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Rheumatoid Arthritis

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Abstract Rheumatoid arthritis (RA) is a systemic, chronic inflammatory disease that is manifested in destructive polyarthritis in association with serological evidence of autoreactivity. It is characterized by chronic pain and joint destruction, premature mortality and an elevated risk of disability, with high costs for those suffering from this disease and for society. If this condition is not treated, joint destruction from bone erosion can be expected, as well as progressive inabilities, leading eventually to disability, after a time period that can vary from only a few months to many years, depending on prognostic factors. A serious consequence for those suffering from this disease is the loss of their ability to work, especially in the case of manual workers, since many of them lose their income during the first two years of their illness (1). This situation contrasts with the statement asserting that RA is currently the most common potentially-treatable cause of disability in the western world (2). This might be proven true if treatment would be given to patients during the early stages of the disease – which is recommended in order to change the paradigm of RA therapy toward the immediate application of new effective therapies or schemes combining these therapies.

New agents capable of inducing the remission of this disease have been introduced in clinical practice over the last decade. These include anti-IL1 and anti-IL6 agents, TNFα blockers, B cell depleters and regulators of lymphocyte co-stimulation.

Keywords Rheumatoid arthritis · early arthritis · biological therapy

Rheumatoid arthritis is clinically recognized as an inflammatory process affecting the joints, however the outstanding number of extra-articular clinical manifestations make this a systemic, autoimmune disease characterized by different clinical patterns. The symptoms accompanying the early stages of this disease may vary from one individual to another, and this frequently makes early diagnosis difficult.

Epidemiology

Rheumatoid arthritis (RA) is distributed universally. There are no reports of areas or ethnic groups in which this disease is not found, and its prevalence does not appear to significantly vary among the groups studied. In Latin America some studies were recently conducted on the prevalence of RA in the population above the age of 15 years. In Mexico (3) a prevalence of 0.3% (95% CI: 0.1–0.6) was found in 2500 subjects. Similarly, the EPISER study conducted in Spain found a prevalence of 0.5% (4).

Incidence

The figures reported are variable. The highest probable, defined annual global incidence rate for RA is 90 cases/100,000 inhabitants in a clinic in Holland. Studies in Finland and Japan demonstrated estimated annual rates of 42 cases/100,000 inhabitants, and 45 cases/100,000 inhabitants, respectively. A decrease in the incidence of RA among women was observed in the last ten years of follow-up (from 92/100,000 between 1960 and 1964, down to 40/100,000 in 1974) (5). The same downward tendency was found between 1970 and 1982 among British females.

It has been stated that this diminishing, selective tendency for females is due to the use and protecting effect from contraceptives, the use of which was disseminated in the mid 1960s. A change in the pattern of illness toward less severity, as suggested in retrospective studies, receives less support in recent literature, which underscores that the long-term clinical course of this disease has changed very little. It is worth commenting that there is consistent information in the literature on cigarette smoking and an

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increased risk of suffering from rheumatoid arthritis. Mortality: the severity of the disease is associated with shared epitope (SE). All human leukocyte antigen (HLA)-DRB1 alleles associated with rheumatoid arthritis encode a conserved amino acid sequence (QKRAA, QRRAA, or RRRAA) at position 70–74 in the third hypervariable region (HVR3) of the DRbeta(1) chain, which is commonly called the shared epitope.

The global causes of death are similar to the general US population. Some studies mention an excess of deaths from infections, renal and gastrointestinal diseases. Generally, differences are not observed in the frequency of malignant neoplasias in relation to the general population. RA patients die younger than the general population, and this has been observed between the third and tenth years following baseline observation.

Among the factors associated with mortality, the following risk factors for premature death have been identified by different studies and study designs: advanced age, male, greater functional impairment, positive rheumatoid factor, number of swollen joints, co-morbidity and low level of formal education. The economic impact of arthritis is clearly evident. Females with symmetrical polyarthritis earned 26.5% of the wages received by females without arthritis, while males received 47.5% of the wages earned by males without arthritis In Spain the annual average cost was US $10,419.00. Predictors of the high costs were the HAQ disability index, not being able to carry out household tasks, and not being able to work (6).

