Epidemiology, Pathophysiology, and Diagnosis of Rheumatoid Arthritis: A Synopsis

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Abstract

Rheumatoid arthritis (RA) is one of the more common autoimmune disorders, affecting approximately 1% of the population worldwide. The exact cause of RA is not known; however, initiation of disease seems to result from an interaction among genetic susceptibility, environmental triggers, and chance. RA is characterized by dysregulated inflammatory processes in the synovium of the joint that eventually leads to the destruction of both cartilaginous and bony elements of the joint, with resulting pain and disability. Systemic inflammation associated with RA is associated with a variety of extra-articular comorbidities, including cardiovascular disease, resulting in increased mortality in patients with RA. RA is also associated with several psychosocial disorders. Classification criteria for RA that were promulgated jointly by the American College of Rheumatology and the European League Against Rheumatism in 2010 emphasize early detection of RA so that effective management can be initiated before pathological changes become irreversible.

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For author information and disclosures, see end of text.

Rheumatoid arthritis (RA), one of the more common chronic inflammatory diseases, is characterized by inflammation and swelling of the synovium of the joint, with subsequent destruction of articular structures.[1] Patients with active RA also experience systemic inflammation that is associated with a variety of comorbidities, most importantly cardiovascular disease, which contribute to the increased morbidity and mortality noted in this group compared with the general population.[2,3]

The pain, fatigue, and disability associated with RA result in a significant reduction in health-related quality of life.[4] Additionally, RA imposes a substantial economic burden upon patients, due to both increased cost of medical care and loss or reduction of employment, frequently during peak working years.[5,6]

This article is the first in a 3-article supplement that will review the pathophysiology, treatment, and managed care implications of RA. This article will examine the epidemiology and pathophysiology of RA and provide guidance regarding diagnosis based on current disease classification criteria.

Epidemiology

The most recent estimate of the worldwide prevalence of RA was published as part of the Global Burden of Disease 2010 study, which was a comprehensive effort to measure epidemiological levels and trends of 291 diseases in 187 countries.[7] For the purposes of this study, RA was defined using the American College of Rheumatology (ACR) 1987 criteria for the classification of RA.[8] In 2010, the global prevalence of RA in patients from 5 to 100 years of age was estimated to be 0.24% (95% confidence interval [CI], 0.23%-0.25%). The prevalence of RA was approximately 2 times higher in females

(mean, 0.35%; 95% CI, 0.34%-0.37%) than males (mean, 0.13%; 95% CI, 0.12%-0.13%). The value for global prevalence of RA in 2010 was not perceptibly changed from the prevalence of RA determined in 1990 (mean, 0.25%; 95% CI, 0.24%-0.26%).[7]

Although the exact cause of RA is unknown, initiation of disease seems to result from an interaction among genetic susceptibility, environmental triggers, and chance.[9] In a study of monozygotic and dizygotic twins, the genetic contribution to the variance in liability to RA, which is equivalent to the heritability of RA, was estimated to be 53% based on data from the United Kingdom and 65% based on data from Finland.[10] Among the genetic factors linked to RA susceptibility are differences in human leukocyte antigen (HLA)-DRB1 alleles, especially in patients who are positive for rheumatoid factor (RF) and anti-citrullinated protein antibody (ACPA).[11] The presence of a common amino acid motif (QKRAA) in these alleles seems to be associated with a particular susceptibility to RA and is referred to as the shared epitope.[9] There is also evidence of gene-environment interactions; for example, there is an increased incidence of RA in HLA-DRB1 individuals who smoke cigarettes.[12] Chromosome 6, which contains the genes for HLA-DRB1, also contains genes that influence a number of immune processes, including modulation of tumor necrosis factor (TNF).[13]

A variety of environmental factors have been implicated as potential triggers for RA. Hormonal influences on RA in women have been an area of active research, given that RA occurs more often in women. For example, in a case-control study, oral contraceptive use was not associated with a reduced risk of RA; however, breastfeeding for 13 or more months was associated with a reduced risk of RA compared with never breastfeeding (odds ratio, 0.46; 95% CI, 0.24-0.91).[14]

