Available online on 15.09.2022 at ijmspr.com

International Journal of Medical Sciences and Pharma Research

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Comprehensive Review on Rheumatoid Arthritis

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Article Info:

Article History:

Received 23 Sep 2022
Reviewed 30 Oct 2022
Accepted 14 Nov 2022
Published 30 Nov 2022

Cite this article as:

Rohit N, Thakur BS, Jain A, Jain PK, Khare B, Jat YS, Comprehensive Review on Rheumatoid Arthritis, International Journal of Medical Sciences & Pharma Research, 2022; 8(3):39-45

DOI: http://dx.doi.org/10.22270/ijmspr.v8i3.58

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Abstract

Rheumatoid arthritis (RA) is a chronic inflammatory, systemic, progressive, autoimmune disease in which the body's immune system whose major role is to protect the health by attacking foreign bacteria and viruses are mistakenly, attacking the joints resulting in thickened synovium, pannus formation & destruction of bone, cartilage. Many complications can follow such as permanent joint damage requiring arthroplasty, rheumatoid vasculitis and elty's syndrome requiring splenectomy if it remains unaddressed. Still now researchers are unable to know the exact cause of this disease. However, it is believed that age, gender, genetics and environmental exposure (cigarette smoking, air pollutants and occupational) play a role in development of RA. As there is no cure for RA, the treatment goals are to reduce the pain and stop/slow the further damage. The identification of novel autoantibodies has improved diagnostic accuracy, and newly developed classification criteria facilitate the recognition and study of the disease early in its course. New clinical assessment tools are able to better characterize disease activity states, which are correlated with progression of damage and disability and permit improved follow up. In addition, better understanding of the pathogenesis of RA through recognition of key cells and cytokines has led to the development of targeted disease-modifying antirheumatic drugs. Altogether, the improved understanding of the pathogenetic processes involved, rational use of established drugs and development of new drugs and reliable assessment tools have drastically altered the lives of individuals with RA over the past 2 decades. In this review, we discuss the epidemiology, pathophysiology, diagnosis and management of RA.

Keywords: Rheumatoid arthritis, Pathogenesis, Disease modifying anti-arthritic drugs, Genetics, Environmental, Autoantibodies

Introduction

Arthritis is concern with the Inflammation of one or more joints characterized by swelling, warmth, redness of the overlying skin, pain & restriction of motion. Over 200 diseases may cause arthritis including rheumatoid arthritis, osteoarthritis, gout, tuberculosis & other infection. Most common types of arthritis are as follows[1].

1. Adult Rheumatoid Arthritis: it's occurs between 25 and 50 years of age. It's affects women three times more than men.

2. Juvenile Rheumatoid Arthritis (Still's Disease): it's occurring before 7 years of age.

3. Osteoarthritis: Second most frequent type of arthritis. This type affects the hyaline cartilage in weight bearing joints. Usually occurs because of destruction of bone coverings at the joints due to repeated use or trauma.

4. Ankylosing Spondylitis: Most prevalent in males with the age of onset ranging from 20 to 40 years of age. It affects the axial skeleton and large peripheral joints of the body. Common symptoms include recurrent back pain and early morning stiffness.

Rheumatoid arthritis is a chronic, symmetrical, inflammatory autoimmune disease characterized by autoantibodies to immunoglobulin G (IgG; that is, rheumatoid factor (RF)) and citrullinated proteins (that is, anti-citrullinated protein antibodies (ACPAs)). That initially affects small joints, progressing to larger joints and eventually affecting the skin, eyes, heart, kidneys and lungs. Often, the bone and cartilage of joints are destroyed and tendons and ligaments weaken[2]. All this damage to the joints causes deformities and bone erosion that is usually very painful for a patient. Common symptoms of rheumatoid arthritis include morning stiffness of the affected joints for more than 30 minutes, fatigue, fever, weight loss, joints that are tender, swollen and warm and rheumatoid nodules under the skin. The onset of this disease is usually from ages 35-60 with remission and exacerbation. It can also afflict young children even before age 16 and is referred to as juvenile rheumatoid arthritis (JRA), which is similar to RA except that rheumatoid factor is not found[3-6]. In the West, the prevalence of RA is believed to be 1–2%[7] and 1% worldwide[8]. RA is a heterogeneous disease, with variable clinical presentation and pathogenetic mechanisms involved between individuals with the same formal diagnosis or across different disease stages. Indeed, although autoantibodies are an important characteristic of RA (seropositive RA), some individuals are negative for these autoantibodies (seronegative RA). Clinically, the diagnosis of rheumatoid arthritis can be differentiated with osteoarthritis (OA) as; the affected areas in RA are the proximal interphalangeal (PIP)

