of the DRB1 chain, that encode the positively charged P4 peptide-binding pocket known as the RA 'shared epitope', which is associated with an increased risk of RA development. The presence of HLA DRB1 alleles is associated with severe joint damage, bone erosion, and increased mortality. Smoking, dietary factors, exposure to UV light, and infections, particularly with Porphyromonas gingivalis, have been linked to autoantibody formation and subsequent RA development. Cigarette smoke is the most important environmental factor associated with rheumatoid arthritis. It is suggested that it may be involved in the initial break of tolerance and can induce self-protein citrullination and maturation of anti-citrullinated protein antibodies (ACPAs).Porphyromonas gingivalis, via citrullination of host peptides, can lead to the development of an autoimmune response. This process is catalysed by protein arginine deiminase where 'self 'proteins of arginine residues are converted to citrulline residues. P. gingivialis expressing PADi4 leads to a breach in tolerance, promoting the development of ACPAs. Studies have shown that a diet low in omega 3 fatty acids contributes to ACPA production. Normally, omega 3 fatty acids lower the risk of ACPA production, in addition to preventing the onset of arthritis after ACPA detection [1][2][3].

3. EPIDEMIOLOGY

RA has a relatively constant population prevalence rate of 0.1%–1.0%. It can affect any gender, race, or ethnic group; however, it has a predilection for females with a female to male ratio of 3:1, and its prevalence increases with age. Approximately 80% of patients develop RA between the ages of and 35-50 years, with a disease prevalence of 5% for women over 65 years of age. RA frequently affects persons from North America and Northern Europe, with a

mean annual incidence rate of 0.05%. Studies show that the prevalence rate of RA in the United States increased during the period from to 2004-2014, affecting approximately 1.28-1.38 million in 2014 [4][5][6][7].

4. HISTOPATHOLOGY

In the early stages of rheumatoid arthritis, inflammatory cells infiltrate the synovium, and the synovial fluid is filled with pro-inflammatory mediators that perpetuate inflammation due to the interactions of fibroblast-like synoviocytes with cells of the innate (monocytes, macrophages, mast cells, and dendritic cells) and adaptive (T and B lymphocytes) immune systems. As RA progresses, there is proliferation of monocytes and hyperplasia of the intima and subintimal layers of the synovial membrane from to 1-3 layers to 8-12 layers, increased vascularity due to angiogenesis and fibrin deposition on the synovial surface and in the joint space. Hyperplasia of the intima layer is caused by proliferation of fibroblast-like synoviocytes (FLS) and their resistance to apoptosis, whereas thickening of the subintimal layer results from migration and retention of infiltrated cells, such as lymphocytes and mast cells. The extent of synovial hyperplasia directly relates to the severity of cartilage erosion which results in the formation of a pannus. Pannus is an invasive synovial tissue formed at the junction between the synovium, cartilage, and bone, subsequently resulting in cartilage, subchondral bone, and soft tissue destruction. Pannus formation results in small villous projections in the joint space. Increased vascular endothelial growth factor expression and osteoclastogenesis stimulated by IL-6 contribute to pannus formation. Large amounts of matrix-degrading enzymes, such as gelatinase and collagenase, secreted by synoviocytes further perpetuate cartilage erosion. Rheumatoid nodules are frequently observed in patients with RA. These nodules typically involve the dermis and subcutis. Histologically, they are characterised by a central red necrotic area with streaks and granulations. The central necrotic area has fibrin deposition, which is responsible for the red colour, collagen, proteins, and cellular debris. It is enclosed by a pattern of palisading microphages and perivascular granulation tissue infiltrated by inflammatory cells, consisting of plasma cells, lymphocytes, and histiocytes [2][4][8][9].

5. IMMUNOPATHOGENESIS

Cigarette smoke and viral and bacterial infections act as triggering events allowing activated antigen-presenting cells to interact with and activate previously generated autoreactive lymphocytes, resulting in failure of immunologic tolerance and eventual tissue destruction. Anti-citrullinated protein antibodies (ACPAs), detected in approximately 67% of RA patients, contribute to RA development. ACPAs can be IgA, IgG, or IgM isotypes. They bind to citrullinated protein residues of type II collagen, fibronectin, fibrinogen, and vimentin, causing complement activation, inflammation, and joint damage. Inflammation in RA is mediated by autoreactive TH1/TH17 T cells produced in the lymph nodes or by activated antigen-presenting cells (APCs) that present autoantigen-derived peptides via the major histocompatibility complex (MHC-II) to CD 4+ T helper cells. The synovium is infiltrated by leukocytes, and the