In an analysis of data from the Nurses' Health Study, the risk of RA in women with the "shared epitope," a series of alleles of the third hypervariable region of the HLA-DRB1 molecule that are associated with RA, increased in a cumulative manner with history of smoking.[12] Other potential environmental triggers that have been associated with RA include infectious agents (eg, Epstein-Barr virus, cytomegalovirus, *Proteus* species, *Escherichia coli*) and their products (eg, heat-shock proteins).[9] Although these entities have been frequently associated with RA, whether they are a cause of the disease remains unclear. Proposed mechanisms include molecular mimicry, potential adjuvant effect of pathogens in priming autoreactive immune responses, and bystander activation of autoreactive cells.[15]

Pathophysiology

The synovitis, swelling, and joint damage that characterize active RA are the end results of complex autoimmune and inflammatory processes that involve components of both the innate and adaptive immune systems.[9] In a susceptible individual, the interaction of environment and genes results in a loss of tolerance of self-proteins that contain a citrulline residue. These proteins are generated via post translational modification of arginine residues to citrulline residues by the enzyme peptidylarginine deiminase.[9] Patients with shared epitopes generate citrullinated peptides that are no longer recognized as "self" by the immune system, which consequently develops ACPAs against them.[16] Comparison of magnetic resonance imaging (MRI) and synovial biopsy data from healthy individuals with MRI and biopsy data from patients positive for RF and/or ACPA demonstrate that systemic autoantibody production precedes inflammation and adhesion molecule formation in the synovium, indicating that perhaps some secondary event is required to initiate involvement of the synovium in RA.[17] In a study of 79 patients with RA, the initial appearance of RF and ACPA preceded the development of clinical RA involving the synovium by a median of 4.5 years.[18]

Synovitis occurs as a consequence of leukocyte infiltration into the synovium. The accumulation of leukocytes in the synovium does not result from local cellular proliferation but rather from migration of leukocytes from distant sites of formation in response to expression of adhesion molecules and chemokines by activated endothelial cells of synovial microvessels.[9] The interior of the inflamed synovium is hypoxic,[19] presumably as a result of the proliferation of synovial cells and reduction in synovial capillary flow as a consequence of increased fluid volume in the synovium.[20] Hypoxia, in turn, stimulates angiogenesis in the synovium, perhaps by inducing the formation of factors that stimulate vessel formation such as vascular endothelial growth factor.[21]

Immune activation and RA disease progression is a complex process that involves interactions between components of both the adaptive and innate immune pathways. The nature of these interactions is greatly affected by the local cytokine and chemokine environment of the synovium in which they take place. In established RA, the synovial membrane is populated by a variety of

inflammatory cell types that work together to cause joint destruction.[9]

The importance of the adaptive immune pathway in RA is suggested by the presence of dendritic cells, a major class of antigen-presenting cells that expresses a variety of cytokines, HLA class II molecules, and costimulatory molecules in close proximity to clusters of T cells in the synovium. Dendritic cells present antigens to T cells that are present in the synovium and also serve as one component of the T-cell activation process.[22] Activation of T cells requires 2 signals. The first signal is antigen presentation to the T-cell receptor. The second signal, the costimulatory signal, requires interaction of the cell surface protein CD80/86 on the antigen-presenting (dendritic) cell with the CD28 protein on the T cell.[23] Blockade of the costimulatory signal through competitive inhibition of CD80/86 interferes with T-cell activation and downstream events.[24] The effectiveness of CD80/86 blockade as a treatment for RA validates the concept that T cells play an active role in the pathophysiology of RA.[9]