Pathogenesis

There are different effector pathways and cellular groups involved in the cascade of events leading to the initiation, progression and persistence of the autoinflammatory reaction produced by the irreversible destruction of joint tissue. The perpetuation of the rheumatoid process depends on the involvement of different cellular lines, including synovial cells (such as fibroblast and endothelial and perivascular cells), macrophages, dendritic cells and other immunocompetent cells such as T and B lymphocytes (7).

The inflammatory process and subsequent joint destruction are mediated by the activation of intracellular signaling pathways that stimulate the production of cytokines such as IL-1, TNFα, chemokines, growth factors and adhesion molecules. Adipocytokines are periarticular factors that contribute toward maintaining joint inflammation and that increase the destructive potential of synovial fibroblasts. Adipocytokines such as adiponectin and resistin are found in rheumatoid synovial tissue and may have proinflammatory, destructive effects on the synovial matrix (8).

Elevated concentrations of proinflammatory cytokines such as IL-1 and TNFα are found in both serum and synovial fluid of patients with active disease, in comparison to controls. These cytokines stimulate the release of metalloproteinases by fibroblasts, osteoclasts and condrocytes (9). They also stimulate the expression of adhesion molecules in endothelial cells, increasing the recruitment of neutrophils in joints. These neutrophils release elastases and proteases that degrade proteoglycans in the superficial layer of articular cartilage.

Aside from their local effects, these proinflammatory cytokines manage to enter the bloodstream and are distributed throughout the entire organism, generating both constitutional symptoms and extra-articular manifestations.

Genetic predisposition is significant and is a fundamental determinant in susceptibility to RA. There is concordance between monozygotic twins and a well-defined family predisposition.

Clinical Manifestations

Articular Manifestations

Symmetrical inflammation of large and small articulations accompanied by morning stiffnes are common symptoms of rheumatoid arthritis. Nearly all patients have wrist and hand joints involvement. Compromised metacarpophalangic joints in the initial stages of the disease can lead to an early diagnosis.

In general, any joint can be affected by the disease, and progressive joint damage is accompanied by a diminished quality of life – which can cause varying degrees of functional disability.

Extra-Articular Manifestations

The disease can affect different organs and systems (Table 3.1).

Pathological Features

Early changes in rheumatoid synovial tissue are manifested in hyperplasia of synovial lining cells (SLC), edema, vascular proliferation and lymphocyte infiltration. The pathological changes in asymptomatic articulations include SLC hyperplasia with T CD4+ cell infiltration. B cells are scarce, and vascular proliferation and fibrin deposition are infrequent. In symptomatic joints, the histology of synovial tissue reveals vascular proliferation, polymorphonuclear cell infiltration and fibrin deposition. Vascular proliferation is measured by the production of vascular endothelial growth factors, fibroblastic growth factors, IL-8 and monocyte chemotactic protein (MCP-1) (10).

TABLE 3.1. Extra-articular manifestations.

