Overview of Epidemiology, Pathophysiology, and Diagnosis of Rheumatoid Arthritis

Allan Gibofsky, MD, JD, FACP, FCLM

Abstract

Rheumatoid arthritis (RA) is a common autoimmune systemic inflammatory disease affecting approximately 1% of the worldwide population. The interaction of genetic and environmental factors results in a cascade of immune reactions, which ultimately lead to the development of synovitis, joint damage, and structural bone damage. These, in turn, lead to pain, disability, and emotional, social, and economic challenges. A number of extra-articular manifestations and comorbidities are present in patients with RA, which result in increased mortality. The American College of Rheumatology and European League Against Rheumatism recently published updated disease classification criteria in an effort to identify RA earlier so that effective treatment can be employed to prevent irreversible changes.

(Am J Manag Care. 2012;18:S295-S302)

Rheumatoid arthritis (RA) is a common, chronic, inflammatory, autoimmune disease of unknown etiology affecting approximately 1% of the world population.[1-3] The synovium, or membrane present in the synovial joints that lines the joint capsules and creates synovial fluid for the joints in the hands and feet, is the first structure affected. The subsequent inflammatory changes lead to cartilage and bone destruction.[1,4] In addition, the corresponding systemic inflammation may result in disorders of multiple organ systems.[1] The health-related quality of life in patients with RA is significantly reduced by the pain, fatigue, loss of bodily function, and heavy economic burden associated with disease progression.[5] It is also recognized that mortality in patients with RA is increased compared with the general population.[6] This manuscript is the first of 3 in this supplement designed to review the pathophysiology, treatment, and managed care implications of RA. This article will provide an overview of the diagnosis, pathophysiology, epidemiology, symptoms, assessment, and prognosis of RA.

Symptoms and Diagnosis

The diagnosis of RA is made clinically based primarily on physical examination findings.[1] The 2 main classification criteria are summarized in Table 1.[7,8] The classification criteria published in 1987 by the American College of Rheumatology (ACR), formerly the American Rheumatism Association, have been criticized for their focus on identifying patients with more-established RA disease (ie, those who have already developed chronic erosive disease).[8] Consequently, the 1987 criteria failed to identify patients with early disease, who could gain the most benefit from available therapies.[7] Recently, the ACR and European League Against Rheumatism (EULAR) created a joint working group with the primary goal of developing classification criteria to identify patients earlier in the disease process.[8] As with the 1987 effort, the 2010 classification criteria are a means to identify patients for clinical trials, to differentiate patients with synovitis, and to determine the group at highest risk for developing persistent or erosive RA. However, the 2010 ACR/EULAR classification criteria also created a schematic for identifying definite RA.[8]

There are some important differences between the 1987 and 2010 classification criteria for RA, as shown in Table 1.[7,8] The 1987 criteria required a score of at least 4 from a tally of 7

For author information and disclosures, see end of text.

Table 1. Comparison of Historical and Current Classification Criteria for RA[7,8]

	1987 Criteria[7]		2010 Criteria[8]	
Criteria	**Description**	**Score**	**Description**	**Score**
Morning stiffness	In and around joints, for at least 1 hour	1	Clinical synovitis/swelling in at least 1 joint not explained by another disease	NA
Joint involvement	Physician observed soft tissue swelling or fluid in 3 of 14 possible joints	1	1 large joint 2-10 large joints 1-3 small joints (with or without large joint) 4-10 small joints (with or without large joint) >10 joints (at least 1 small)	0 1 2 3 5
Arthritis of hand joints	At least 1 swollen hand or wrist area	1	NA	NA
Symmetric arthritis	Simultaneous bilateral involvement	1	NA	NA
Rheumatoid nodules	Subcutaneous nodules over bony prominences, extensor surfaces, or in juxtaarticular regions observed by physician	1	NA	NA
Serology	Positive RF serum test	1	Negative RF and negative ACPA Low-positive RF or ACPA High-positive RF or ACPA	0 2 3
Radiographic changes	Erosions or unequivocal bony decalcification in or adjacent to the involved joints, but not consistent with osteoarthritis	1	NA	NA
Acute phase reactants	CRP and ESR	NA	Normal CRP and ESR Abnormal CRP or ESR	0 1
Duration of symptoms	First 4 criteria must be present for at least 6 weeks	NA	<6 weeks ≥6 weeks	0 1
Criteria score required		≥4/7		≥6/10

ACPA indicates anti-citrullinated protein antibody; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; NA, not applicable; RF, rheumatoid factor.