When T-cell activation does occur, naïve T helper (Th) cells differentiate into 3 major subpopulations (Th1, Th2, and Th17) with distinct cytokine production profiles and functions.[25] Although RA has long been considered to be a disease that is mediated by Th1 cells, recent interest has been focused on the Th17 subpopulation. Dendritic cells and macrophages both secrete transforming growth factor β, interleukin (IL)-1β, IL-6, IL-21, and IL-23, cytokines that support Th17 differentiation and suppress production of regulatory T cells, thus shifting the homeostatic balance in the synovium toward inflammation.[9] In turn, Th17 cells produce IL-17A, IL-17F, IL-22, IL-26, interferon-g, the chemokine CCL20, and the transcription factor ROR-g.[26] Production of IL-17A stimulates fibroblast-like synoviocytes (FLSs) and macrophage-like synoviocytes to upregulate production of IL-26, which induces production of the inflammatory cytokines IL-1β, IL-6, and TNF-α by monocytes; these cytokines stimulate further differentiation of Th17 cells.[27] In addition to antigen-driven inflammatory pathways, inflammation can be mediated through antigen-nonspecific pathways initiated by cell-to-cell contact between activated T cells and macrophages and fibroblasts.[28,29]

Humoral adaptive immunity also plays an integral role in the pathogenesis of RA. The contribution of B cells to autoimmune disease can be mediated through several potential mechanisms. Defects in B-cell tolerance checkpoints can result in autoreactive B cells that act as antigen-presenting cells that are capable of activating T cells. B cells can also produce both pro- and anti-inflammatory cytokines. Finally, B cells can function as antibody-producing cells. Separately or in combination, these mechanisms can contribute to RA pathogenesis.[30] Additional support for the involvement of B cells in RA is provided by the successful use of agents that deplete specific B-cell populations for the management of RA. Rituximab, a monoclonal antibody directed against CD20-positive B cells, has demonstrated success in RA clinical trials and is currently approved for use in patients with RA who are refractory to TNF inhibitors.[31,32]

Cells of the innate immune system, including macrophages, mast cells, and natural killer cells, are located in the synovial membrane, whereas neutrophils are typically found in the synovial fluid. Macrophages, in particular, are important effectors of synovitis that act through phagocytosis; antigen presentation; and the release of pro-inflammatory cytokines, reactive oxygen intermediates, prostanoids, and matrix-degrading enzymes.[9] Toll-like receptors (TLRs) on monocytes, macrophages, and dendritic cells serve to initiate the inflammatory and immune response upon exposure to an immunogenic stimulus, such as a microbial pathogen. Activation of TLRs results in the rapid expression of proinflammatory cytokines that mediate an immune response that recruits neutrophils, monocytes, and lymphocytes. Macrophages and dendritic cells accumulate processed antigen and migrate to peripheral lymphoid tissue where antigen is presented to cells of the adaptive immune system with resultant activation of cellular immunity and production of antibodies. In most cases, the combination of innate and adaptive immune system responses will eliminate the pathogen, leading to cessation of the immune response. In the setting of RA, however, the inflammatory response is not terminated following clearance of the pathogen but rather remains chronically activated.[33]

Intracellular signaling pathways are also involved in the pathogenesis of RA. All of the various cytokines, chemokines, antibodies, and antigens that contribute to inflammation bind to receptors on the cell surface of specific target cells. Receptor binding typically results in a cascade of intracellular signaling events that ultimately converges upon the nucleus of the cell and alters gene expression in ways that can affect cell function. In particular, changes in gene expression in immune cells are frequently associated with production and secretion of inflammatory mediators in response to a particular stimulus. Secretion of these mediators into

the extracellular milieu results in further amplification and/or modification of the original signal. Examples of intracellular signaling pathways include the mitogen-activated protein kinase (MAPK) pathway, the Janus kinases (JAK) pathway, the signal transducers and activators of transcription (STAT) pathway, spleen tyrosine kinase (Syk) signaling, and the nuclear factor κ-light-chain enhancer of activated B cells (NF-κB) pathway. Cross-communication between pathways has been reported. Intracellular signaling pathways are essential for a normal immune response, and aberrations in these pathways may contribute to autoimmune disease.[34] The first generation of small molecules directed against intracellular targets is now being used for the treatment of RA.[35] Further understanding of these pathways will likely lead to the identification of additional therapeutic targets.

