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Rheumatoid Arthritis, Pathophysiology and Management

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ABSTRACT

Introduction: Rheumatoid arthritis is considered one of the most common, and particularly attacks the joint causing significant individual and community burden, and present with articular as well as extra articular manifestation. Treatment modalities of rheumatoid arthritis have dramatically improved in recent years, significantly decreasing long-term auricular and extra-auricular complications.

Aim of the work: this review was aimed to study the pathophysiology, clinical picture, and management of rheumatoid arthritis, with focus on the newer modalities.

Methodology: We conducted this review using a comprehensive search of MEDLINE, PubMed, and EMBASE, January 1985, through February 2017. The following search terms were used: rheumatoid arthritis, chronic inflammatory disorders, genetic of rheumatoid arthritis, management of rheumatoid arthritis, DMARD, biological agents

Conclusion: The newer modality of treatment must include disease-modifying antirheumatic drug (DMARDs) which must be started as early as possible. Combining DMARDs with corticosteroids will result in significantly better outcomes than monotherapy with any DMARD, and decrease long term morbidity associated with this condition.

Keywords: chronic inflammatory disorders, management of rheumatoid arthritis, DMARD, biological agents, rheumatoid arthritis

INTRODUCTION

Among chronic inflammatory diseases, rheumatoid arthritis is considered one of the most common, and particularly attacks the joint causing significant individual and community burden. However, it can also attack other organs and cause extra-articular manifestations. These extra-articular manifestations include vasculitis, pulmonary involvement, and rheumatic nodules. Treatment modalities of rheumatoid arthritis have dramatically improved in recent years, with introduction of new management guidelines and diagnostic criteria. This revolution in management has caused significant decrease in long-term auricular and extra-auricular complications [1].

Individuals with rheumatoid arthritis will suffer from significant comorbidities resulting from defects of the musculoskeletal system, and leading to physical functions decline, increased risk of long-term complications, and decreased quality of life. On the other hand, the community will also be affected by both the high medical expenses of management, and the reduced capacity of community members from the functional disability. To decrease this burden of the disease, efforts aim at early diagnosis, proper management, and continuously creating new treatment modalities [2].

METHODOLOGY

- **Data Sources and Search terms**

We conducted this review using a comprehensive search of MEDLINE, PubMed, and EMBASE, January 1988, through February 2017. The following search terms were used: rheumatoid arthritis, chronic

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inflammatory disorders, genetic of rheumatoid arthritis, management of rheumatoid arthritis, DMARD, biological agents

- **Data Extraction**

Two reviewers have independently reviewed the studies, abstracted data, and disagreements were resolved by consensus. Studies were evaluated for quality and a review protocol was followed throughout.

The study was done after approval of ethical board of King Abdulaziz university.

PATHOPHYSIOLOGY

Genetics

Current understanding of rheumatoid arthritis genetics was established with large studies using novel genetic technologies. With single nucleotide polymorphisms, Genome-wide association studies have located hundreds of loci that predisposed to the development of the disease. Most of these loci are involved in immunity mechanisms, and some of them are also associated with other inflammatory diseases. The most important system associated with the development and prognosis of rheumatoid arthritis is the HLA system. This strong association led to the suggestion of peptide binding involvement in the pathogenesis of the disease. The HLA type does not only predicts the disease occurrence, but also can predict severity, possible complications, and mortality [3].

Less important than HLA, several loci are strongly associated with rheumatoid arthritis in different mechanisms. These loci act by cytokine signaling, altered co-stimulatory pathways, innate immune activation, and/or lymphocyte receptor activation threshold, and include CD28, CD40, PTPN22, and others [3].

Characteristic antibodies that are present in patients include autoantibodies against IgG (also known as the rheumatoid factor) which are present in up to 70% of patients. Another important marker is the autoantibodies against citrullinated peptides (ACPAs), which is more specific than the rheumatoid factor [3].

The pathogenesis of the disease is strongly related to epigenetics by both genetic and environmental integrations. Ten positions have been associated with higher risk of the disease in a recent large study. Normally, the biology of leucocytes and fibroblasts is regulated via a DNA methylation and histone acetylation. Dysfunctions in this system were associated with rheumatoid arthritis. Current approach involves studying the effects of treatment with microRNAs on rheumatoid arthritis patients [4].