and metacarpophalangeal (MP) joints, unlike osteoarthritis, which typically affects the distal interphalangeal (DIP). Osteoarthritis is the most common type of arthritis and is caused by wear and tear rather than an autoimmune condition. It has no effects on the lungs, heart or immune system. Also, osteoarthritis typically affects only one side of the body, as opposed to the symmetrical nature of rheumatoid arthritis. Another differentiating factor is that the patient suffers from persistent morning stiffness for at least one hour or more. Osteoarthritis may have morning stiffness but it typically resolves or decreases within 20-30 minutes[9,10]. The goals of treatment for rheumatoid arthritis are to reduce joint inflammation, pain, maximize joint function, and to prevent joint destruction and deformity. Treatment regimen consists of combinations of pharmaceuticals, weight-bearing exercise, patient education, and rest. Treatments are generally customized to the patient's need depending on their overall health. This includes factors such as disease progression, joints involved, age, overall health, occupation, compliance, and education about their disease[11]. Over the past 2 decades, we have witnessed new genetic and pathogenetic insights and an update of classification criteria that comprise information from cohorts of patients with very early RA as well as newly characterized autoantibodies to facilitate early recognition of the disease. New developments in disease assessment and therapeutic strategies, and the evolution and approval of a variety of novel therapies, have also been reported. Altogether, the tremendous evolution of the field has considerably improved the prognoses of most individuals with RA. Although we cannot yet cure RA, remission is now an achievable goal. However, many patients still cannot attain remission and more work is needed to provide every patient with the benefit of therapeutic success[12].

Epidemiology

In 2005, RA was prevalent in about 1.3 million adults in the United States and 2 years later, it affected an estimated 1.5 million adults. More recent data on RA prevalence in the U.S. are not available yet in the literature. RA can occur in all races and ethnic groups. The prevalence of RA in developed countries is 0.5%to 1% of the population (0.6% in the U.S.). Women have a two-to-three times greater predisposition for developing RA compared with men. RA onset generally occurs in middle age and is more common in older adults, but it can also develop in children and young adults. The lifetime risk of developing an inflammatory autoimmune rheumatic disease is 1 in 12 (8.3%) for women and 1 in 20 (5%) for men. Specifically, the lifetime risk of developing adult-onset RA is 1 in 28 (3.6%) for women and 1 in 59 (1.7%) for men. Over time, RA severity has declined, particularly owing to earlier diagnosis and more effective drug regimens, but trends in RA incidence, prevalence and mortality vary based on the studied population[13-17].

Etiology

The exact cause of RA is still unknown, but genes, environmental factors, and hormones may be involved in its autoimmune development and progression. Certain risk factors appear to increase the risk of RA, including older age (highest incidence in people aged 60 years); gender (higher incidence in women); genetics (especially human leukocyte antigen [HLA] class II geno types, such as HLA-DRB1); smoking (tobacco, cigarettes); history of live births (higher RA risk with nulliparity); early life exposures (if mother smoked, child has greater risk of RA); and obesity (higher risk with increasing body weight). Patients who are seropositive for anticitrullinated protein antibodies (ACPAs) or rheumatoid factors (RFs) also have an increased risk of RA. Interestingly, women who breastfeed their children appear to have a lower risk of RA. Before the advent of effective disease-modifying antirheumatic drugs (DMARDs) and biological therapies, patients with RA had a higher likelihood of dying from premature atherosclerosis, cancer, and infection[13-15].

