
Rheumatoid Arthritis, Its Diagnostic Approach and How to Treat It

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ABSTRACT

Introduction. Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease characterized by symmetrical erosive polyarthritis leading to progressive disability. It is more common in women, with a 3:1 ratio. Environmental risk factors are smoking, exposure to silica and textile dust.

Materials and methods. Fifteen articles and three books on rheumatoid arthritis were chosen to identify the most accurate diagnostic methods and the most effective and innovative treatments.

Discussion. Related autoantibodies, such as rheumatoid factors, anti-citrullinated antibodies and anti-carylated antibodies can be found in serum long before the disease develops.

The interaction between genetic and environmental factors causes a breakdown of immune tolerance and triggers systemic autoimmunity. It has been shown that the lungs, oral mucosa, and gastrointestinal tract are initial sites where the immune system can become activated and produce RA.

Different imaging techniques are available for diagnosis: plain radiography, Doppler ultrasound, and magnetic resonance imaging. Doppler ultrasound was found to be more sensitive in identifying minimal synovitis and more sensitive than plain radiography in detecting joint erosions. As pharmacological treatment, it has been concluded that the first-line drug is methotrexate, as it relieves signs and symptoms, improves physical function, and prevents or slows the progression of joint damage. We also observed that NSAIDs help in the inflammatory and symptomatic control of RA.

Conclusion. The quality of life of affected patients has been maintained thanks to the early detection of the disease, since there are several treatments (physical therapies, aerobic exercises, medications, etc.), which help to stop the evolution of this disease and thus allow the patient to lead a daily life.

KEYWORDS: Rheumatoid arthritis, antibodies, diagnosis, and treatment.

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INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease characterized by symmetrical erosive polyarthritis leading to progressive disability.¹ It has a prevalence of 1% and is more common in women than in men with a 3:1 ratio. It is more frequent in patients between the fourth or fifth decade of life in the female sex and in the male sex in the sixth to eighth decade, however, it can be seen at any age.²

Genetic factors are known to favor the onset and intensity of RA, the HLA-DRB1 allele is linked to the disease, and the

probability of RA is also associated with the development of RA.

The risk of a first-degree relative of a patient sharing the diagnosis of RA is two to ten times higher than in the general population.³

Environmental risk factors to be considered are smoking, exposure to silica and textile dust, as well as dietary factors such as obesity.⁴

Regarding the clinical picture, we must take into account that classic RA is the one that involves small joints such as those

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of the hands and feet, the proximal metacarpo-phalangeal joint is the most affected. Patients will report morning stiffness that usually lasts more than one hour (symptoms are more severe in the mornings), joint deformity, in addition to the presence of a positive Morton's sign in the physical examination, which is the pain presented when we make a slight compression on the edges of the hands and feet. Similarly, synovitis is very common, patients will often describe walking on marbles. As a family history, they may report having a first-degree relative with RA. However, RA can also be accompanied by extra-articular manifestations such as rheumatoid nodules, dry keratoconjunctivitis, atherosclerosis, normochromic normocytic anemia, and

thrombosis, among others. The most severe manifestation of RA is atlantoaxial subluxation.⁵

THEORETICAL FRAMEWORK

The diagnosis of rheumatoid arthritis can be made in several ways; however, it is mainly based on clinical history and physical examination. On the other hand, we can make use of diagnostic criteria such as the criteria of the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR). These presented the most current criteria for the diagnosis of RA; they must have a total score of at least 6 points. The criteria are shown below.⁶

Table 1. American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) criteri

ACR and EULAR Criteria		Points
Joint involvement	1 large	0
	2-10 large	1
	1-3 small	2
	4-10 small	3
	>10 (at least 1 small)	5
Serology	FR negative and ACPA	0
	FR low positive or ACPA low positive	2
	High positive FR or high positive ACPA	3
Acute phase reagents	Normal CRP and normal ESR	0
	Abnormal PCR or abnormal ESR	1
Duration of symptoms	<6 weeks	0
	>6 weeks	1

Abbreviations: Anti-citrullinated protein antibodies (ACPA). C-reactive protein (CRP). erythrocyte sedimentation rate (ESR). Rheumatoid factor (RF).