synovial fluid is filled with pro-inflammatory mediators, resulting in inflammation (synovitis) due to fibroblast-like synoviocytes (FLSs) interacting with monocytes, macrophages, dendritic cells (DCs), mast cells, and autoreactive T and B lymphocytes. Recruitment of DCs is thought to be due to increased expression of CC chemokine receptor 6 (CCR6) on DCs which interacts with the chemokine ligand 20 (CCL20) expressed in synovial tissue. DCs produce IL-12 and IL-23, promoting antigen-specific Th17 responses, leading to imbalances between Th1 and Th2 subsets and Th-17 responses. Cytokines contribute extensively to the inflammatory processes in RA. Macrophages and fibroblasts are activated by autoreactive T cells in the synovium via the secretion of TNF-α, IL -17, IFN-γ, and receptor activator of nuclear factor kappa-B ligand (RANK-L). This, in turn, results in the production of pro-inflammatory cytokines (TNF-α, IL 1β and IL-6) from activated macrophages, perpetuating inflammation. TNF-α plays an important role in the pathogenesis of RA, as it can induce the production of IL 1β and IL-6, thereby attracting leukocytes into the synovium and contributing to the establishment of inflammation. TH17 cells produce IL-17A, promoting neutrophil recruitment and production of IL-6, IL-8, and granulocyte-macrophage colony-stimulating factor (GM-CSF) from fibroblastic cells, resulting in local inflammation and disease progression. Activated T cells also aid autoreactive B cells in the production of autoantibodies, mainly ACPAs and rheumatoid factor (RF). These autoantibodies result in immune complex formation and deposition in joints and other tissues, leading to inflammation and tissue damage. Chronic inflammation, due to increased secretion of pro-inflammatory cytokines in the synovium, fibroblast-derived matrix metalloproteases (MMPs), and osteoclast generation results in cartilage destruction, bone resorption, and subsequent bone erosion, the hallmark feature of RA. Hyperplastic synovium is a key factor contributing to cartilage damage. In RA, there is reduced secretion of hyaluronic acid and lubricin which are normally secreted by the synovial cell and have protective effects on the synovium. This results in dysfunction of the FLS, causing FLS adhesion and invasion of the joint cartilage. Cartilage damage is mediated by MMPs synthesised by FLS, causing disruption of the type II collagen network, proteinases, and tissue inhibitors of metalloproteinases (TIMPs). These proteinases allow for neutrophil accumulation and the survival of T and B cells in the synovium. TNF-α, IL-6, and IL-1β are pro-osteoclastogenic cytokines that suppress bone formation, thereby promoting bone resorption and cartilage degradation by enhancing RANK-L secretion. RANK-L binds to RANK receptors on osteoclast progenitor cells and promotes osteoclastogenesis. IL-17 induces osteoclast formation from osteoclast precursor cells and the production of RANK-L from osteoblasts and synoviocytes, thereby decreasing bone formation and contributing to bone erosion. ACPAs, derived from the activation of autoreactive B cells, are also implicated in the development of bone erosion. They increase bone resorption by activating macrophages via immune complexes which secrete proinflammatory cytokines (TNF-α and RANKL), promoting osteoclast differentiation. In addition, ACPAs recognise citrullinated vimentin found on the surface of osteoclast progenitor cells, contributing directly to bone loss and erosion [1][2][4][10][11].

Signs and Symptoms

WEST INDIAN JOURNAL OF IMMUNOLOGY
An official Journal of the West Indies Immunology Society
ISSN: 2958-6917

Most clinical manifestations of Rheumatoid Arthritis are caused by immune complexes that activate the complement system, leading to tissue damage. Signs and symptoms develop slowly and may vary in intensity. These include stiffness in one or more joints with associated joint tenderness and discomfort during movement. Clinical findings include symmetrical inflammation of the small joints of the hands and feet, namely the proximal interphalangeal joints (PIP), metacarpophalangeal joints (MCP), and metatarsophalangeal joints (MTP). Other affected joints include the shoulder, elbow, knees, and ankles [1]. Patients experience morning stiffness of the affected joints lasting for more than an hour with a limited range of motion. RA patients may report that they are unable to make a full fist in the morning and feel as if they are walking on pebbles. Fever, fatigue, weight loss, and rheumatoid nodules may occur. Rheumatoid nodules (RNs) are the most common skin manifestations (20 %) observed in RA and mainly occur in patients with high RF titres. It is rare in patients with seronegative RA. RNs occur more frequently in Caucasian populations, with a male predominance. They are usually present on sites of recurrent mechanical pressure, such as the extensor surfaces of the olecranon, forearm, heels, and toes [4]. Physical examination revealed painful, swollen, warm, and tender joints. On palpation, synovial thickening was detected as a boggy or spongy feel. Discomfort or tenderness is elicited when the MTP joints of the feet are squeezed. Fluctuations were used to detect the presence of joint effusion. With the progression of RA, deformities may occur, and the surfaces of the subluxed bone may falsely represent joint swelling. In the late stage of RA, boutonniere deformity, swan-neck deformity, and ulnar deviation of the MCP are present in the hands, and hallux valgus is seen in the feet. RA may present as steroid-responsive polymyalgia rheumatica in some elderly patients, and symmetrical arthritis typically seen in RA would only be present once the steroid dose is reduced. Rheumatoid arthritis also has extra-articular manifestations involving the heart, lungs, eyes, skin, musculoskeletal, and neurological systems [12] [13] [14].