Type of manifestation	Observations and references
I. Hematopoietic system	
a. Anemic syndrome	50% males, 60–65% females
b. Thrombocytosis	5–10%, Zvaifler et al. (11) May vary according to series, 12–52%; does not predispose to thrombosis
c. Thrombocytopenia	Only exceptional cases
d. Eosinophilia >4%	12.7%. Up to 40% has been observed. More than 5% associated with MEAR and late appearance
e. Leucopenia	Only exceptional cases
II. Reticuloendothelial system	
A. Red cell aplasia	Only exceptional cases
B. Adenomegalia	29%, Zvaifler et al. (11) (118). 82%, non-rigorous studies
III. Subcutaneous nodules	20–30% in seropositive patients, Zvaifler et al. (11) 27%, Massardo et al. (12)
IV. Cardiovascular system	
A. Heart attack	Is rare. Coronary vasculitis Autopsies 15–20%. Anecdotal clinical series
B. Valvular disease	25% with alteration in mitral valve. Autopsies 6–62%. Anecdotal clinical series
C. Mesenteric thrombosis	Only exceptional cases
D. Pericardial effusion	Pericarditis in active RA 10%. Autopsy 40%. Necropsy 11–50%. Clinical series 1.6–2.4%
E. Sinus bradycardia	Conduction disorder. Autopsy: unknown. Clinical series 8–10%.
F. Myocarditis	Diffuse-unspecified endothelial compromise
V. Rheumatoid vasculitis	<1% in most studies. Is more frequent in males, 15 of 50 patients reported by Scott et al. (13) died before 5 years of follow-up. 8% Digital vasculitis. 8% Chilean population, Massardo et al. (12)
VI. Respiratory apparatus	
A. Upper Cricoaritenoides	50% in autopsies. 72.25% in patients with active RA
B. Lower	
1. Pleural effusion	Prevalence <5%, Jurik et al. (14); Joseph et al. (15) More common in males than in females. 21% of 516 patients in the course of evolution. Postmortem, 40–75%
2. Diffuse interstitial fibrosis	1.6% of patients with RA. 41% of 41 patients with alteration in diffusion capacity. 47% with normal thorax X-ray. Zvaifler et al. (11), Anaya et al. (15)
3. Bronchiolitis	Report on cases associated with medication: Metotrexate, D-Penicilin
4. Kaplan Syndrome	2–6%, Shannon et al. (16)
VII. Neurological	
A. Compression neuropathy	
1. Carpal tunnel syndrome	56 cases out of 627 patients. Zvaifler et al. (11) From electromyography (EMG): 50% of patients with RA; 30% are symptomatic
2. Tarsal tunnel syndrome	15–25% from EMG; few are symptomatic
B. Angiopathic neuropathy	4 out of 627 patients. Sensitive-motor neuropathy
C. Autonomic neuropathy	Only exceptional cases
VIII. Eye	
A. Episcleritis	0.17%
B. Scleritis	0.67%
C. Uveitis	Anecdotal. Occurs as a complication of scleritis
D. Brown Syndrome	Only exceptional cases
IX. Sjögren syndrome	14.3%. 29% in Chile, Massardo et al. (12)
Keratoconjunctivitis sicca	11 to 35%
X. Muscular compromise	
A. Muscular weakness	Evident in 80%. Evidence of diminishing I and II fibers in immobilized muscle 25–30%
B. Vasculitis in muscle	Biopsies 9%, Sokoloff.
XI. Renal compromise	7.9% die from non-specific chronic nephritis, Laakso et al. (17) 5.3% die from uremia. Boers et al. (18)
XII. Gastrointestinal compromise	No specific injury. Few cases of amyloidosis. Few reports of arteritis in celiac arteries.
XIII. Felty Syndrome	Variable in published series. 1.89% in Chile by Massardo et al. (12)
XIV. Still Syndrome	Variable in published series. Less than 1%
XV. Amyloidosis	3.3 to 60%, according to autopsy series prior to 1970. Prevalence of 13.3% between 1935 and 1954. Missen et al.

Anaya et al. (19)

Serological Features

Typically, serological markers such as sedimentation rate and reactive C protein are used to measure the disease activity. Reumatoid factor and other autoantibodies that can serve as useful serological markers for establishing the diagnosis and prognosis of the disease.

Until recently, the serum determination of the rheumatoid factor – an immunoglobulin aimed at the constant fraction (cF) of IgG immunoglobulins – was the only test used in the study of this pathology. In fact, the presence of this immunoglobulin is considered as a classification criterion for the illness (20).

Nevertheless, the rheumatoid factor is not highly sensitive or specific (sensitivity 66%, specificity 87%) (21), and can be found in other autoimmune illnesses, neoplasic illnesses, chronic infections, and even in healthy persons (22).

Re-introducing the measurement of antibodies against cyclic citrullinated peptides derived from filagrin (anti-CCP1) (23) has contributed as a valuable instrument which, when used together with the rheumatoid factor (RF), provides important information regarding the prognosis of the disease. The presence of these antibodies has been associated with the development of erosions (24). Ideally, RF and anti-CCP measurements are recommended for patients suspected of having RA. These measurements provide valuable information regarding the risk factors of patients, since those who test serologically positive for one or both of these factors are at greater risk for developing a chronic erosive inflammatory disease.

Diagnostic Criteria

With the objective of distinguishing rheumatoid arthritis from other types of arthritis, the American Rheumatism Association developed classification criteria for this illness (25). The criteria are useful in the case of established RA, providing 91–94% sensitivity and 89% specificity for diagnosing this illness. However, the criteria are not sufficiently reliable when applied to patients with early arthritis. Consequently, the criteria are useful for standardizing patients and for determining their inclusion in clinical studies, however they may be less useful in making decisions regarding a clinical diagnosis.