The inflammation of RA is also associated with characteristic changes in mesenchymal tissue. FLSs, which are normally resident in the synovium, proliferate and change their phenotype in the setting of RA.[9] In the inflamed synovium, cell contact between FLSs and T cells results in the induction of a variety of inflammatory mediators and adhesion molecules, including IL-6, TNF, interferon-g, intracellular adhesion molecule-1, and vascular cell adhesion molecule-1.[36] Altered FLSs invade the cartilage of the joint and produce a variety of proteases that contribute to joint destruction.[37]

Assessment of Disease Activity

A variety of tools for assessment of disease activity have been developed for use in clinical trials and in the office setting. These are used both to standardize definitions and to guide treatment. In particular, the development of standardized measures of disease activity, which define remission, low disease activity, and high disease activity, is required for use of a "treat-to-target" strategy using pharmacologic therapy. In the "treat-to-target" paradigm, the baseline disease activity of a patient is determined and therapy is initiated with the primary goal of maximizing long-term health-related quality of life. After therapy is initiated, progress toward the goal is reassessed at regular intervals and therapy is adjusted based on the degree of goal attainment.[38]

The Disease Activity Score using 28 joints (DAS28) is one of the most commonly used assessments of disease activity in RA clinical trials. The DAS28 includes an evaluation of 28 joints for swelling and tenderness by the physician, separate physician and patient assessments of global disease activity, and a laboratory assessment of inflammation (either erythrocyte sedimentation rate [ESR] or plasma level of C-reactive protein [CRP]). The resultant numbers are plugged into an empirical formula to generate a DAS28 value. DAS28 scores have been used in clinical trials to define levels of disease activity. The definitions of disease activity, which were calculated using the DAS28(ESR) formula, were low (DAS28 ≤3.2), moderate (3.2< DAS28 ≤ 5.1), and high (DAS28 >5.1). A DAS less than 2.6 corresponds to a state of remission according to the American Rheumatism Association criteria.[39] There is some discrepancy between DAS28 values calculated using CRP and ESR. Given the more common current usage of CRP for calculation of DAS28, disease activity cut points were developed for DAS28(CRP) in 2010. In this schema, disease remission is defined as DAS28 less than 2.3, low disease activity is from 2.3 to 3.8, moderate disease activity is from 3.8 to 4.9, and high disease activity is greater than 4.9.[40] DAS assessment is used in both clinical trials and clinical practice.

Other commonly used scales in clinical trials and clinical practice include the simplified disease activity index (SDAI), which is the numerical sum of 5 measured parameters (tender and swollen joint count, physician and patient global assessments of disease, and CRP), and the Routine Assessment of Patient Index Data 3 (RAPID3), which is a measure of physical function, pain, and global status.[41,42] Other scales commonly used in clinical trials include the ACR response, which measures percentage improvement from baseline, and the Clinical Disease Activity Index (CDAI), which is calculated as the sum of the swollen and tender joint count and the physician and patient global assessments.[43,44] The CDAI is probably the easiest scale to use, as it is simply an arithmetic sum of 4 measured parameters. As a result of its simplicity, it is perhaps the most widely used scale in clinical practice. Based on the limitations of current measurements of disease activity, there is considerable interest in developing novel markers for early RA.

Patient-reported outcomes are also routinely used to assess current patient status and outcome of treatment of RA, particularly functional status and quality of life. Functional status is typically measured with the Health Assessment Questionnaire (HAQ) or one of its numerous variants. The HAQ consists of a series of 41 questions in 8 categories that evaluate patient difficulties with activities of daily living over the past week.[44,4] General quality of life in patients with RA has typically been evaluated with the Short Form 36, whereas disease-specific quality

of life can be measured with the Rheumatoid Arthritis Quality of Life instrument.[45,46]

In 2011, a joint committee of the ACR and the European League Against Rheumatism (EULAR) suggested 2 possible approaches to defining clinical remission in clinical trials of RA. A patient can be considered to be in remission when scores on the tender joint count, swollen joint count, CRP (in mg/dL), and patient global assessment (0-10 scale) are all less than or equal to 1, or alternatively, when the score on the SDAI is less than or equal to 3.3.[47]