6. INVESTIGATIONS

Laboratory investigations

Laboratory investigations for rheumatoid arthritis include detection of rheumatoid factor (RF) (antibodies directed against the Fc fragment of IgG), anti-citrullinated protein antibodies (ACPAs), elevated erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) levels. Approximately 45 %–75% of patients tested positive for RF; however, it should be noted that the presence of RF alone is not diagnostic of rheumatoid arthritis, as it is also present in connective tissue disorders such as Sjogren syndrome and systemic sclerosis. ACPAs have greater specificity for RA diagnosis than RF and can be detected in serum for up to 10 years before the occurrence of symptoms. The presence of ACPAs and RF increases the diagnostic specificity of RA. Assessment of synovial ACPAs can be used to differentiate RA from non-RA arthritis conditions. ESR and CRP indicate the presence of joint inflammation in persons with arthritis, and elevated levels of these inflammatory markers indicate higher disease

activity. These markers can also aid in evaluating treatment efficacy, as reflected by a decrease in the Disease Activity Score (DAS) [4].

Radiological investigations

X-ray images of the hands and feet were used to assess the structural damage and detect the presence of erosions. However, plain radiographs do not show early changes in the disease. Magnetic resonance imaging (MRI) and ultrasound are more sensitive for the early detection of erosions in the hands and feet, synovitis, and joint effusion. Synovitis is an early sign of RA and is associated with the development of bone erosion. Ultrasound can be used to evaluate soft tissue involvement, along with clinical examination for the detection of subclinical synovitis. Ultrasound shows synovial proliferation via greyscale imaging, and power Doppler imaging provides imaging for neoangiogenesis and active inflammation. MRI scans can also detect pannus formation or synovial hypertrophy [1][2][12][15].

Radiological investigations can be used to assess disease progression.

- Stage 1: No destructive changes observed on X- ray.
- Stage 2: Radiographic evidence of periarticular osteoporosis and subchondral bone destruction without joint deformity.
- Stage 3: Cartilage and bone destruction in addition to periarticular osteoporosis and joint deformity present on radiography.
- Stage 4: Radiographic evidence of fibrous and bony ankylosis in addition to stage 3 criteria [1].

7. COMPLICATIONS

Rheumatoid arthritis is a systemic disease that is associated with cardiovascular, pulmonary, neurological, ocular, musculoskeletal, and skin complications. Extraarticular involvement is more likely to occur in persons who have RF and/or are HLA-DR4 positive.

Cardiovascular Complications

Cardiovascular disease is one of the leading causes of mortality among patients with RA compared to the general population. Pericarditis occurs more frequently in men with active rheumatoid disease. For a female RA patient, the risk of developing myocardial infarction is twice that of a woman without RA, and it is three times higher in long-standing disease. In RA patients, left systolic ventricular function is reduced, and there is an increased incidence of congestive heart failure (CHF). Inflammatory stimuli and anti-rheumatic drugs such as TNF inhibitors and prolonged use of high-dose glucocorticoids and NSAIDs contribute to the development and worsening of CHF. Myocarditis is rare in RA and is associated with active

WEST INDIAN JOURNAL OF IMMUNOLOGY
An official Journal of the West Indies Immunology Society
ISSN: 2958-6917

articular damage and extra-articular manifestations. Chronic inflammation in patients with RA increases the risk of developing valvular nodules, and there is a four-fold increased risk of valvular thickening, contributing to other valvular pathologies such as stenosis or prolapse [16][17].

Pulmonary Complications

Cricoarytenoid arthritis and pulmonary nodulosis are unique complications of RA. Other complications include pleural effusion, spontaneous pneumothorax, empyema, pulmonary fibrosis, and airway diseases such as bronchiectasis and bronchiolitis. Pulmonary involvement accounts for 60 %–80% of systemic complications and manifestations and is increased by opportunistic infections caused by immunosuppressant therapy or pulmonary toxicity due to anti-tumor necrosis factor agents or methotrexate. Interstitial lung disease is associated with high morbidity and mortality in these patients. Continuous inflammation due to dysregulation of the immune response occurs in the airways. This can destroy the peripheral airway or lead to the formation of honeycomb-like structures in the lung parenchyma [16][18].

Neurologic Complications

Neurological manifestations involve both the central (CNS) and peripheral nervous systems (PNS), with symptoms ranging from mild paresthesia in the hand to sudden death resulting from impingement of the medulla. Neurological involvement is most often due to articular inflammation, leading to compression of the spinal cord and peripheral nerves. CNS manifestations include cervical myelopathy which is observed in 50% of patients with RA and rheumatoid meningitis. Arthritis of the atlantoaxial joint and eventual erosion of the odontoid process causes cervical myelopathy. PNS manifestations occur in 30% of RA patients and include carpel tunnel syndrome and mononeuritis multiplex, caused by vasculitis of the vasa vasorum of the nerves with ischemic neuropathy and demyelination. Recently, the use of biological DMARDs has resulted in an increase in the incidence of Guillain-Barré syndrome [16][19][20].