Risk Factors

Other than genetics, environmental factors have been associated with the development of rheumatoid arthritis. These include low educational level, low socioeconomic status, and smoking. Other risk factors include periodontal disease, but this association is not well established yet. Some organisms have also been associated with the disease like *Escherichia coli, Proteus mirablis, and* Epstein-Barr virus. Molecular mimicry have been suggested to be involved in this association [5].

Studies on animals have associated gut microbiome with the development of rheumatoid arthritis. This association has also been suggested with other chronic inflammatory diseases. There was studies thatave been trying to confirm this association in humans. Microbial alteration was found to exist between patients with/without the disease, especially in salivary, oral, and gastrointestinal sites. This alteration was also associated with different response to treatment. However, the reason behind this is still not clear [6].

Autoimmune response

Seropositive rheumatoid arthritis patients have a more severe disease that is associated with more serious joint damage and high mortality rates. The reason of this may be due to the production of immune complexes which will lead to consequent complements activation. Actually, the introduction of antibodies against citrullinated self-proteins was a significant advance in the diagnosis of rheumatoid arthritis. It was also found that ACPAs can be detected circulating in the serum before up to ten years prior diagnosis. In this case, a diagnosis of pre-rheumatoid arthritis is made. Over time, ACPAs concentration will increase along with cytokines, causing the appearance of clinical signs and symptoms of the disease. The presence of ACPAs on different immunoglobins isotypes lead to the suggestion of T-cell help involvement. ACPAs can

also participate in the pathogenesis of the disease by osteoclast activation or macrophages activation [7]. The activation of osteoclasts is suggested to occur via Fc-receptor involvement or by the formation of immune complexes and will eventually lead to bone loss. On the other hand, when treating the disease effectively, concentrations of serum ACPAs and RF will significantly decrease or even disappear (mainly RF). Other antibodies that were detected in patients include acetylated peptide autoantibodies and anti-carbamylated antibodies [8].

Inflammation

The swelling of joints indicates the presence of an inflammation in the synovial membranes caused by activation of the immune system. This inflammation is associated with infiltration of leucocytes into the synovial compartment. This whole process needs involvement of both the adaptive immune system and the innate immune system, and will consequently lead to the destruction of the joint. Small joints biopsies along with detailed analysis of the molecular bases have led to the assumption that several subtypes of synovial involvement exist, and these include: lymphocytic-dominant, fibroid-dominant, and myeloid-dominant. The accurate detection of the type will lead to more proper management and better response to treatment [9].

This inflammatory process in the joints is regulated by advanced mechanisms that involve cytokines and chemokines. These include granulocyte-monocyte colony stimulating factor, tumor necrosis factor, and interleukin 6. Other molecules (like interleukin 1) may be present but are less important in the inflammatory process. The interaction between the previous molecules will cause stimulation of inflammation by endothelial cells activation and accumulation of cells within the joint. Accumulation of cells, along with activation of fibroblasts will lead to the induction of osteoclast activation by activating RANKL. Cartilage tissue is also damaged by the effects of cytokines on chondrocytes. This will lead to degradation of matrix by metalloproteinases and other enzymes [10].

Clinical Evaluation

Signs and Symptoms

Proper history taking and physical examination are critical in the workup of rheumatoid arthritis, as they are enough to establish a provisional diagnosis in many cases. This will lead to the proper choice of further investigations that will either confirm or rule out the disease. In most patients, rheumatoid arthritis will present with slowly progressive polyarthritis. Prior to this, symptoms will include non-specific pain, joint tenderness, or joint swelling. These vague symptoms may be present for a long time with a slowly progressive course before patients seek medical advice. The presence of these symptoms solely makes right diagnosis more challenging and requiring a high clinical suspicion. Specific signs and symptoms of the disease include the present of chronic morning stiffness along with polyarthralgia. Small joints involvement is also highly prevalent in rheumatoid arthritis patients. Joints are usually affected symmetrically with tenderness and swelling. In addition, an important predictor of the diagnosis is the presence of painful hand joins [11].

Symmetric polyarthritis, morning stiffness, metacarpophalangeal or metatarsophalangeal joints involvement, and/or hand arthritis are all signs that make the diagnosis of rheumatoid arthritis likely and help in the exclusion of other causes. It is very important to rule out all joints involved in the disease. This is achieved by carefully examining joints that are swollen or tender, along with accurate estimation of the disease severity [12].