domains, including: morning stiffness, the overall number of joints involved, hand involvement, presence of symmetry, rheumatoid nodules, positive rheumatoid factor (RF) test, and radiographic changes.[7] In the 2010 criteria, patient assessment was recommended for those with clinical synovitis in at least 1 joint not explained by another disease. Assessment involves a scoring system from 0 to 5, based on the number and type of joint(s) involved. An involved joint was defined as joint swelling or tenderness on examination indicative of active synovitis. Large joints include the shoulders, elbows, hips, knees, and ankles. Small joints refer to the metacarpophalangeal (MCP), proximal interphalangeal (PIP), second through fifth metatarsophalangeal (MTP), thumb interphalangeal joints, and wrists. The distal interphalangeal, first carpometacarpal joints, and the first metatarsophalangeal joints are excluded from assessment due to their involvement in osteoarthritis. There was no specific requirement for hand arthritis, rheumatoid nodules, or symmetric arthritis in the 2010 criteria. The authors noted that symmetric involvement was not an independent feature of RA, although the likelihood of bilateral presentation was increased with greater joint involvement and more progressive disease.

Similar to the 1987 criteria, the 2010 criteria utilize the presence or absence of RF (a high-affinity autoantibody directed against the Fc portion of immunoglobulin) as one of the domains. In addition, the 2010 criteria utilize the presence or absence of a marker that was identified more recently, the anti-citrullinated protein antibody (ACPA).[8] 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 labora-

tory 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. Markers of inflammation, the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) level, are scored based on whether they are normal or abnormal according to reference laboratory standards. Unlike the 1987 criteria, the 2010 criteria considered duration of therapy, but not the presence or absence of radiographic changes, to factor into the final score. In the 2010 RA classification criteria, a score of at least 6 out of 10 was considered to be indicative of RA, and hence a patient would be considered for treatment.[8] The authors recommend that the 2010 ACR/EULAR criteria be used for assessment of existing and future patients to facilitate earlier use of treatments capable of altering disease progression.

Epidemiology

From the existing data, some general conclusions may be drawn regarding the epidemiology of RA. The overall world prevalence of RA is approximately 0.5% to 1%, but may be declining in the United States.[8-10] Using data from 1995 and 2005, the prevalence of RA in adult Americans was estimated at 1.29 million (0.6%), down from the previous estimate of 2.1 million. In 1995, the prevalence of RA in American women (1.06%) was nearly double that in men (0.61%). Interestingly, because most data were derived from patients in Minnesota, they may not be generalizable beyond Caucasians.[9] There is regional variation in the prevalence of RA. The incidence appears to be highest in Pima Indians (5.3%) and Chippewa Indians (6.8%), and lowest in people from China and Japan (0.2%-0.3%), suggesting the possibility that genetic factors contribute to RA.[10] These differences in regional RA prevalence also may suggest a role for environmental factors.

The exact cause of RA is unknown. The leading hypothesis for this (and most other autoimmune disorders) is that RA is the result of an environmental exposure or "trigger" in a genetically susceptible individual.[11] Some environmental factors related to gender have emerged. Women who actively take oral contraceptives have a lower incidence of RA (~0.3/1000 women years) compared with women who never took oral contraceptives (~0.65/1000 women years) or those who previously took oral contraceptives (~0.55/1000 women years).[10] Both female subfertility and the immediate postpartum period after a first pregnancy (especially when breastfeeding) appear to increase the risk of RA.[10] Other potential environmental triggers include viral infections, such as those of Epstein-Barr virus, parvovirus, and bacterial infections with organisms such as *Proteus* and *Mycoplasma*. Heat-shock proteins and other stressors (eg, hypothalamic-pituitary-adrenal changes during adverse or traumatic life events) affect immune regulation and cytokine production.[1] Heat-shock proteins create immune complexes that may trigger the production of RF.[1] The gastrointestinal microbiome has also been implicated in triggering autoantibody production, depending on the bacteria present.[1] Several environmental factors are capable of creating posttranslational modifications of barrier tissues through peptidyl arginine deiminase, type IV (PADI4), an enzyme responsible for post-translational citrullination of peptide antigens on arginine residues. PADI4 has the ability to alter citrullination of mucosal proteins, and it is associated with *Porphyromonas gingivalis*, present in periodontal disease and in patients who smoke cigarettes.[1,12] Cigarette smoking appears to be associated with an increased risk of RA, and the development of a positive RF.[12]