Skin Manifestations/Complications

Rheumatoid nodules are the most common skin manifestations of RA. They usually occur in RF-positive patients with longstanding disease and can be an indicator of severe extra-articular complications. Accelerated rheumatoid nodulosis (ARN) occurs as a complication of methotrexate therapy in approximately 8 %–11% of patients. Increased expression of HLA-DRB1*0401 and RF seropositivity was associated with ARN. In ARN, there is a rapid onset and worsening of nodules in patients with longstanding disease. Rheumatoid vasculitis, a type III hypersensitivity reaction, affects about 2-5% of patients with long standing disease. Rheumatoid vasculitis can affect any organ; however, cutaneous involvement is the main presentation in approximately 90% of patients. Vasculitis affects small dermal capillaries, medium-sized arteries, and post-capillary venules. Clinically, it presents as palpable purpura, petechiae, maculopapular erythema, or haemorrhagic vesicles. Some patients may develop

WEST INDIAN JOURNAL OF IMMUNOLOGY
An official Journal of the West Indies Immunology Society
ISSN: 2958-6917

urticarial vasculitis presenting as wheals lasting for more than 24 hours and healing with hyperpigmentation [4][21].

Ocular Complications

Keratoconjunctivitis Sicca, described as an aqueous tear deficiency, is the most common ocular manifestation of RA, affecting at least 10% of patients. It is also seen along with Xerostomia in secondary Sjogren's syndrome. Scleritis, characterised by intense painful inflammation of the sclera, may occur. This can lead to blindness and peripheral ulcerative keratitis with involvement of the peripheral cornea, resulting in corneal melting. Episcleritis, inflammation of the episclera, occurs in less than 1% of patients with RA and usually resolves on its own. Retinal vasculitis affects approximately 1 %–5% of patients with established RA and is usually seen on the periphery of the retina [20][22].

Musculoskeletal Complications

Musculoskeletal complications directly related to inflammation include periarticular bone loss and juxta-articular bone erosion, while osteoporosis, generalised bone loss, and fractures arise secondary to inflammation. A long disease duration results in joint ankylosis. The incidence of femoral neck and vertebral compression fractures has increased due to the development of osteoporosis, resulting in increased mortality. Moreover, drug-induced osteoporosis occurs with prolonged glucocorticoid use. GCs reduce the replication, differentiation, and function of osteoblasts and induce apoptosis of osteocytes, leading to decreased bone mass. Myopathy and myositis are muscle disorders associated with RA. They are associated with active diseases, sarcopenia, and immobilisation. Muscle weakness associated with these disorders commonly occurs because of the use of GC and hydroxychloroquine [16][23][24].

Infections

Patients with RA have a greater risk of developing infections involving the lower respiratory tract, skin, blood stream, and urinary system. The risk of developing tuberculosis or opportunistic infections is increased in these patients due to an immunocompromised state resulting from high-dose glucocorticoid and immunosuppressive drug therapy. The action of these drugs inhibits the immune response, consequently suppressing the release of host inflammatory cytokines, allowing for pathogen survival and replication [16].

Other complications

RA can lead to the development of normochromic normocytic anaemia, chronic leg ulcers, non-Hodgkin lymphoma, Felty syndrome, and Sicca syndrome. Felty syndrome is a rare extraarticular manifestation presenting as a triad of seropositive rheumatoid arthritis with severe joint involvement, splenomegaly, and neutropenia. It is associated with the HLA-

DRB1*04 allele which is a predisposing factor for extraarticular manifestations of RA. 1-3% of RA patients develop Felty syndrome which has an estimated prevalence of 10 per 100,000 population. It usually occurs after long-standing disease, and these patients typically have high titers of RF, circulating immune complexes, rheumatoid nodules, and destructive arthritis. There is an increased risk of melanoma during the first year of diagnosis of Felty syndrome. These patients have an increased risk of lymphoma and leukaemia development, attributed to splenic dysfunction, neutropenia, aggressive rheumatoid disease, and an increased susceptibility to Epstein Barr infection. Neutropenia associated with Felty syndrome further increases the patient's susceptibility to infections [4][25].

Sicca syndrome, also known as Sjogren syndrome (SS), is a systemic autoimmune disorder that presents with dryness of the eyes and mouth due to inflammation and pathology of the lacrimal glands. Rheumatoid arthritis leads to secondary Sjögren's syndrome, which causes oral dryness and salivary gland swelling. Sjogren syndrome associated with RA has a global prevalence rate of 19.5%. Patients with RA who developed SS were more likely to have a longer disease duration and higher levels of RF and/or anti-citrullinated protein antibodies. These patients also had more pre-existing comorbidities (hypertension, malignancies, etc.), subcutaneous nodules, and erosive disease compared to patients with RA alone [26][27].