As diagnostic imaging methods we can rely on simple radiography to see the affected joints, early findings include periarticular soft tissue inflammation, periarticular osteopenia and/or joint effusions. Doppler ultrasound is for the detection of early inflammatory arthritis, when patients present with joint swelling or pain and have questionable synovitis on examination; this study can visualize synovial hyperemia at symptomatic sites of disease. MRI can observe synovial or soft tissue involvement and cartilage defects.⁶

A less common diagnostic method is to determine the

presence of autoantibodies since, in addition to RA being a disease characterized by chronic inflammation, it has the presence of autoantibodies. To demonstrate this, a study was carried out in Cuba, in which 162 patients with RA diagnosis, who were older than 18 years of both genders, participated. The determination of IgG anti-fibrinogen citrullinated fibrinogen peptide antibodies was performed by means of an enzyme-linked immunosorbent assay (ELISA). It was obtained as a result that in 84% of patients with early-stage diagnosis the most detected antibodies were anti-CFP antibodies. The rest of the patients obtained anti-MCV antibodies.⁷

Regarding laboratory studies that are useful to make differential diagnosis with some other disease, patients with

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RA show: ⁵

- Normal white blood cells
- Thrombocytosis and mild normocytic anemia.
- Elevated erythrocyte sedimentation rate and C-reactive protein.
- Positive rheumatoid factor and anti-cyclic citrullinated protein (anti- CCP)
- Normal liver and kidney function
- Normal general urinalysis

If arthrocentesis is performed, it will show inflammatory synovial fluid with white blood cell counts ranging from 5,000 to 25,000 with 60% to 80% polymorphonuclear leukocytes.⁵

The differential diagnoses of RA include many diseases. Osteoarthritis should also be considered in the differential diagnosis and differs from RA because osteoarthritis is associated with joint pain that usually worsens throughout the day and increases with joint use, affecting the distal interphalangeal, proximal interphalangeal, knees, hips, lumbar and cervical spine. Physical examination shows minimal soft tissue swelling and labs are normal. Plain radiography shows joint space narrowing, osteophytes and subchondral bone sclerosis.⁸

Another differential diagnosis is adult Still's disease, the distinguishing features of which are fever $>39^{\circ}\text{C}$ for more than 1 week, leukocytosis $>10,000/\text{mm}^3$ with $>80\%$ polymorphonuclear leukocytes, arthralgias, sore throat, lymphadenopathy, splenomegaly, liver dysfunction and increased serum ferritin. Spondyloarthropathy predominates in males, is characterized by damage to large joints and lower

extremities, lumbar involvement and the affected allele is HLA-B27. Rheumatic fever is a symmetrical polyarthritis causing damage to the lower extremities of large joints; subcutaneous nodules, carditis, chorea and rash.⁵

Before starting treatment, the patient should be evaluated: ⁹

- Assess history of comorbidities
- Rule out active infections, neoplasms, hematological alterations, heart failure and demyelinating diseases.
- Assess if there is a desire for pregnancy
- Perform laboratory studies
- Rule out latent tuberculosis

To treat patients with rheumatoid arthritis, both non-pharmacological and pharmacological treatment should be used.

The most recommended non-pharmacological treatment by physicians is aerobic physical exercise, as it has shown many benefits such as muscle strengthening, manual dexterity, and improved balance, which will help prevent falls. Physical rehabilitation is also recommended as it helps to recover the functional capacity and independence of patients. For all non-pharmacological measures, it is important that they are accompanied by pharmacological treatment, as these help to correct and prevent deformities, as well as reduce pain.⁹

The first-line pharmacological treatment is methotrexate: an initial dose of 10-15 mg per week orally is recommended, the dose should reach a maximum of 4-8 weeks. The use of NSAIDs is recommended for inflammatory and symptomatic control of RA.⁹

Table 2. Conventional synthetic disease-modifying drugs ⁹

Conventional synthetic disease-modifying drugs			
Drug	Posology	Mechanism of action	Adverse effects
Methotrexate	Administered orally Dosage: 10-30 mg/week	It is a reversible competitive inhibitor of dihydrofolate reductase.	Gastrointestinal discomfort, hepatotoxicity, alopecia, infections.
Sulfasalazine	Oral administration Dosage: 2-3 g/day	It is a derivative of 5-aminosalicylic acid. Partially inhibits T and B lymphocytes.	Headache, gastrointestinal discomfort and glucose 6 phosphate deficiency.
Leflunomide	Oral administration Dose: 10-20 mg/day	It is an isoxazole derivative. It inhibits the synthesis of pyrimidines and the proliferation of T lymphocytes.	Gastrointestinal discomfort, hepatotoxicity, alopecia, alopecia.
Hydroxychloroquine	Oral administration Dose: 200-400 mg/day	Derivative of 4 aminoquinoline. Inhibits the function of monocytes and macrophages.	Retinopathy and maculopathy

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Table 3. Biological disease-modifying antirheumatic drugs ⁹