Twin studies show concordance rates of 15% to 30% between monozygotic twins and 5% among dizygotic twins, suggesting that 50% to 60% of RA cases are due to genetic factors.[1,10] Among the genetic factors linked to RA susceptibility are differences in human leukocyte antigen (HLA)-DRB1 alleles, especially in patients positive for RF and ACPA.[1] HLA-DRB1 genotypes appear to affect both disease susceptibility and disease severity.[10] Gene-environment interactions have been observed; there is an increased incidence of RA in HLA-DRB1 individuals who smoke cigarettes. Chromosome 6, which contains the genes for HLA-DRB1, influences a number of immune processes, including production of tumor necrosis factor (TNF).[10]

Pathophysiology

The hallmark swelling, bony erosions, and synovial thickening reflect the underlying inflammatory and autoimmune processes. The interaction of environmental factors and genetic susceptibility leads to altered post-transcriptional regulation and self-protein citrullination early in the disease process.[1] Citrullination is a normal physiologic process in dying cells, and under normal circumstances, the cells do not come in contact with the immune system. When clearance is inadequate, however, peptidylarginine deiminase (PAD) enzymes and citrullinated proteins leak out of the dying cells and contact the immune system. The PAD enzymes citrullinate extracellular proteins containing arginine, creating citrullinated antigens. Patients with certain HLA-DRB1 genotypes, termed shared epitopes, generate peptides no longer recognized as "self" and consequently develop ACPA. Downstream consequences include immune complex development and loss of tolerance to self.[1,13] RF is also indicative of autoantibody production.[1] Van de Sande and colleagues

demonstrated, using contrast-enhanced magnetic resonance imaging (MRI) and joint synovial biopsy of healthy individuals and patients with RF and/or ACPA, that systemic autoantibody production and inflammation precedes inflammation and adhesion molecule formation in the synovium, indicating that perhaps a "second hit" is required to involve the synovium in RA.[14] The initial development of RF and ACPA can precede the development of clinical RA involving the synovium by up to 15 years.[15]

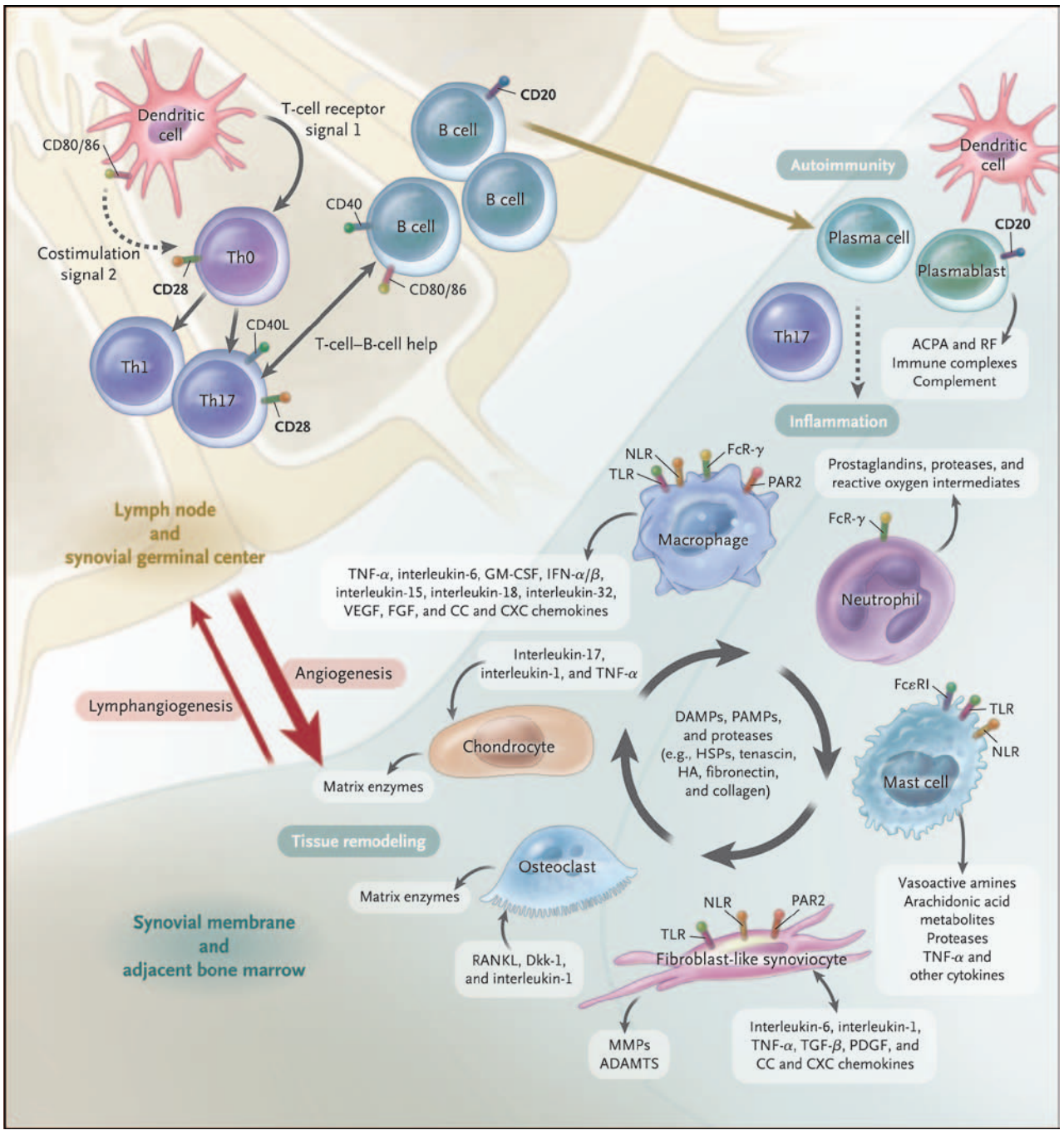
The relationship between loss of self tolerance and synovial involvement is unclear at this time, but synovitis occurs when leukocytes infiltrate the synovium.[1] Leukocyte accumulation reflects cell migration, which is enabled by endothelial activation and expression of adhesion molecules such as E-selectin, intercellular adhesion molecule (ICAM), and vascular cell adhesion molecule.[1,14] Local hypoxia, cytokine release, insufficient lymphangiogenesis (which limits cellular egress), fibroblast activation, and synovial reorganization increase inflamed tissue and may contribute to the joint symptoms of RA.[1]