8. DIFERENTIAL DIAGNOSIS

- Osteoarthritis (OA) can present with typical symptoms of RA, such as joint pain and stiffness; however, it presents as asymmetric inflammation of the joints involving the distal interphalangeal joints (DIP), whereas RA is a symmetric inflammation involving the PIP and MCP. OA is characterised by morning stiffness lasting between and 20-30 min, whereas in RA, it lasts for more than 1 h [14].

- Psoriatic arthritis presents with tender, soft tissue swelling of joints, axial arthritis, and inflammation of the DIP. Patients with psoriatic arthritis are seronegative for RF and ACPA, differentiating them from RA. Genetic predisposition to psoriatic arthritis is associated with HLA Cw6 and B27 genes, whereas RA involves HLA DRB1 or HLA DR 4 [28].

- Septic arthritis is characterised by an acute onset of severe joint pain that worsens with minimal movement, swelling, and erythema of the affected joint and elevated ESR levels. It is differentiated from RA by the absence of both RA autoantibodies and systemic manifestations of the disease and a positive synovial fluid or blood culture [29].

- Systemic lupus erythematosus (SLE) can present with polyarticular inflammatory arthritis in addition to extra-articular manifestations which can be difficult to differentiate from RA. It is associated with a positive RF in some cases, but the ACPA antibody is negative, differentiating it from RA. System-specific antibodies, such as antinuclear antibodies (ANA), are absent in RA [4].

WEST INDIAN JOURNAL OF IMMUNOLOGY
An official Journal of the West Indies Immunology Society
ISSN: 2958-6917

- Sjogren's syndrome, characterised by oral and ocular dryness and salivary gland swelling, is usually observed in extra-articular manifestations of RA. SS can cause polyarthritis, which is characterised by painful, swollen, and tender joints, typical of RA. Positive RF, anti-Ro, and anti-La levels were observed in SS. However, ACPAs are not observed in some patients with RA [4].

Other differential diagnoses include sarcoidosis, parvovirus B-19, and chronic Lyme disease. Parvovirus B-19 and chronic Lyme disease can present with polyarthritis. However, specific autoantibodies and extra-articular manifestations characteristic of RA are absent in these diseases [1][12].

9. TREATMENT/MANAGEMENT

The goals of treatment for rheumatoid arthritis are to reduce joint pain and inflammation, maximise joint function, and subsequently prevent joint destruction and deformity. A strategic approach is employed when managing RA, as therapeutic options are altered based on the response to treatment, disease activity, and prognostic factors.

The DAS28-ESR score was used to assess disease activity in patients with RA. It combines the information obtained from the number of tender and swollen joints out of 28, erythrocyte sedimentation rate in (mm), and patient global assessment/general health which can predict treatment options.

- DAS28-ESR: < 2.6: Remission
- DAS28-ESR: ≥ 2.6 to ≤ 3.2 Low disease activity
- DAS28-ESR >3.2 to ≤ 5.1: Moderate disease activity
- DAS28-ESR >5.1: High disease activity

According to the 2021 American College of Rheumatology guidelines, once RA has been diagnosed, treatment with conventional disease-modifying anti-rheumatic drugs (cDMARDs) is initiated, and oral methotrexate (MTX) should be the first choice for a period of three months as monotherapy is preferred over double or triple therapy. Other conventional DMARDs include leflunomide and sulfasalazine [30].

The NICE (2021) guidelines state that hydroxychloroquine, an antimalarial drug, can be considered as an alternative first-line treatment to oral methotrexate, leflunomide, and sulfasalazine to treat mild or palindromic disease. It decreases the production of monocyte-derived proinflammatory cytokines. If there is no improvement in symptoms after 12 weeks of MTX treatment or no remission is achieved after 24 weeks with optimum dosage, a combination of cDMARDs can be used. Glucocorticoids may be used as a bridging treatment for three months when starting new cDMARDs. [31] Short-term glucocorticoids are used at the lowest dose to treat disease flares [1].

If disease activity is moderate or high despite the use of two or more cDMARDs, targeted synthetic DMARDs such as tofacitinib and baricitinib are used in combination with

methotrexate. They are Janus kinase inhibitors, and tofacitinib inhibits JAK1 and JAK3, whereas baricitinib mainly inhibits JAK2 and, to a lesser extent, the phosphorylation of JAK1 and JAK3. This, in turn, reduces cell differentiation, proliferation, and the production of proinflammatory cytokines. Tofacitinib can be administered as a monotherapy in cases where MTX treatment is contraindicated [31] [32].