Prognosis

The objective of RA therapy is to rigorously control inflammation, in order to prevent the illness from advancing, and thus help patients avoid becoming disabled. To reach this objective, it is necessary to diagnosis the illness early, identify patients with the highest probability of rapid progression, and initiate more intensive therapy with patients having this more severe prognosis. The recognized factors indicating a more severe prognosis for patients with early RA are a large number of swollen joints, high PCR or high sedimentation rate levels from the beginning, a positive rheumatoid factor (RF) together with anti-CCP antibodies, the development of erosions discovered early through magnetic resonance images, serious functional disability observed, limited formal education and adverse socioeconomic conditions, plus cigarette smoking (26).

Therapy

"Window of Opportunity" Concept

The "window of opportunity" refers to a very brief period when arthritis begins, and when radiological progression is established. This concept is based on the premise that intense therapeutic intervention at the very beginning of RA was able to "reprogram" the rate at which radiographic damage progressed (18), while a delay of three to nine months in initiating disease-modifying antirheumatic drugs (DMARDS) negatively impacted radiographic progression at the end of two years (27). The "window of opportunity" concept asserts that the use of the most powerful therapies currently available will be more effective, the shorter the duration of RA, and this will eventually lead to a lowered probability of disability. This has sparked hope that in the future affected patients will not require joint replacements or orthopedic surgery and will register a lower rate of mortality caused by premature arteriosclerosis. There has been a notable change since the year 2000 toward an improved RA prognosis for patients receiving therapy during the window of opportunity. Nevertheless, this concept has been challenged and it is not universally accepted.

Treatment of rheumatoid arthritis is aimed at the clinical remission of this condition in patients, and when this is not possible, to at least reduce the progression of the illness (28).

Symptomatic treatment aimed at controlling the pain produced by inflammation includes non-steroid anti-inflammatory drugs, as well as analgesics and corticosteroids. The latter appear to have an impact on the progression of the illness, with a dose of no more than 10 mg daily.

Disease-modifying drugs or DMARDS, which have various immunosuppressing mechanisms, modify the progression of the illness, however unfortunately they have not been able to induce a remission in the conditions of most patients. These drugs continue to be significant in managing these conditions, and this is especially true for methotrexate, particularly in a combined form and with increased effectiveness when administered in the early stages of the illness.

Various scientific groups and associations have reached a consensus that a new type of medication, which is relatively new, should be added to RA treatment, when after eight to twelve weeks, the response to established treatment is minimal or negative. For the moment, the addition of TNFα blocking agents is recommended, for example infliximab, etanercep and adalimumab. Nevertheless, given the degree of effectiveness of other methods for inhibiting inflammation, such as B cell depletion and the inhibition of lymphocyte co-stimulation, other potentially effective agents, specifically rituximab and abatacept, are also currently taken into consideration for controlling the disease in patients who have not responded positively to TNF agents.