Pathophysiology

Rheumatoid arthritis patients contain antibodies to citrullinated proteins. Citrulline is an amino acid generated by post-translational modification of arginyl residues by peptidyl arginine deaminases. These antibodies are called anti-citrullinated protein antibodies (ACPA). ACPA can be IgG, IgM, or IgA isotypes. ACPA can bind citrullinated residues on self-proteins like vimentin, fibronectin, fibrinogen, histones and type 2collagen. The binding of antibodies to proteins leads to complement activation. The presence of antibodies in rheumatoid arthritis is referred to as seropositive RA. 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 level increases[18,19]. The synovium in rheumatoid arthritis is infiltrated by immune cells, which include innate immune cells (monocytes, dendritic cells, mast cells) and adaptive immune cells (Th1 (T-helper1), Th17 (T-helper 17), B cells, and plasma cells). Cytokines and chemokines like tumor necrosis factor (TNF), interleukin-6 (IL-6), and granulocyte-monocyte colony-stimulating factors activate endothelial cells and attract immune cells within the synovial compartment. The fibroblast in the rheumatoid synovium changes to an invasive phenotype. Fibroblast and inflammatory cells lead to osteoclast generation resulting in bone erosion, the hallmark feature of rheumatoid arthritis[20].The mechanism behind environment-triggered RA is thought to be due to the repeated activation of innate immunity. Cigarette smoking induces peptidyl arginine deiminase (PAD) expression in alveolar macrophages, which leads to the conversion of arginine to citrulline in the airway[21]. This process creates a "neoantigen" that activates an immune response and leads to the formation of anti-citrullinated protein antibodies (ACPAs). Anti-carbamylated protein (anti-CarP) antibodies are anti-posttranslationally modified protein antibodies (AMPA) associated with RA[18]. Carbamylation is a cyanide-mediated chemical reaction in which lysine is converted into homocitrulline. 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[18]. Anti-acetylated protein antibodies have recently been associated with RA (in approximately 40%of RA patients), predominately in seropositive patients[18]. Acetylation is an enzymatic process thought to be mediated by bacteria, which may provide the link to RA and microbiome dysbiosis. The exact mechanism at this time remains unclear[18]. It is important to note that synovial biopsies in seropositive patients with arthralgia were essentially unremarkable[22]. 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[20].

Histopathology

One of the earliest histopathologic findings in RA is new synovial blood vessels growth; this leads to the transmigration of lymphocytes and polymorphonuclear leukocytes into the synovial fluid. Angiogenesis is required to support the highly catabolic synovium and is accomplished via proinflammatory cytokines such as tumor necrosis factor (TNF) [23]. With angiogenesis, cytokines activate endothelial cells to produce adhesion molecules which in turn facilitate cell migration into the synovium. Despite angiogenesis, RA synovial fluid is a

hypoxic environment, leading to increased production of cyclooxygenase (COX) 2-derived nociceptive eicosanoids and matrix metalloproteinases (MMPs) [24]. This further stimulates an inflammatory response in the synovium. During the early phase of the disease, the influx of inflammatory cells into the synovial membrane leads to a proliferation of monocytes and thickening of the synovial membrane with small villous projections into the joint space[23]. Rheumatoid nodules initially have a small vessel vasculitis phenomenon followed by a chronic inflammatory granulomatous phase. The development of rheumatoid nodules is frequent in rheumatoid arthritis, involving the dermis or subcutis in peri-articular areas. When multiple, this phenomenon can be related to methotrexate therapy and is called accelerated rheumatoid nodulosis[25]. The size is variable and can range from a few millimeters to centimeters. It appears grossly as a whitish fibrous lesion with yellowish areas, corresponding to collagenous necrobiosis. The histological appearance can be indistinguishable from granuloma annulare. There are areas of irregular geographic-like necrobiosis of the dermis and hypodermis surrounded by histiocytes arranged in a well-developed palisade, occasional lymphocytes, and neutrophils. Occasionally, giant cells and mast cells can be present. Fibrin and collagen are present in the center of the necrobiotic areas. The surrounding dermis and hypodermis have a perivascular infiltrate of plasma cells[25].