It should be noted that there is an increased susceptibility to herpes zoster virus in elderly patients receiving tofacitinib therapy, and the risk is greater in patients taking tofacitinib in combination with glucocorticoids. The 2015 ACR guidelines recommend that herpes zoster vaccine should be administered before starting tofacitinib or biological DMARDs in the treatment of elderly patients aged ≥ 50 years with RA. A two-week waiting period after vaccination was recommended before starting the biologics. [33]

Biological DMARDs should be added if poor prognostic markers are identified. These include early joint damage, the presence of high serum titers of autoantibodies, high acute phase reactant levels, and high disease activity which are associated with rapid disease progression. Biological DMARDs consist of tumour necrosis factor (TNF) inhibitors, such as adalimumab, etanercept, infliximab, and golimumab. Tocilizumab (interleukin 6 inhibitor), rituximab (anti-B cell), and abatacept (T-cell stimulation inhibitor). Rituximab in combination with methotrexate is used in the treatment of severe active RA in patients who are intolerant of biological DMARDs, including at least one TNF inhibitor or those that have a poor response to treatment. Rituximab is administered every 6 months and therapy should only be continued if there is an improvement in the DAS28 of 1.2 points or more [31]. For patients who did not show improvement in symptoms with rituximab and other biological DMARDs, including one or more TNF inhibitors, tocilizumab in combination with methotrexate is recommended. Tocilizumab is a recombinant IgG1 monoclonal antibody that binds to and blocks the IL-6 receptor, thereby decreasing the inflammatory cascade, thereby reducing inflammation. Before the initiation of biological DMARD therapy, active and latent hepatitis infections should be ruled out. TNF-α inhibitors increase the risk of reactivation in patients with prior exposure to hepatitis B (HBV) as it decreases the inflammatory cell response against hepatitis infection, resulting in an increase in viral replication, subsequently inhibiting the destruction of the infected cells. Anti-TNF-α therapy may cause reactivation in patients with hepatitis B surface antigen (HBsAg)-positive or HbsAg-negative with detectable HBV DNA, as well as persons with hepatitis B core protein (HBcAg)-positive and HBsAg-negative. However, TNF-α inhibitors can be used safely in patients with HBsAg-positive and undetectable HBV DNA. Patients with hepatitis C receiving antiviral medication can be treated as patients with RA. Another pharmacological agent implicated in the treatment of RA is non-steroidal anti-inflammatory drugs (NSAIDs), including acetylsalicylate, ibuprofen, and naproxen. They are used to relieve pain and join inflammation through the inhibition of cyclooxygenase (COX), which prevents prostaglandin, prostacyclin, and thromboxane synthesis. The side effects of NSAIDs include nausea, vomiting, and gastrointestinal bleeding [14].

Specific therapies for the extra-articular manifestations of RA are unavailable; however, patients with severe congestive heart failure (CHF) class III or IV should avoid TNF inhibitors

and use non-TNF inhibitors (tocilizumab and abatacept) as they may worsen the symptoms of CHF, leading to increased mortality and hospitalisation. [1] Conventional DMARDs, such as methotrexate, sulfasalazine, and hydroxychloroquine, and most biological DMARDs can improve cardiovascular (CV) risk through the regulation of chronic inflammation [16].

Methotrexate reduces CV risk in RA patients by its effects on cholesterol and free radicals, in addition to blocking the effects of pro-atherosclerotic cytokines such as IL-1, IL-6, and TNF-α. Sulfasalazine can reduce CV morbidity in RA patients by inhibiting platelet function, and TNF inhibitors reduce inflammation, thereby decreasing CVD risk. Patients receiving anti-TNF medications have a reduced risk of developing MI. For mild pericarditis, aspirin or NSAIDs are used, and for moderate and severe cases, glucocorticoids (prednisone) are required. Glucocorticoids (GCs) are the treatment of choice for myocarditis; however, in patients who do not respond to GCs, immunosuppressive drugs such as azathioprine and cyclophosphamide are used. [17]

Cyclosporin A and DMARDs, such as infliximab, can be used to improve tear production and treat severe keratoconjunctivitis. Corticosteroids and cyclophosphamide can be used to treat vasculitis. Rheumatoid arthritis (RA) is a progressive disease with no cure. Relapse and remission frequently occur throughout the disease process, and approximately 40 % of patients will be disabled in a 10-year period. Patients, including those who received target treatment, should have review appointments (6 months /year) to assess joint damage and disease activity. Symptoms that suggest complications such as vasculitis should be monitored, and patients should be evaluated for the development of comorbidities [1][20][34][35].