Biologic disease-modifying antirheumatic drugs		
Drug	Posology	Mechanism of action
Infliximab	Intravenous administration so it is necessary to keep the patient under observation for the less than 1-2 hours after its administration Dose: 3-5 mg/kg in the weeks 0, 2 and 6 and every 8 weeks thereafter. weeks.	It is an antibody chimeric monoclonal that inhibits human functional activity of TNF-alpha
Adalimumab	Subcutaneous administration Dosage: 40 mg every two weeks	Recombinant human monoclonal antibody anti-TNF alpha that binds to TNF and blocks its interaction with p55 and P75 receptors.
Etanercept	Subcutaneous administration Dosage: 50 mg every week or 25 mg in two weekly doses.	Genetically constructed dimeric human protein by fusion of the soluble extracellular domain of human TNF receptor 2.

Table 3. Biological disease-modifying antirheumatic drugs ⁹

Table 4. Disease-modifying antirheumatic drugs ⁹

Synthetic disease-modifying antirheumatic drugs		
Drug	Indications	Posology
Tofacitinib	Indicated in moderate to severe RA	The dose is 5 mg every 12 hours orally.
Baricitinib	Indicated in moderate to severe RA	The dose is 4 mg daily orally and in those over 75 years of age it is 2 mg daily.

Effective control of inflammation by disease-modifying antirheumatic drugs (DMARDs) or combination therapies of DMARDs and glucocorticoids is known to delay structural damage in RA. The introduction of tumor necrosis factor (TNF) blockers as a pharmacological option is a good alternative as it produces profound and sustained inhibition of bone erosion. It also favors the delay of structural damage.¹⁰

A retrospective study was started in 2014 and 138 patients were studied, which ended in September 2020. The inclusion criteria were patients of Chinese origin aged 18 to 75 years who had deformity in their fingers or toes and disability. 118 were female, 115 had positive RF, and 118 showed abnormalities on ultrasound findings. 15 patients were treated with conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) plus disease-modifying antirheumatic

drugs. 54 patients were treated with csDMARDs plus continuous passive motion devices. 16 patients were treated with csDMARD plus glucocorticoids. 50 patients were treated with two disease-modifying antirheumatic drugs and only 3 patients were treated with three disease-modifying antirheumatic drugs.

As results, 48.7% of the patients achieved complete remission and 51.3% partial remission. Only 31 patients had an increase in synovitis.¹¹

In August 2017, a committee of experts from the Mexican College of Rheumatology met to update their guidelines for the pharmacological treatment of rheumatoid arthritis. Rheumatologists and methodological advisors from various health institutions participated and as recommendations they mention that the use of prednisone <10 mg/day in patients with RA gives very good results. In early RA (less than 6

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months of evolution) low doses of glucocorticoids are recommended to reduce disease activity and radiographic progression. The use of high doses of intravenous glucocorticoids is only recommended in patients with severe extra-articular manifestations.

On the other hand, the new oral JAK inhibitors, which are low molecular weight compounds administered orally, were shown to have high efficacy in RA.¹² They achieved low disease activity in up to 40% of patients and remission in 25%.¹³ Of the currently available JAK inhibitors, tofacitinib, baricitinib, upadacitinib, filgotinib and peficitinib have been widely used in many regions for the treatment of RA.¹² One of the most important conclusions they reached was that methotrexate is still considered the cornerstone of treatment. They also emphasized that Tocilizumab should not be given during pregnancy as there is a risk of miscarriage.¹³

It should be noted that leukotriene B4 (LTB4) blocking levels in serum, synovial fluid and synovial tissue are increased in patients with RA. These data suggest that LTB4 and its high-affinity receptor BLT1 are contributing to the pathogenesis of this disease. LTB4 is a key mediator in a cascade of complement, lipids, cytokines, and chemokines that first initiates and then maintains neutrophilic inflammation in RA. That is why several clinical trials have been done where patients have been treated with LTB4 and BLT1, however, there is no significant improvement in the joints. But it has been seen that the use of biological agents, such as monoclonal antibodies (mAb) against TNF and interleukin 6 (IL-6) have given good results in arthritis and inhibit bone destruction.¹⁴

In Sweden, a study was carried out on patients with RA, to find out the side effects caused by the drugs they were taking; the framework taken to see improvement was route of administration, reduction of inflammation, pain and fatigue, short- and long-term side effects, severe side effects and psychological and appearance side effects. It was found that the most frequent mild side effects were nausea and headache; the most frequently reported severe side effect was an allergic reaction. Among the least common were weight loss, mood swings, hair loss, fatigue, and inability to continue with their daily life.¹⁵