Diagnosis

Laboratory testing usually reveals anemia of chronic disease and thrombocytosis. Neutropenia may be present if Felty syndrome is present. About 75% to 85% of patients with RA will test positive for rheumatoid factor (RF), ACPA, or both[18]. These patients are designated as seropositive RA. About 45% to 75% of patients with rheumatoid arthritis test positive for rheumatoid factor. However, the presence of rheumatoid factor is not diagnostic of rheumatoid arthritis. It may be present in other connective tissue diseases, chronic infections, and healthy individuals, albeit in low titers. Anti-citrullinated protein antibodies (ACPA) are found in about 50% of patients with early arthritis, which are subsequently diagnosed with rheumatoid arthritis. If both RF and ACPA are positive, the sensitivity and specificity of the diagnosis increase substantially. Acute phase reactants, such as erythrocyte sedimentation rate (ESR) and levels of C-reactive protein (CRP) are usually elevated in patients with active disease and should be obtained. Synovial fluid examination usually reveals a leukocyte count between 1500 to 25,000/cubic mm and is predominantly polymorphonuclear cells. Cell counts higher than 25000/cubic mm are rare and can be seen with very active disease; however, they warrant workup to rule out underlying infection. The synovial fluid in RA will also reveal low C3 and C4 levels despite elevated serum levels[26]. With advanced disease, joint involvement on plain radiographs will reveal periarticular osteopenia, joint space narrowing, and bony erosions. Erosions of cartilage and bone are considered pathognomonic findings for RA. However, these findings are consistent with advanced disease[27]. Magnetic resonance imaging (MRI) and ultrasonography are useful in early disease before radiographic evidence of bone erosion occurs[28]. A decreased signal from the bone marrow on T1-weighted images and gadolinium-enhanced images indicates bone marrow edema. MRI can also reveal synovial thickening, which has been shown to predict the future presence of bony erosions[29]. The clinical utility of MRI and its incorporation into the diagnostic criteria for RA remains to be determined. Due to the varied clinical presentation and lack of universal pathognomonic testing for RA, diagnosing the disease can be challenging. Traditionally the presence of at least four of the following criteria for at least six weeks would classify the patient as having RA. These criteria were: morning stiffness, arthritis of three or more joints, arthritis of the hands, symmetric arthritis, elevated acute phase reactants, elevated rheumatoid factor, and radiologic evidence of RA. These criteria separated inflammatory from non-inflammatory arthritis but were not very specific for RA. It was also not sensitive for early-stage RA, which was a significant drawback[30]. With the development of serologic markers, the diagnostic criteria were redefined. The 2010 American College of Rheumatology and the European League Against Rheumatism (ACR/EULAR) diagnostic criteria for RA are outlined below. It includes four different domains, which are as follows:

2010 ACR/EULAR Diagnostic Criteria for RA[31]

- Number and site of involved joints
  - 2 to 10 large joints = 1 point (shoulders, elbows, hips, knees, and ankles)
  - 1 to 3 small joints = 2 points (metacarpophalangeal joints, proximal interphalangealjoints, second through fifth metatarsophalangeal joints, thumb interphalangeal joints, and wrists)
  - 4 to 10 small joints = 3 points
  - Greater than 10 joints (including at least 1 small joint) = 5 points
- Serological testing for rheumatoid factor or anti-citrullinated peptide/protein antibody
  - Low positive = 2 points
  - High positive = 3 points
- Elevated acute phase reactant (erythrocyte sedimentation rate [ESR] or C-reactive protein [CRP]) = 1 point
- Symptom duration at least six weeks = 1 point

A total score of greater than or equal to 6 classifies the patient as having RA. It is important to note that joint involvement refers to any swollen or tender joint on examination. Imaging studies may also be used to determine the presence of synovitis/joint involvement. The 2010ACR/EALAR criteria excluded distal interphalangeal joints, first carpometacarpal joints, and first metatarsophalangeal joints from these criteria. Also, these criteria may only be applied to those patients where the joint involvement is not better explained by other inflammatory diseases, such as systemic lupus erythematosus or psoriasis. Specific testing must be obtained to rule out these diseases. The new criteria were noted to better predict the probability of RA, have the same sensitivity as the previous criteria for the diagnosis of RA and have a higher specificity as well as higher negative predictive value[30].