References

1. Chauhan K, Jandu JS, Goyal A, Bansal P, Al-Dhahir MA. Rheumatoid Arthritis. 2020 Nov 5. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan–. PMID: 28723028.
2. Lin YJ, Anzaghe M, Schülke S. Update on the Pathomechanism, Diagnosis, and Treatment Options for Rheumatoid Arthritis. Cells. 2020 Apr 3;9(4):880. doi: 10.3390/cells9040880. PMID: 32260219; PMCID: PMC7226834.
3. Scherer HU, Häupl T, Burmester GR. The etiology of rheumatoid arthritis. J Autoimmun. 2020 Jun;110:102400. doi: 10.1016/j.jaut.2019.102400. Epub 2020 Jan 22. PMID: 31980337.
4. Lora V, Cerroni L, Cota C. Skin manifestations of rheumatoid arthritis. G Ital Dermatol Venereol. 2018 Apr;153(2):243-255. doi: 10.23736/S0392-0488.18.05872-8. Epub 2018 Jan 24. PMID: 29368864.
5. Senthelal S, Li J, Goyal A, et al. Arthritis. [Updated 2020 Aug 10]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK518992/
6. Alamanos Y, Drosos AA. Epidemiology of adult rheumatoid arthritis. Autoimmun Rev. 2005 Mar;4(3):130-6. doi: 10.1016/j.autrev.2004.09.002. PMID: 15823498

7. Hunter TM, Boytsov NN, Zhang X, Schroeder K, Michaud K, Araujo AB. Prevalence of rheumatoid arthritis in the United States adult population in healthcare claims databases, 2004-2014. Rheumatol Int. 2017 Sep;37(9):1551-1557. doi: 10.1007/s00296-017-3726-1. Epub 2017 Apr 28. PMID: 28455559
8. Hitchon CA, El-Gabalawy HS. The synovium in rheumatoid arthritis. Open Rheumatol J. 2011;5:107-14. doi: 10.2174/1874312901105010107. Epub 2011 Dec 30. PMID: 22279509; PMCID: PMC3263474.
9. Sudoł-Szopińska I, Kontny E, Maśliński W, Prochorec-Sobieszek M, Kwiatkowska B, Zaniewicz-Kaniewska K, Warczyńska A. The pathogenesis of rheumatoid arthritis in radiological studies. Part I: Formation of inflammatory infiltrates within the synovial membrane. J Ultrason. 2012 Jun;12(49):202-13. doi: 10.15557/JoU.2012.0007. Epub 2012 Jun 30. PMID: 26673660; PMCID: PMC4579739.
10. McInnes IB, Schett G. The pathogenesis of rheumatoid arthritis. N Engl J Med. 2011 Dec 8;365(23):2205-19. doi: 10.1056/NEJMra1004965. PMID: 22150039.
11. NJ, Xu J. Rheumatoid arthritis: pathological mechanisms and modern pharmacologic therapies. Bone Res. 2018 Apr 27;6:15. doi: 10.1038/s41413-018-0016-9. PMID: 29736302; PMCID: PMC5920070.
12. Taylor PC. Update on the diagnosis and management of early rheumatoid arthritis. Clin Med (Lond). 2020 Nov;20(6):561-564. doi: 10.7861/clinmed.2020-0727. PMID: 33199320; PMCID: PMC7687323.
13. Schumacher HR Jr. Clinical diagnosis of rheumatoid arthritis. Drugs Today (Barc). 1998 Mar;34(3):225-9. doi: 10.1358/dot.1998.34.3.485177. PMID: 15094851.
14. Bullock J, Rizvi SAA, Saleh AM, Ahmed SS, Do DP, Ansari RA, Ahmed J. Rheumatoid Arthritis: A Brief Overview of the Treatment. Med Princ Pract. 2018;27(6):501-507. doi: 10.1159/000493390. Epub 2018 Sep 2. PMID: 30173215; PMCID: PMC6422329.
15. Heidari B. Rheumatoid Arthritis: Early diagnosis and treatment outcomes. Caspian J Intern Med. 2011 Winter;2(1):161-70. PMID: 24024009; PMCID: PMC3766928.
16. Kim JW, Suh CH. Systemic Manifestations and Complications in Patients with Rheumatoid Arthritis. J Clin Med. 2020 Jun 26;9(6):2008. doi: 10.3390/jcm9062008. PMID: 32604884; PMCID: PMC7356332.
17. Rawla P. Cardiac and vascular complications in rheumatoid arthritis. Reumatologia. 2019;57(1):27-36. doi: 10.5114/reum.2019.83236. Epub 2019 Feb 28. PMID: 30858628; PMCID: PMC6409824.
18. Farquhar H, Vassallo R, Edwards AL, Matteson EL. Pulmonary Complications of Rheumatoid Arthritis. Semin Respir Crit Care Med. 2019 Apr;40(2):194-207. doi: 10.1055/s-0039-1683995. Epub 2019 May 28. PMID: 31137060.
19. DeQuattro K, Imboden JB. Neurologic Manifestations of Rheumatoid Arthritis. Rheum Dis Clin North Am. 2017 Nov;43(4):561-571. doi: 10.1016/j.rdc.2017.06.005. Epub 2017 Aug 31. PMID: 29061242.
20. Young A, Koduri G. Extra-articular manifestations and complications of rheumatoid arthritis. Best Pract Res Clin Rheumatol. 2007 Oct;21(5):907-27. doi: 10.1016/j.berh.2007.05.007. PMID: 17870035.