Extra-articular manifestations and comorbidities

Insufficiently treated patients will progress to develop extra-articular signs and symptoms. These include interstitial lung disease and vasculitis. Secondary amyloidosis, cardiovascular diseases, and lymphoma, are also important complications that are highly associated with long-term rheumatoid arthritis. However, the risk of all previously mentioned complications will significantly decrease when following proper novel guidelines of treatment. Methotrexate, and TNF inhibitors are one of the most important drugs in management of rheumatoid arthritis, but they are highly associated with the development of nodulosis (which cannot be distinguished from nodules resulting from the disease) [12].

Investigations

Laboratory tests

Typically, patients with rheumatoid arthritis will have increased Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). These markers are still not specific enough to make the diagnosis. However, the degree of CRP increase has been found to be associated with imaging changes and disease severity. Measurement of acute phase reactants can also be beneficial for follow up after treatment initiation, and to detect relapses [13].

The next step will be measurement of RF and anti-CCP, which has a significantly higher specificity than RF, but same sensitivity. The ideal management requires measuring both RF and anti-CCP to provide sufficient diagnostic sensitivity and specificity, and to be able to diagnose patients with seronegative rheumatoid arthritis. Another helpful method is to analyze synovial fluid following arthrocentesis. This will help diagnose rheumatoid arthritis and rule out other non-inflammatory causes of arthritis. A previous study has found that anti-CCP in synovial fluid were associated with high sensitivity and specificity for the diagnosis of rheumatoid arthritis [14].

Imaging

On imaging, several characteristic features may be present, including narrowing of the joint space, subluxation, and erosions in late stages. The standard method to evaluate the anatomical dysfunctions caused by the disease is plain radiography. However, when it comes to recent arthritis, plain radiography may not play an important role, and the only findings are mild juxta-articular osteoporosis and swelling of the tissues. In these cases, bone erosions can be predicted in the presence of synovitis, which is not shown in plain radiography. A study on patients with recent arthritis and symptoms for less than three months, bone erosions were detected in radiography only in 12.8% of cases [15].

Other imaging modalities that provide more sensitive results include MRI and ultrasound. In early cases, ultrasound is significantly more sensitive in erosions detection than X-ray, and its sensitivity is about 63%. MRI is also associated with sensitivity that can reach up to 98%. Moreover, MRI help distinguish between rheumatoid arthritis and other causes of polyarthritis. Therefore, it is recommended to maximize the use of MRI in patients with signs of early arthritis to detect possible erosions [16].

Differential Diagnosis

Rheumatoid arthritis diagnosis does not depend on specific diagnostic criteria, but rather in presentation with sufficient history and examination. Usually, a patient with rheumatoid arthritis will present with swollen, tender joints along with morning stiffness. Initial investigations will show elevation of ESR and CRP levels, although this is not specific enough to make a diagnosis. in this phase, other differential diagnoses can include osteoarthritis, infectious arthritis, reactive arthritis, Lyme disease, connective tissue diseases, and other possible causes. Differential diagnosis will further depend on the presence of other signs and symptoms like alopecia, Sicca syndrome, rash, positive antinuclear antibodies, Raynaud's phenomenon, elevated muscle enzymes, and/or mouth ulcers [17].

In 2010, new criteria for diagnosing rheumatoid arthritis were proposed to replace the American College of Rheumatology (ACR) criteria. These criteria provide more reliable measures of chronicity and prognosis. It was developed after analyzing the results of large cohort studies, and requires the presence of at least single joint with swelling. Thereafter, joints involvement extent will be assessed by MRI or ultrasound and subsequently classified as active or clinically swollen joints. RF, ACPA, and other serological markers, duration of symptoms, and the presence of systemic inflammation manifestations, all also have an effect. This score is associated with a sensitivity that is 21% higher than the previous one although less specific [18].

Treatment

Therapeutic approaches

To decrease the rate of damage progression, the most important therapy is the use of disease-modifying antirheumatic drugs (DMARDs). AMARDs work by inhibiting the inflammation causing a significant improvement in damage rate. On the other hand, NSAIDs improve physical functioning by relieving pain, but do not affect the rate of joint damage. Glucocorticoids can also be used to decrease the severity of symptoms, but their use can cause significant long-term adverse events [19].