The underlying factors associated with immune activation and disease progression involve the adaptive and innate immune pathways, along with cytokines, growth factors, and intracellular signaling molecules. The genetic variation of immune activation in patients with RA leads to the cascade of immunity and destruction present in RA. The **Figure** demonstrates that the synovial membrane becomes infiltrated with various inflammatory cell types, which ultimately work together to cause joint destruction.[1] Dendritic cells express cytokines (interleukin [IL]-12, 15, 18, and 23), HLA class II molecules, and costimulatory molecules (CD80/86), and are involved in antigen presentation and T-cell activation. T cells require 2 signals for activation, where the first signal is antigen-specific and involves T-cell receptors and IL-2. The second signal, or costimulatory signal, involves interaction of CD80/86 on the antigen-presenting (dendritic cell) and CD28 on the T cell.[1,16] Blockade of the costimulatory signal through competitive inhibition of CD80/86 prevents T-cell activation and the downstream events.[17] When T-cell activation does occur, T helper (Th) cells (eg, Th0, Th1, Th17) are recruited. Th17 cells produce IL-17A, IL-17F, IL-21, IL-22, and TNF-α. Dendritic cells and recruited macrophages both secrete transforming growth factor β, IL-1β, IL-6, IL-21, and IL-23 to support Th17 differentiation, creating an inflammatory environment. IL-17A works with TNF-α to promote the activation of fibroblasts and chondrocytes. Non-specific T-cell contact-activation is mediated through CD40 and CD40 ligand, CD200 and CD200 ligand, ICAM-1, and leukocyte-function-associated antigen-1. Th17 cells also trigger humoral adaptive immunity mediated by synovial B-cells. B-cells are triggered by factors including a proliferation-inducing ligand, B-lymphocyte stimulator, and CC and CXC chemokines.[1] B cells secrete autoantibodies, present antigens to T cells, and stimulate synovial fibroblasts through the secretion of cytokines (eg, lymphotoxin-β [Ltβ] and TNF).[15] Derived plasma cells also are involved in autoantibody production, autoantigen presentation, and cytokine production involving IL-6, TNF-α, and Ltβ.[1,18]