An estimate of the rate of real-world remission of RA during treatment was obtained by applying the 2011 ACR/EULAR criteria for remission to 2 large cohorts of patients in clinical practice. The probability of remission at a given clinic visit using the ACR/EULAR criteria was 7.5% in one cohort and 8.9% in the other. For patients who achieved remission, the probability of remaining in remission ranged from 6.0% to 14.1% after 2 years. Based on this 2011 analysis, less than 3% of all RA patients can be expected to experience a remission lasting 2 years or longer.[48] Additionally, some patients in clinical remission have been noted to show radiographic evidence of disease progression or synovitis on MRI or ultrasound examination.[49]

An analysis of clinical and radiological follow-up data for 290 patients with RA showed that patients who experienced rapid radiological progression in the first year after RA diagnosis were more likely to experience functional disability over an 8-year period compared with patients without rapid progression.[50] Although radiographic imaging is a useful and specific way to evaluate disease progression and the effectiveness of treatment, it is less useful for routine monitoring in the office setting, and thus is not included in the previously discussed ACR/EULAR criteria for remission. The 2012 update of the ACR RA treatment recommendations reviews other indicators of poor prognosis in patients with RA, including functional limitation on standardized health questionnaires, extra-articular disease, positive RF, positive ACPA, and bony erosions documented by radiograph.[51]

Disease Burden

In a radiographic study of 42 patients with early RA, 45% of patients experienced bone erosion of the joints within 4 months after diagnosis.[52] Aside from causing joint damage that results in pain, disability, and work limitation, RA is a systemic disease that can continue to have manifestations even after the joint damage is controlled. A more complete consideration of the burden of RA must also include the comorbidities, psychosocial deficits, and impairment of health-related quality of life that accompany the extra-articular manifestations of RA (**Figure**).[53]

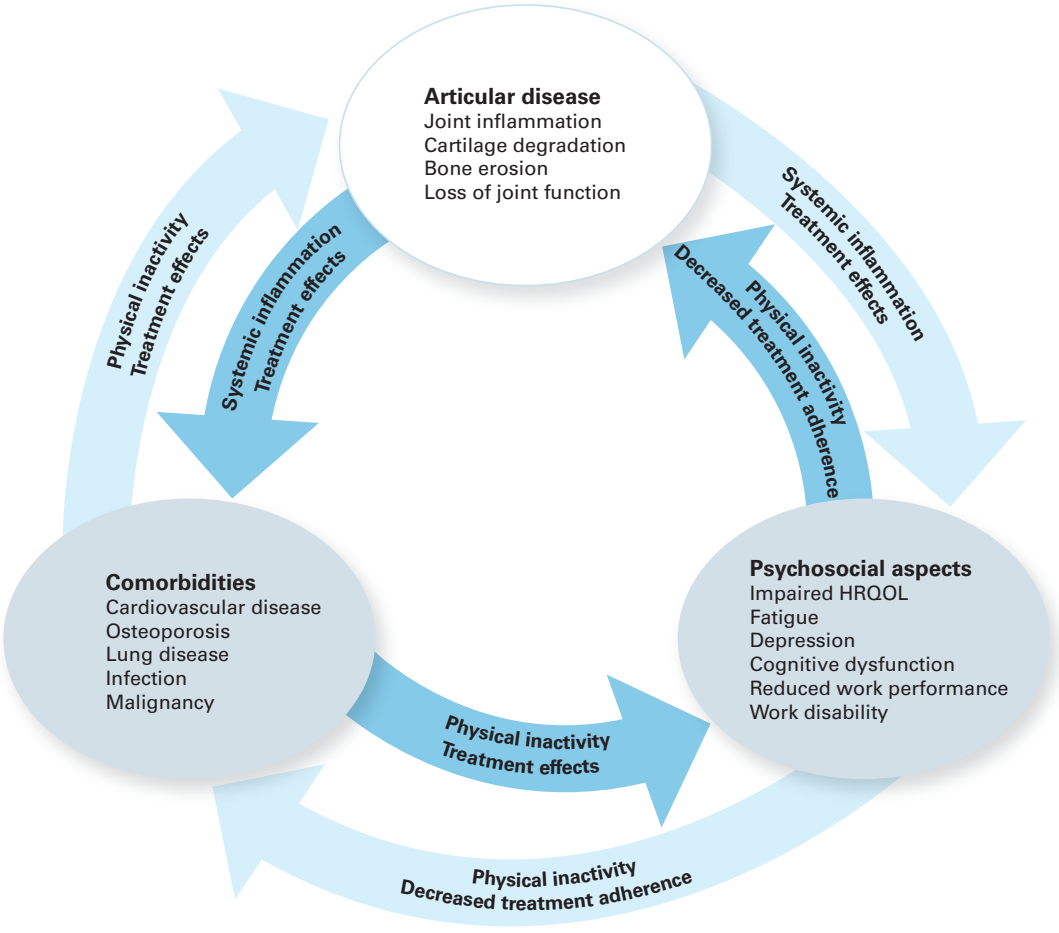
Systemic comorbidities associated with RA include cardiovascular disease, pulmonary disease, gastrointestinal disease, cancers, and psychiatric disease.[2] Cardiovascular disease has attracted particular interest, as it appears to be an important source of mortality in RA. The results of a 2008 meta-analysis that included more than 110,000 patients from 24 observational studies showed that patients with RA have a 50% increased risk of cardiovascular disease compared with the general population. Mortality risks for ischemic heart disease and cerebrovascular accident were increased by 59% and 52%, respectively.[54]