21. Cojocaru M, Cojocaru IM, Silosi I, Vrabie CD, Tanasescu R. Extra-articular Manifestations in Rheumatoid Arthritis. Maedica (Bucur). 2010 Dec;5(4):286-91. PMID: 21977172; PMCID: PMC3152850.
22. Zlatanović G, Veselinović D, Cekić S, Zivković M, Dorđević-Jocić J, Zlatanović M. Ocular manifestation of rheumatoid arthritis-different forms and frequency. Bosn J Basic Med Sci. 2010 Nov;10(4):323-7. doi: 10.17305/bjbms.2010.2680. PMID: 21108616; PMCID: PMC5489043.
23. Heinlen L, Humphrey MB. Skeletal complications of rheumatoid arthritis. Osteoporos Int. 2017 Oct;28(10):2801-2812. doi: 10.1007/s00198-017-4170-5. Epub 2017 Aug 4. PMID: 28779302.
24. Pereira RM, Carvalho JF, Canalis E. Glucocorticoid-induced osteoporosis in rheumatic diseases. F21243296; PMCID: PMC2999719.
25. Owlia MB, Newman K, Akhtari M. Felty's Syndrome, Insights and Updates. Open Rheumatol J. 2014 Dec 31;8:129-36. doi: 10.2174/1874312901408010129. PMID: 25614773; PMCID: PMC4296472.
26. Carsons SE, Patel BC. Sjogren Syndrome. [Updated 2021 Feb 25]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK431049.
27. Harrold LR, Shan Y, Rebello S, Kramer N, Connolly SE, Alemao E, Kelly S, Kremer JM, Rosenstein ED. Prevalence of Sjögren's syndrome associated with rheumatoid arthritis in the USA: an observational study from the Corrona registry. Clin Rheumatol. 2020 Jun;39(6):1899-1905. doi: 10.1007/s10067-020-05004-8. Epub 2020 Mar 4. PMID: 32130579; PMCID: PMC7237400.
28. Veale DJ, Fearon U. What makes psoriatic and rheumatoid arthritis so different? RMD Open. 2015 Apr 28;1(1):e000025. doi: 10.1136/rmdopen-2014-000025. PMID: 26509055; PMCID: PMC4613157.
29. Momodu II, Savaliya V. Septic Arthritis. [Updated 2021 Feb 5]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK538176/
30. Fraenkel L, Bathon JM, England BR, St Clair EW, Arayssi T, Carandang K, Deane KD, Genovese M, Huston KK, Kerr G, Kremer J, Nakamura MC, Russell LA, Singh JA, Smith BJ, Sparks JA, Venkatachalam S, Weinblatt ME, Al-Gibbawi M, Baker JF, Barbour KE, Barton JL, Cappelli L, Chamseddine F, George M, Johnson SR, Kahale L, Karam BS, Khamis AM, Navarro-Millán I, Mirza R, Schwab P, Singh N, Turgunbaev M, Turner AS, Yaacoub S, Akl EA. 2021 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. Arthritis Rheumatol. 2021 Jun 8. doi: 10.1002/art.41752. Epub ahead of print. PMID: 34101376.
31. National Institute for Health and Care Excellence. Drug treatment of rheumatoid arthritis [Internet]. [London]: NICE; 2021 [updated 2021 June; cited 2021 June]. Available from: https://pathways.nice.org.uk/pathways/rheumatoid-arthritis
32. Amrhein J, Drynda S, Schlatt L, Karst U, Lohmann CH, Ciarimboli G, Bertrand J. Tofacitinib and Baricitinib Are Taken up by Different Uptake Mechanisms Determining

the Efficacy of Both Drugs in RA. Int J Mol Sci. 2020 Sep 10;21(18):6632. doi: 10.3390/ijms21186632. PMID: 32927842; PMCID: PMC7556031.

33. Betancourt BY, Biehl A, Katz JD, Subedi A. Pharmacotherapy Pearls in Rheumatology for the Care of Older Adult Patients: Focus on Oral Disease-Modifying Antirheumatic Drugs and the Newest Small Molecule Inhibitors. Rheum Dis Clin North Am. 2018 Aug;44(3):371-391. doi: 10.1016/j.rdc.2018.03.010. Epub 2018 Jun 12. PMID: 30001781; PMCID: PMC6047536.
34. Köhler BM, Günther J, Kaudewitz D, Lorenz HM. Current Therapeutic Options in the Treatment of Rheumatoid Arthritis. J Clin Med. 2019 Jun 28;8(7):938. doi: 10.3390/jcm8070938. PMID: 31261785; PMCID: PMC6678427.
35. Felis-Giemza A, Olesińska M, Świerkocka K, Więsik-Szewczyk E, Haładyj E. Treatment of rheumatic diseases and hepatitis B virus coinfection. Rheumatol Int. 2015 Mar;35(3):385-92. doi: 10.1007/s00296-014-3195-8. Epub 2014 Dec 31. PMID: 25549599; PMCID: PMC4335127.