Cells of the innate immune system, including macrophages, mast cells, and natural killer cells, also are important in the pathophysiology of synovial inflammation in RA. Macrophage maturation is mediated by granulocyte colony-stimulating factor and granulocyte-macrophage colony-stimulating factor. Macrophages are activated by toll-like receptors and nucleotide-binding oligomerization domain-like receptors. Macrophages secrete TNF-α, IL-1, IL-6, IL-12, IL-15, IL-18, IL-23, and are involved in the release of matrix degradation enzymes, phagocytosis, antigen presentation, and reactive oxygen intermediates. Neutrophils, present in the synovial fluid, synthesize inflammatory prostaglandins, proteases, and reactive oxygen intermediates. Mast cells release cytokines, chemokines, proteases, and vasoactive amines.[1]

Intracellular signal transduction pathways may also be involved in the pathogenesis of RA, since cytokine release reflects the way cells respond to environmental stress.[18] Janus kinase pathways, mitogen-activated protein kinases (MAPKs), p38 MAPK, c-Jun N-terminal kinase, nuclear factor-κB (NF-κB), and receptor activator of nuclear factor kappa-B ligand (RANKL) all may contribute to response to inflammation.[1,18] Fibroblast-like synoviocytes change characteristics in the setting of RA. In RA, fibroblast-like synoviocytes express altered levels of cytokines, chemokines, adhesion molecules, matrix metalloproteinases, and tissue inhibitors of metalloproteinase. The reason for the resulting synovial hyperplasia is incompletely understood, but the altered fibroblast-like synoviocytes contribute to local cartilage destruction, synovial inflammation, and T-cell and B-cell survival. The altered fibroblast-like synoviocytes are resistant to apoptosis, possibly through mutations of tumor-suppressor gene P53, expression of heat-shock proteins, modulation of the endoplasmic reticulum, and cytokine-induced activation of NF-κB, which favors fibroblast-like synoviocyte survival in the presence of ligation with the TNF-α receptor.[1] In addition, RANKL and macrophage colony-stimulating factor promote osteoclast differentiation and articular cartilage invasion.[1]

■ **Figure.** Adaptive and Innate Immune Processes Within the Joint in Rheumatoid Arthritis[1]



The costimulation-dependent interactions among dendritic cells, T cells, and B cells are shown as occurring primarily in the lymph node; these events generate an autoimmune response to citrulline-containing self-proteins. In the synovial membrane and adjacent bone marrow, adaptive and innate immune pathways integrate to promote tissue remodeling and damage. Positive feedback loops mediated by the interactions shown among leukocytes, synovial fibroblasts, chondrocytes, and osteoclasts, together with the molecular products of damage, drive the chronic phase in the pathogenesis of rheumatoid arthritis. ACPA indicates anti-citrullinated protein antibody; ADAMTS, a disintegrin and metalloprotease with thrombospondin-1–like domains; DAMP, damage-associated molecular pattern; Dkk-1, dickkopf-1; FcR, Fc receptor; FcεRI, high-affinity IgE receptor; FGF, fibroblast growth factor; GM-CSF, granulocyte–macrophage colony-stimulating factor; HA, hyaluronan; HSP, heat-shock protein; IFN-α/β, interferon-α/β; MMP, matrix metalloproteinase; NLR, nucleotide-binding oligomerization domain–like receptor; PAMP, pathogen-associated molecular pattern; PAR2, protease-activated receptor 2; PDGF, platelet-derived growth factor; RANKL, receptor activator of nuclear factor κB ligand; RF, rheumatoid factor; TGF-β, transforming growth factor β; Th0, type 0 helper T cell; Th1, type 1 helper T cell; Th17, type 17 helper T cell; TLR, toll-like receptor; TNF-α, tumor necrosis factor α; VEGF, vascular endothelial growth factor.
From McInnes IB, Schett G. The pathogenesis of rheumatoid arthritis. *N Engl J Med.* 2011;365(23):2205-2219.

Table 2. Extra-Articular Manifestations of Rheumatoid Arthritis[1,2,11,22]