RA is also associated with a heavy burden of psychosocial comorbidities, which have received considerably less attention than the other comorbidities. RA is associated with decreased health-related quality of life, increased fatigue and depression, and impaired cognitive function.[54] Considering that the focus in clinical trials of therapies for RA has typically been on joint-related symptoms, the ability of currently available therapies for RA to address the psychosocial aspects of RA is unclear.

Symptoms and Diagnosis

The most recent classification criteria for RA were developed by a joint committee of the ACR and EULAR and published in 2010.[55] These classification criteria can be applied to any patient who has active synovitis in at least 1 joint that is not explained by a non-RA diagnosis. Numerical scores are assessed in 4 domains of RA: joint involvement, serology, acute phase reactants, and duration of symptoms. A patient with a score of 6 or more points out of 10 can be classified as having RA.[55] The 2010 ACR/EULAR classification criteria replaced the ACR criteria promulgated in 1987[8]; its primary weakness was a failure to identify patients with early disease who could benefit from early initiation of therapy. Although the 2010 classification criteria were designed to identify patients with RA for clinical trials, the cutoff score of 6 or greater based on these criteria is also the preferred approach for diagnosing RA clinically.[55] Testing in other cohorts will be required to provide further evidence regarding validity of the classification criteria for diagnosis.

Figure. A Schematic of RA Disease Burden[53]



HRQOL indicates health-related quality of life; RA, rheumatoid arthritis.
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According to the 2010 ACR/EULAR classification criteria, values for RF and ACPA, markers of autoimmune dysfunction, are scored according to ranges of values, where normal is defined as less than the upper limit of normal (ULN) for the laboratory or assay, low-positive is between the ULN and less than 3 times the ULN, and high-positive is greater than 3 times the ULN. ESR and CRP levels are scored based on whether they are normal or abnormal according to reference laboratory standards. The 2010 classification criteria factor duration of therapy, but not the presence or absence of radiographic changes, into the final score. The authors of the 2010 ACR/EULAR classification criteria recommend that the guidelines be used for assessment of existing and future patients to facilitate earlier use of therapies capable of altering disease progression.[55]

Conclusions

RA, a common autoimmune disease, is associated with inflammation and swelling of the synovium of the joint and, if left untreated, often results in destruction of both the bony and cartilaginous elements of the joint and resultant disability. A variety of comorbidities associated with systemic inflammation contribute to the increased mortality seen in patients with RA compared with the general population. Although the pathophysiology of RA is not completely understood, the process generally involves dysregulated inflammation, with antigen presentation, T-cell activation, and autoantibody production all serving as mediators in the inflammatory process. Diagnosis of RA is based on the patient history and physical examination demonstrating synovitis in multiple joints. Indices of disease activity have been

developed to guide treat-to-target approaches to pharmacological intervention.

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