Treatment / Management

First line management: NSAIDS and corticosteroids

The overall goals of first line treatment are to relieve pain and decrease inflammation. Medications considered as fast-acting drugs are non-steroidal anti-flammatory drugs (NSAIDs) including acetylsalicylate (Aspirin), naproxen (Naprosyn), ibuprofen (Advil and Motrin), and etodolac (Lodine). Aspirin is an effective anti-inflammatory for rheumatoid arthritis when used at higher doses, due to inhibition of prostaglandins. This is one of the oldest NSAIDs used for joint pain. Side effects of aspirin at high doses include tinnitus, hearing loss and gastric intolerance. There are other NSAIDs that are newer to the market than aspirin but are just as effective. In addition, these drugs require a patient to take fewer dosages a day. NSAIDs work by inhibiting cyclooxygenase to prevent synthesis of

prostaglandins, prostacyclin and thromboxanes. Common side effects are nausea, abdominal pain, ulcers and gastrointestinal (GI) bleeding. These symptoms can be reduced if taken with food or with antacids, proton pump inhibitors, or misoprostol (Cytotec) An even newer NSAID called celecoxib (Celebrex) is a selective Cox-2 inhibitor that has less risk of GI side effects[32]. Corticosteroids are more potent anti-inflammatory medications compared to NSAIDs, however, they come with greater side effects. For this reason, they are only indicated for a short period of time at low dosages, during exacerbations or flares of rheumatoid arthritis. Intra-articular (IA) injections of corticosteroid can be used for local symptoms of inflammation[33]. They work by preventing phospholipid release and decreasing actions of eosinophils, therefore decreasing inflammation. Their side effects include bone thinning, weight gain, diabetes, and immunosuppression. Advising the patient to take calcium and vitamin D supplementation can prevent thinning of bone. Side effects can be reduced by gradually tapering the doses as the patient achieves improvement. It is important not to abruptly discontinue injected or oral corticosteroids as it can lead to hypothalamic-pituitary-adrenal axis suppression (HPA) or flares of rheumatoid arthritis[34].

Opioid analgesics

Whittle *et al*., addressed the question of the use of opioid analgesics in patients with pain due to rheumatoid arthritis[35]. From their conclusions, weak opioids such as codeine, dextropropoxyphene, and tramadol may have an effective role in short term management of pain caused by rheumatoid arthritis, however the adverse effects outweigh the benefits. They recommend that other analgesics be considered first[36].

Second line management: disease-modifying anti-rheumatic drugs (DMARDs)

The overall goals of second line treatment are to promote remission by slowing or stopping the progression of joint destruction and deformity. These medications are considered slow acting drugs because they take weeks to months to be effective. DMARDs can also reduce the risk of developing lymphoma that can be associated with rheumatoid arthritis[37]. Methotrexate (MTX) is the initial second-line drug (also considered as an anchor drug). It is an analogue to folic acid that competitively inhibits the binding of dihydrofolic acid (FH2) to the enzyme that is responsible for converting FH2 to folinic acid (FH4). Without FH4, purine and pyrimidine metabolism is impaired, and amino acid and polyamine synthesis is inhibited. MTX is an immunosuppressive drug that requires regular blood tests due to its side effects of liver problems, cirrhosis, and bone marrow deterioration. Folic acid supplementation can reduce the risk of side effects. It is an effective DMARD, has lower incidence of side effects compared to the other DMARDs, and has dose flexibility, meaning that dosages can be adjusted as needed[38]. Until now, there is convincing date available showing the benefits of combination of conventional synthetic DMARDs (csDMARDs) over MTX monotherapy. However biological DMARDs (bDMARDs) combined with csDMARDs, are reported to be better than MTX but with more side effects and is very costly[39]. Hydroxychloroqyine (Plaquenil) is an antimalarial drug and can be used long term in the treatment of rheumatoid arthritis. This drug decreases the secretion of monocyte-derived proinflammatory cytokines. Common side effects include problems in the gastrointestinal tract, skin, and central nervous system. In particular, the eye can be affected when used at higher dosages. Patients on this medication require routine consultation with an ophthalmologist[40]. Sulfasalazine (Azulfidine) is a DMARD typically used in the treatment of irritable bowel disease. Combined with anti-inflammatory medications, this DMARD can be to treat rheumatoid arthritis. The mechanism of action of this drug in the treatment of rheumatoid arthritis has not been identified. It is thought that sulfapyridine, a reduced form of the medication after administration, may reduce secretions of interleukin 8 (IL-8) and monocyte chemoattractant protein (MCP). This drug carries side effects of gastrointestinal and central nervous system symptoms as well as rash. It is usually well tolerated among patients, but it should be avoided in patients with sulfa allergies since it contains sulfa and salicylate compounds[41]. Gold salts, such as aurothioglucose (Solganal), auranofin (Ridaura), gold sodium thiomalate (Myochrysine), and D-penicillamine (Depen, Cuprimine) have been used frequently in the treatment of rheumatoid arthritis. These DMARDs require frequent blood and urine tests due to damage to the bone marrow and the kidneys. These medications have not been used recently due to more effective treatments, particularly methotrexate. Other immunosuppressive medications, azathioprine (Imuran), cyclophsphamide (Cytoxan), chlorambucil (Leukeran), and cyclosporine (Sandimmune), can also be employed but are typically reserved for patients with very aggressive rheumatoid arthritis or complications of the disease[42,43].