DMARDs are classified into two major groups: biological and synthetic. Synthetic DMARDs are

further subdivided into conventional and targeted. Conventional synthetics use has dramatically increase although we still do not have sufficient information on their mechanisms of action. On the other hand, targeted-synthetic DMARDs act by affecting specific targets that are found during the inflammation process. Targeted DMARDs include tofacitinib and baricitinib, which act by inhibiting Janus kinase (JAK) [20].

Conventional synthetic DMARDs and glucocorticoids

Recent guidelines recommend the initiation of treatment with conventional DMARDs, most commonly methotrexate, along with glucocorticoids in a low dose. This approach is supported by solid evidence to be effective as an initial treatment. This regimen was first tested in a trial that compared its effect with the effect of methotrexate with another biological agent. This trial found no significant outcomes difference between the two regimens. Later trials also found the combination of methotrexate with glucocorticoids also reviled similar outcomes to other combinations but with significantly decreased rates of adverse events. The dose of methotrexate should start low and increase by 30 mg every week (or about 0.3 mg/kg). This applies to the use if methotrexate in either oral or subcutaneous routes. When using sulfasalazine, the dose can reach 3 g per day. The administration of glucocorticoids can be by oral, intravenous, or intramuscular routes. Usually low doses less than 7.5 mg are given in combination with methotrexate and are sufficient to achieve significant improvement in joints status. However, the use of glucocorticoids should not continue for more than six months, and them tapered and stopped. By then, DMARDs will have achieved improvements and can continue alone [21; 22].

Among conventional DMARDs, methotrexate is considered to be one of the safest and most effective drugs and is the first choice. However, its superior effect when compared to other DMARDs is still not well established. On the contrary, sulfasalazine and leflunomide were shown in some trials to achieve similar outcomes but with relatively higher doses. Other DMARDs include hydroxychloroquine and chloroquine, which originally are antimalarials. Old regimens use parenteral gold, but this is associated with high toxicity [21].

Biological DMARDs

Biological DMARDs work on several mechanisms and pathway. The current available agents target TNF, interleukin 6 receptors, T-cell co-stimulation, or B-cells. Agents that target interleukin 1 are only effective in few cases. Five agents are available and approved for inhibition of TNF. These are infliximab (which is used intravenously), etanercept, adalimumab, golimumab, and certolizumab pegol (which are used subcutaneously). Etanercept acts by constructing TNF-receptors, and is associated with significantly less risk of TB reactivation than other DMARDs. However, all the others are monoclonal antibodies for TNF. When a patient has a positive TB test, proper prophylaxis should be administrated [23].
Tocilizumab (a monoclonal antibody against interleukin 6 receptors) is another biological DMARD that acts by inhibiting interleukin 6. Abatacept is another monoclonal antibody that inhibits T-cell co-stimulation and the function of myeloid cells. Rituximab is also a monoclonal antibody that acts on CD20 B-cells [24].

Targeted Synthetic DMARDs

Tofacitinib is the first targeted DMARD to get approval for the use of rheumatoid arthritis. It works by inhibiting JAK receptors causing a reduction in signal transduction and cell activation. The use of tofacitinib was approved in a combination with methotrexate twice a day. Interestingly, monotherapy of tofacitinib has shown better efficacy than monotherapy of methotrexate. Baricitinib is a JAK ½ inhibitor that is not still approved for treatment (reference?).

Tapering Therapy

When sufficient treatment is achieved, it should be maintained for a sufficient time. This will cause maximization of physical functions, improvements in quality of life, and higher ability to work. Later, treatment should be tapered gradually. The reduction of glucocorticoids followed by stopping the treatment, should be achieved over a period of six months. Biological agents, on the other hand, are associated with a high risk of exacerbation of the disease when are stopped. However, when the agent is discontinued

over a long time, this risk is relatively lower. When exacerbation occurs, patients usually are put back on their regimens with good response in most cases. In conclusion, it is recommended to gradually reduce the dose of biological DMARDs rather than sudden cessation, to avoid exacerbations [25].

CONCLUSION

The progressive, chronic course of rheumatoid arthritis can be influenced by proper and sufficient treatment. The treatment must include DMARDs which need to start as early as possible. Most recent criteria for RA has classified patients according to their predicted survival allowing for more accurate management. Combining DMARDs with corticosteroids will result in significantly better outcomes than monotherapy with any DMARD, and will significantly decrease the risk of long term complications and the development of bone erosions.

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