Organ or Organ System	Disease Description	Contributing Factor(s)
Blood vessels	Major cutaneous vasculitis, atherogenesis, stroke, vasculitis of other organs	Complement immune complexes, IL-6, TNF-α
Bone	Low bone mineral density, fractures, osteoporosis	TNF-α, RANKL, dickkopf-1
Brain and nerves	Fatigue, reduced cognitive function, serotonin transporter alterations, HPA axis alterations, low stress tolerance, depression, stroke, cervical myelopathy, neuropathy	TNF-α, IL-6, IL-1
Cardiovascular system	Pericarditis, myocardial infarction	Complement immune complexes, IL-6, TNF-α
Kidney	Glomerulonephritis	Inflammatory response, unspecified
Liver	Acute phase response (C-reactive protein), iron redistribution, altered lipid metabolism	IL-6
Mouth	Xerostomia, secondary Sjögren's syndrome, periodontitis	Inflammatory response, unspecified
Muscle	Insulin resistance, sarcopenia	TNF-α, IL-1
Ophthalmic	Scleritis, episcleritis, retinal vasculitis, kerato-conjunctivitis sicca, secondary Sjögren's syndrome	Inflammatory response, unspecified
Pulmonary	Pleuritis, pulmonary fibrosis, bronchiolitis obliterans organizing pneumonia	Inflammatory response, antirheumatic medication
Spleen	Felty's syndrome	Inflammatory response, unspecified
Other	Amyloidosis, subcutaneous rheumatoid nodules, rheumatoid nodules in other locations	Presence of rheumatoid factor, inflammatory response, antirheumatic medication

HPA indicates hypothalamic-pituitary-adrenal; IL, interleukin; TNF-α, tumor necrosis factor α.

TNF-α and IL-6 are thought to play the most central role in the pathogenesis of RA. TNF-α activates cytokines, chemokine expression, and endothelial-cell adhesion molecules, protects fibroblasts, promotes angiogenesis, suppresses regulatory T cells, and promotes pain. IL-6 promotes leukocyte activation and autoantibody production, and contributes to anemia, cognitive dysfunction, and dysregulation of lipid metabolism.[1] Both TNF-α and IL-6, as well as RANKL, amplify osteoclast activation and differentiation.[1]

Disease Burden and Prognosis

The complex pathophysiology of RA leads to synovial hyperplasia, cartilage damage, and bony erosion, usually affecting up to 80% of patients within 1 year of diagnosis. Eroded bone does not appear to demonstrate any evidence of repair in RA, suggesting that the main goal should be to prevent bony erosion, as noted in the 2010 ACR/EULAR classification criteria.[1,8] Joint damage leads to pain and disability.[19] Up to one-third of patients are work-disabled within 2 years of disease onset, and approximately 50% are work-disabled after 10 years.[15,19] The physical, emotional, and social impact of RA contributes to poor health-related quality of life.[19] Disease severity is correlated with the degree of pain and physical functioning, although patients score their pain worse than physicians estimate.[20,21]

The disease burden of RA is not limited to the affected joints and its physical impact. RA is associated with a number of systemic complications related to the underlying disease process. Table 2 summarizes the components of extra-articular RA.[1,2,11,22] A number of organs and organ systems are potentially involved in RA, particularly in severe disease.[2] It appears that persistence of inflammatory mediators contributes to the extra-articular involvement. Patients with extra-articular manifestations of RA appear to have higher mortality, especially among men relative to women.[2] It appears that a majority of the deaths in patients with RA are related to cardiovascular disease.[1,6] The decline of mortality in the general population over the last 40 years has not been mirrored in the RA population, and it does not appear to be explained solely by traditional cardiovascular risk factors, such as dyslipidemia, smoking, diabetes, and hypertension.[1,6,23] Cardiovascular mortality appears to be at least 1.5-fold higher in the RA population than in the general population, and it probably relates to a combination of differences in traditional cardiovascular risk factors and RA disease–related factors.[1,6]

Assessment of Disease Activity

The prognosis of RA is affected by the severity of the disease and the effectiveness of treatment.[24] Clinical remission, defined as the absence of significant signs and symptoms of inflammation with or without additional treatment, occurs in 20% or less of patients. In contrast, remission or achievement of low disease activity (LDA), usually with continuing treatment, may be achieved in up to 75% of patients.[24] Despite achievement of LDA, radiographic evidence of the progression of joint damage and synovitis through monitoring of MRI or ultrasound results have been noted.[24] More than one-third of patients with clinical remission exhibit signs of synovitis on ultrasound.[25] In addition, rapid radiological progression in the first year after diagnosis is prognostic for functional disability over 8 years compared with persons without rapid progression.[26] Although radiographic evidence of disease progression 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.