Newer medications

Leflunomide is an oral medication that is converted to malononitrilamide, which inhibits the synthesis of ribonucleotide uridine monophosphate pyrimidine (rUMP). It relieves symptoms and retards the progression of rheumatoid arthritis. It is recommended to be used in combination with methotrexate, but can be used as monotherapy if patients do not respond to methotrexate. Side effects include hypertension, gastrointestinal upset, liver damage, leukopenia, interstitial lung disease, neuropathy, rash and bone marrow damage. The biologics, also known as biological disease-modifying anti-rheumatic drugs (bDMARDs), are rapidly effective in retarding the progression of joint damage caused by rheumatoid arthritis. They are considered to be a more "direct, defined and targeted" method of treatment. Nonetheless, biologics pose the potential for serious side effects, such as increased risk of infections. Other common side effects include neurologic disease similar to multiple sclerosis and lymphoma. Tumor necrosis factor (TNF) is a messenger protein that promotes inflammation in joints. Biologic medications such as etanercept (Enbrel), infliximab (Remicade), adalimumab (Humira), golimumab (Simponi), and certolizumab pegol (Cimzia) are all TNF-inhibitors. These inhibitors prevent the recruitment of cells that cause inflammation, causing rapid symptom relief. They are recommended if other second line medications are not effective. Unfortunately, these medications tend to be very expensive and their role in treating patients at various stages of rheumatoid arthritis and mechanism of action is a matter of continuous investigations. These medications are often used in combination with other DMARDs, especially methotrexate. TNF inhibitors are contraindicated in patients with congestive heart failure of demyelinating diseases. Each of these biologic medications has different modes of administration. Anakinra (Kineret) is a drug that is injected subcutaneously daily and works by binding to interleukin 1 (IL-1), a chemical messenger of inflammation. This medication can be used in combination with other DMARDs or as monotherapy, however due to a lower response rate than other biologics, it is not used as frequently. Rituximab (Rituxan) is useful in rheumatoid arthritis because it depletes B cells, responsible for inflammation and production of abnormal antibodies. Typically used in the treatment of lymphoma, this drug can be used in the case of rheumatoid arthritis when TNF-inhibitors have failed. In addition, rituximab has shown benefits of treating complications of rheumatoid arthritis, such as

vasculitis and cryoglobulinemia. It is administered as an intravenous infusion in two doses, two weeks apart, and every six months. Abatacept (Orencia) is a biologic medication that works by blocking T cell activation. This is given as an intravenous infusion once a month or subcutaneously once a week. It is used in patients who were not effectively treated with traditional DMARD medications. Tocilizumab (Actemra) is a biologic that works by blocking interleukin 6 (IL-6), a chemical messenger of inflammation. It is administered via intravenous infusion given monthly or via weekly subcutaneous injections. It is also used for patients who have not been effectively treated with traditional DMARD medications. Lastly, Tofacitinib (Xeljanz) has a different mechanism of action and works by blocking Janus kinases within cells, which are enzymes of inflammation. For this reason, it is known as a JAK inhibitor. This medication is used for patients who are not effectively treated with methotrexate. Tofacitinib is taken orally twice daily alone or in combination with methotrexate. This medication should not be used in combination with traditional biologic medications or other potent immunosuppressants[44].