References

1. Young, A, et al. How does functional disability in early rheumatoid arthritis (RA) affect patients and their lives? Results of 5 years of follow-up in 732 patients from the Early RA Study (ERAS). *Rheumatology* 2000; 39(6): 603–11.
2. Emery P, M. Salmon, Early rheumatoid arthritis: Time to aim for remission? *Ann Rheum Dis* 1995; 54(12): 944–7.
3. Cardiel MH, Rojas-Serrano J. Community based study to estimate prevalence, burden of illness and help seeking behavior in rheumatic diseases in Mexico City. A COPCORD study. *Clin Exp Rheumatol* 2000; 20: 617–24.
4. Carmona I, Ballina J, Gabriel R, Laffon A. The burden of musculoskeletal diseases in the general population of Spain: Results from a national survey. *Ann Rheum* 2002; 60: 1040–5.
5. Doran MF, Pond GR, Crowson CS, O'Fallon WM, Gabriel SE. Trends in incidence and mortality in rheumatoid arthritis in Rochester, Minnesota, over a forty-year period. *Arthritis Rheum* 2002; 46: 625–61.
6. Lajas C, Abasolo L, Bellajdel B, Hernandez-GarcÚa C, Carmona L, Vargas E, Lazaro P, Jover JA. Costs and predictors of costs in rheumatoid arthritis: A prevalence – based study. *Arthritis Rheum* 2003; 49: 64–70.
7. Muller-Ladner U, Pap T, Gay RE, et al. Mechanisms of disease: The molecular and cellular basis of joint destruction in rheumatoid arthritis. *Nat Clin Pract Rheumatol* 2005; 1(2): 102–10.
8. Bokarewa M. Resistin, an adipokine with potent proinflammatory properties. *J Immunol* 2005; 174: 5789–95.
9. Smith JB, Haynes MK. Rheumatoid arthritis – a molecular understanding. *Ann Intern Med* 2002; 136: 908–22.
10. Kaiser M, Younge B, Johannes B, et al. Formation of new vasa vasorum in vasculitis production of angiogenic cytokines by multinucleated giant cells. *Am J Pathol* 1999; 155: 765–74.
11. Ustinger PD, Zvaifler NJ, Ehrlich GE. Rheumatoid Arthritis. *J.B. Lippincott company* 1985.
12. Massardo L et al. Clinical expression of rheumatoid arthritis in Chilean patients. *Sem Arthritis Rheum* 1995; 25: 203–213.
13. Scott DGI et al. Systemic rheumatoid vasculitis: A clinical and laboratory study of 50 cases. *Medicine* 1981; 60: 288–295.
14. Jurik AG et al. Prevalence of pulmonary involvement in rheumatoid artritis and its relationship to some caracteristics of the paients. *Scand J Rheumatol* 1982; 11: 217–224.
15. Joseph J et al. Connective tissue disease and the pleura. *Chest* 1993; 104: 262–270.
16. Shannon TM et al. Non-cardiac menifestations of rheumatoid arthritis in the thorax. *J Torca Imagin* 1992; 7: 19–29.
17. Laakso M et al. Mortality from amyloidosis and renal disease in patient with rheumatoid arthritis. *Ann Rheum Dis* 1986; 45: 665–667.
18. Boers M, et al. Randomised comparison of combined step-down prednisolone, methotrexate and sulphasalazine with sulphasalazine alone in early rheumatoid arthritis. *Lancet* 1997; 350(9074): 309–18.
19. Anaya JM, Pineda R, Gomez L, Galarza-Maldonado C, et al. (eds.). Artritis reumatoide, bases moleculares cli′ nicas y terape′ uticas. CIB, *Medellin*; 2006: 288–9.
20. Arnett FC, Edworthy SM, Bloch DA, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheuma* 1988; 31: 315–24.
21. Golbach-Mansky R, Lee J, McCoy A, et al. Rheumatoid Arthritis associated autoantibodies in patients with sinovitis of recent onset. *Arthritis Res* 2000; 22: 236–43.
22. Correa P, Tobon GJ, Citera G, et al. Anticuerpos anti-CCP en artritis reumatoide: Relaciæn con caracterÚsticas clÚnicas, citocinas Th1/Th2 y HLA-DRB1. *Biomedica* 2004; 24:140–52.
23. Schellekens GA, Visser H, de Jong BAW, et al. The diagnostic properties of rheumatoid arthritis antibodies recognizing a cyclic citrullinaded peptide. *Arthritis Rheum* 2000; 43: 155–63.
24. Symmons DPM. Classification criteria for rheumatoid arthritis-time to abandon rheumatoid factor? *Rheumatology* 2007; 46: 725–6.
25. Arnett FC, Edworthy SM, Bloch DA, et al. The ARA 1987 revised criteria for the classification on rheumatoid arthritis. *Arthritis Rheum* 1988; 31(3): 315–24.
26. Young A. Early rheumatoid arthritis. *Rheum Dis Clin North Am* 2005; 31(4): 659–79.
27. Lard LR, et al. Early versus delayed treatment in patients with recent-onset rheumatoid arthritis: Comparison of two cohorts who received different treatment strategies. *Am J Med* 2001; 111(6): 446–51.
28. Cardiel M, Galarza-Maldonado, Pons-Estel B. First Latin American position paper on the pharmacological treatment of rheumatoid arthritis. *Rheumatology* 2006; 45: ii7–22.