A number of disease activity indexes have been developed for use in clinical trials and the office setting to standardize definitions and guide treatment. The development of standardized measures of disease activity (which define remission, LDA, and high disease activity [HDA]) allows for a "treat-to-target" strategy using pharmacologic therapy.[15] These targets allow physicians and patients to set goals for treatment. A detailed review of the indices/scales is beyond the scope of this manuscript, but a few will be briefly highlighted. The Disease Activity Score (DAS) 28 is a scoring of 28 tender or swollen joints, a patient global assessment, and a physician global assessment, along with ESR (DAS28-ESR) or CRP (DAS28-CRP).[24] Values define HDA, moderate disease activity (MDA), LDA, or remission. Changes in scores define improvement or worsening in disease, depending on the direction of the change. Other commonly used scales include the simplified disease activity index (SDAI), the clinical disease activity index (CDAI), the routine assessment of patient index data 3 (RAPID3), and the ACR criteria for percent improvement in involved joint count (eg, ACR20, ACR50, and ACR70).[27,28] Importantly, all of these indices are slightly different in the number and type of data points collected. It should be noted that ACR criteria and CDAI are generally used in randomized clinical trials, whereas RAPID3 (a measure of physical function, pain, and global status) is used mostly by US rheumatologists in clinical practice. A recent study compared HDA, LDA, and the achievement of remission (defined by 8 different indices) in patients treated with anti-TNF agents and found a large variation in resulting classification of LDA, HDA, and remission according to the various indices.[29] In keeping with these limitations of disease activity indices and their reliance on joint involvement, there is much interest in developing novel markers for early RA, and investigations are ongoing.[30]

For use in clinical trials, the ACR/EULAR recently recommended incorporation of 1 of 2 possible approaches to define clinical remission.[31] The investigators may select a Boolean criterion, wherein all 4 of the following must be satisfied: tender joint count of 1 or fewer, swollen joint count of 1 or fewer, C-reactive protein level of 1 mg/dL or less, and patient global assessment of 1 or fewer (on a 0-10 scale). Alternatively, the SDAI may be used with a target score of 3.3 or less.[31]

Established indices focus primarily on articular measures, but do not account specifically for extra-articular manifestations. The 2012 update of the 2008 ACR RA treatment recommendations provides guidance to determine disease activity (LDA, MDA, HDA, or remission) and features of poor prognosis.[32,33] Poor prognosis is associated with any of the following features of disease: functional limitation on standardized health questionnaires, extra-articular disease, positive RF, positive ACPA, or bony erosions documented by radiograph.

Conclusion

RA, a systemic autoimmune disease involving the joints and other organs, is associated with pain, disability, and mortality. Recent focus on identification of the disease earlier in the process, before extensive joint and bone damage occurs, brings hope for further improvements in the management of RA. Antigen presentation, T-cell activation, autoantibody production, TNF-α, and IL-6 are central mediators in the pathophysiology of articular and extra-articular RA. Standard disease activity indices may be used to guide treat-to-target approaches to pharmacologic intervention, which is the focus of the next article in this supplement.

Author affiliation: Weill Medical College of Cornell University, Hospital for Special Surgery, New York, NY.

Funding source: This activity is supported by an educational grant from Bristol-Myers Squibb.

Author disclosure: Dr Gibofsky reports consultancy/advisory board membership, honoraria, lectureship, and stock ownership with Abbott, Amgen, Genentech, Pfizer, and UCB. He also reports stock ownership with Johnson & Johnson and GlaxoSmithKline.

Authorship information: Analysis and interpretation of data; drafting of the manuscript; and critical revision of the manuscript for important intellectual content.

Address correspondence to: Mail to: Allan Gibofsky, MD, Hospital for Special Surgery, 535 E 70th St, New York, NY 10075. E-mail: gibofskya@hss.edu.

REFERENCES

1. McInnes IB, Schett G. The pathogenesis of rheumatoid arthritis. *N Engl J Med.* 2011;365(23):2205-2219.

2. Turesson C, Jacobsson L, Bergström U. Extra-articular rheumatoid arthritis: prevalence and mortality. *Rheumatology (Oxford).* 1999;38(7):668-674.

3. Moreland L. Unmet needs in rheumatoid arthritis. *Arthritis Res Ther.* 2005;7(suppl 3):S2-S8.

4. McCain JA Jr. Unmet needs in the treatment of rheumatoid arthritis. *Managed Care.* 2009;18(suppl 5):1-6.

5. Bansback N, Marra CA, Finckh A, Anis A. The economics of treatment in early rheumatoid arthritis. *Best Pract Res Clin Rheumatol.* 2009;23(1):83-92.

6. Gonzalez A, Kremers HM, Crowson CS, et al. Mortality trends in rheumatoid arthritis: the role of rheumatoid factor. *J Rheumatol.* 2008;35(6):1009-1014.