Follow-up of the disease should be done frequently every one to three months, if the disease is active. If there is no improvement within three months of starting treatment or if the therapeutic target was not reached at 6 months, treatment should be adjusted.¹⁰

The criteria for remission of rheumatoid arthritis are: ⁹

- A. Number of painful joints less than or equal to 1
- B. Number of swollen joints less than or equal to 1
- C. CRP less than or equal to 1 mg/dl
- D. Overall patient assessment less than or equal to 1

A patient is in remission when he/she meets all 4 criteria

MATERIALS AND METHOD

This article was carried out through a research based on several books such as: "Harrison's Principles of Internal Medicine", "Clinical Diagnosis and Treatment", "Traumatology and Orthopedics for the medical degree"; in addition to articles obtained from "Clinicalkey", "Elsevier", "Springer". Fifteen articles and three books on rheumatoid arthritis were chosen to identify the most accurate diagnostic methods and the most effective and innovative treatments.

DISCUSSION

It is important to mention that nowadays the development of RA is considered a multistep process: genetic and environmental factors; systemic autoimmunity; symptoms without clinical arthritis; unclassified arthritis and RA. These factors may lead to a breakdown of immune tolerance resulting in the production of autoantibodies, which explain the presence of the mentioned symptoms.

Related autoantibodies such as rheumatoid factors, anti-citrullinated antibodies and anti-carbamylated antibodies can be found in serum long before the disease develops.

In the investigation of the different articles, we found that heritability represents a very important risk factor since between 50 to 70% of patients with RA have a family history; it is also determined that there is an increase in the prevalence in patients who smoke. Other factors were textile dust, dietary factors, obesity, hormonal factors or the use of certain medications.

The interaction between genetic and environmental factors causes a breakdown of immune tolerance and triggers systemic autoimmunity. It has been shown that in lungs, oral mucosa and gastrointestinal tract are the initial sites where the immune system can become activated and produce RA.

For the diagnosis of RA, different techniques have been described that can be helpful, but it is important to emphasize that the main tool for diagnosis is the patient's clinical manifestations. Different imaging techniques are available for diagnosis: plain radiography, Doppler ultrasound, and magnetic resonance imaging. Doppler ultrasound was found to be more sensitive in identifying minimal synovitis and is more sensitive than plain radiography in detecting joint erosions; it monitors the activity and progression of the disease and evaluates persistent inflammation; in addition it has a low cost for patients and avoids radiation exposure.

The severity of bone and cartilage damage is closely related to the patient's physical function, so non-pharmacological treatment is indicated, which consists of aerobic physical exercise and physical rehabilitation, as this can help patients recover their functional capacity, muscle strengthening and, most importantly, their independence.

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As soon as the diagnosis of RA is made, treatment should be initiated, since it is a therapeutic emergency that requires specialized, early, individualized, and multidisciplinary care. As pharmacological treatment, it has been concluded that the first-line drug is methotrexate, since it reduces signs and symptoms, improves physical function, and prevents or decreases the progression of joint damage. We also observed that NSAIDs help in the inflammatory and symptomatic control of RA. Glucocorticoids present an analgesic and anti-inflammatory effect, which prevent the progression of RA structural damage.

Oral JAK inhibitors (tofacitinib, baricitinib, upadacitinib, figocitinib and peficitinib), were found to have high efficacy in rheumatoid arthritis. Low disease activity of up to 40% and 25% disease remission were achieved. But it has also been seen that the use of monoclonal antibodies against TNF and IL-6 have given good results in arthritis and inhibit bone destruction.

CONCLUSIONS

Rheumatoid arthritis is a chronic systemic, inflammatory, autoimmune disease that directly affects the synovial membrane.

Throughout the years, there has been uncertainty about the origin of the diseases. In the mentioned articles on RA, it explains that there are several factors that contribute to the appearance of this disease, and it shows that according to statistics, the highest percentage of patients with this pathology is related to hereditary factors. For this reason, it is recommended to be in constant review of pathological changes in the body through the previously mentioned studies.

This research clarifies the wide variety of symptoms presented by the disease, which can range from simple arthralgia to loss of joint functionality.

It was concluded that the quality of life of affected patients has been maintained thanks to the early detection of the disease, since there are several treatments (physical therapies, aerobic exercises, medications, etc.), which help to stop the evolution of this disease and thus allow the patient to lead a daily life.

The relevance of the disease should be taken into consideration since some patients only see RA as a simple pain, when in fact this disease can go beyond. Because of this, it is important to know more about the damage it can cause and be alert with the slightest symptoms for a timely prevention in patients.

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