Surgery

Joint surgery in patients with rheumatoid arthritis reached a peak high in the 1990s. However, a 2010 study shows that patients aged 40 through 59 with rheumatoid arthritis had decreased rates of joint surgery. In contrast, patients over age 60 had increased rates of surgery[45]. Surgery is a last resort option for treatment of rheumatoid arthritis. Indications include intractable joint pain or functional decline due to joint destruction after all nonsurgical approaches have failed. At this point, the disease is considered "end-stage." The goal of surgical management is to relieve pain for the patient and to restore the function of the joints. A patient needing surgical treatment should be evaluated based on their customized needs because there are many different options of surgery. A tenosynovectomy involves the excision of inflamed tendon sheaths or repairing a recent tendon rupture, most commonly in the hand[46]. Radiosynovectomy is an alternative to surgical synovectomy; involves intra-articular injection of small radioactive particles, a cost-effective procedure and multiple joints can be treated simultaneously[47]. Repair of ruptured tendons can also be done through arthroscopy, most commonly in the rotator cuff of the shoulder. Excision of an inflamed synovium via arthroscopy or open synovectomy is not commonly used any longer due to the availability of more effective medical treatment options. Another option of surgery is an osteotomy. In this procedure, weight bearing bones are realigned to correct valgus or varusdeformities, most commonly in the knee[48]. Joint fusion can be done to stabilize joints that are not easily replaceable such as the ankle, wrist, thumb and cervical spine. A procedure for soft tissue release can be done to correct severe contractures around joints causing decrease range of motion. This soft tissue release is an older procedure that is not commonly utilized[49]. Small joint implant arthroplasty can be done to reduce pain and improve hand function, most commonly in the metacarpophalangeal joints. Metatarsal head excision arthroplasties are done to alleviate severe forefoot pain. Lastly, a total joint replacement (TJR) is the removal of the damaged joint and replacing it with a metallic, plastic or ceramic prosthesis. This is most commonly done in the shoulder, elbow, wrist, hip, knee, and ankle[50,51] . The major contraindication for surgical joint replacements is the presence of active systemic articular infection.

Other therapies

It has been found that in contrast to previous suggestions, there are no specific foods that patients with rheumatoid arthritis should avoid. The idea that diet can "aggravate" symptoms is no longer accepted as true. Home remedies have been proven to be helpful for patients suffering from rheumatoid arthritis, although they are not as effective as DMARDs. Fish oils and omega-3 fatty acid supplements have been beneficial for the short-term symptoms of rheumatoid arthritis. Cumin has shown to have anti-inflammatory effects for patients with this disease. Calcium and vitamin D supplementation can be helpful for prevention against osteoporosis. Lastly, folic acid is helpful in preventing the side effects of methotrexate. Patients with rheumatoid arthritis also benefit from physical and occupational therapy. It is recommended that patients perform exercise regularly to maintain joint mobility and to strengthen muscles around the joints. A movement exercise that are less traumatic for joints but are good for muscle strength include swimming, yoga and tai chi. Applying heat and cold packs before and after exercise minimizes painful symptoms. Studies are being done on different types of connective tissue collagen in order to better understand and reduce rheumatoid arthritis disease activity. Lastly, with the scientific advancements and enhanced understanding of the molecular mechanisms, newer and better treatment options will become available in the near future[44].

Conclusion

Rheumatoid arthritis is a debilitating chronic inflammatory disease, capable of causing joint damage as well as long-term disability. Early diagnosis and intervention is essential for the prevention of serious damage and loss of essential bodily functions. The treating physician should consider adhering to treat-to-target (T2T) recommendations by first outlining the aims and then implement protocols to achieving and assessing them. Furthermore, early referral to a specialist can also help ensuring better treatment outcomes. With the advances in the field of molecular medicine, we have better an understanding of disease mechanisms, thus aiding in the designing of more effective treatments. Old treatment modalities have been optimized and new ones have been produced. Gene array analysis is proving beneficial in finding out which patients will be more responsive to specific medications. This customization will allow for more rapid treatment and decrease the likelihood of progressive disease that can be avoided during the experimental phase to seek an appropriate treatment for a particular patient. Gene array analysis is also being used to determine which patients are at greater risk for more aggressive forms of rheumatoid arthritis. It is foreseen that treatment methods will face tremendous improvements for the management of rheumatoid arthritis.

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