7. Arnett FC, Edworthy SM, Bloch DA, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum.* 1988;31(3):315-324.

8. Aletaha D, Neogi T, Silman AJ, et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Arthritis Rheum.* 2010;62(9):2569-2581.

9. Helmick CG, Felson DT, Lawrence RC, et al; National Arthritis Data Workgroup. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part I. *Arthritis Rheum.* 2008;58(1):15-25.

10. Silman AJ, Pearson JE. Epidemiology and genetics of rheumatoid arthritis. *Arthritis Res.* 2002;4(suppl 3):S265-S272.

11. Gibofsky A, Winchester RJ, Patarroyo M, Fotino M, Kunkel HG. Disease associations of the Ia-like human alloantigens: contrasting patterns in rheumatoid arthritis and systemic lupus erythematosus. *J Exp Med.* 1978;148(6):1728-1732.

12. de Pablo P, Chapple ILC, Buckley CD, Dietrich T. Periodontitis in systemic rheumatic diseases. *Nat Rev Rheumatol.* 2009;5(4):218-224.

13. van Venrooij WJ, van Beers JJ, Pruijn GJ. Anti-CCP antibodies: the past, the present and the future. *Nat Rev Rheumatol.* 2011;7(7):391-398.

14. van de Sande MG, de Hair MJ, van der Leij C, et al. Different stages of rheumatoid arthritis: features of the synovium in the preclinical phase. *Ann Rheum Dis.* 2011;70(5):772-777.

15. Isaacs JD. The changing face of rheumatoid arthritis: sustained remission for all? *Nat Rev Immunol.* 2010;10(8):605-611.

16. Huppa JB, Davis MM. T-cell-antigen recognition and the immunological synapse. *Nat Rev Immunol.* 2003;3(12):973-983.

17. Birbara CA. Management of inadequate response to TNF-α antagonist therapy in rheumatoid arthritis: what are the options? *The Internet Journal of Rheumatology.* 2008;5(2). doi:10.5580/1ddb.

18. Rasheed Z, Haqqi TM. Update on targets of biologic therapies for rheumatoid arthritis. *Curr Rheumatol Rev.* 2008;4(4):246.

19. Combe B. Progression in early rheumatoid arthritis. *Best Prac Res Clin Rheumatol.* 2009;23(1):59-69.

20. Gvozdenovic E, Koevoets R, van der Heijde D, Huizinga T, Allaart R, Landewé R. Assessment of global disease activity in RA patients monitored in the METEOR database: the patient's versus the rheumatologist's opinion. *Ann Rheum Dis.* 2012;71(suppl 3):653.

21. Somers TJ, Shelby RA, Keefe FJ, et al. Disease severity and domain specific arthritis self-efficacy: relationships to pain and functioning in patients with rheumatoid arthritis. *Arthritis Care Res (Hoboken).* 2010;62(6):848-856.

22. Myasoedova E, Crowson CS, Turesson C, Gabriel SE, Matteson EL. Incidence of extraarticular rheumatoid arthritis in Olmsted County, Minnesota, in 1995-2007 versus 1985-1994: a population-based study. *J Rheumatol.* 2011;38(6):983-989.

23. Boyer JF, Gourraud PA, Cantagrel A, Davignon JL, Constantin A. Traditional cardiovascular risk factors in rheumatoid arthritis: a meta-analysis. *Joint Bone Spine.* 2011;78(2):179-183.

24. Machold KP. Prevention and cure of rheumatoid arthritis: is it possible? *Best Prac Res Clin Rheumatol.* 2010;24(3):353-361.

25. Zufferey P, Möller B, Brulhart L, Tamborrini G, Scherer A, Ziswiler HR. Persistence of ultrasound synovitis in the patients fulfilling the DAS and/or the new ACR/EULAR RA remission definitions: results of the SONAR score applied to the patients of the SCQM cohort. *Ann Rheum Dis.* 2012;71(suppl 3):149.

26. van den Broek M, Dirven L, de Vries-Bouwstra J, et al. The clinical relevance of rapid radiological progression in the first year of treatment during 8 years of follow-up of early rheumatoid arthritis patients. *Ann Rheum Dis.* 2012;71(suppl 3):329.

27. Smolen JS, Breedveld FC, Schiff MH, et al. A simplified disease activity index for rheumatoid arthritis for use in clinical practice. *Rheumatology (Oxford).* 2003;4292:244-257.

28. Felson DT, Anderson JJ, Boers M, et al; American College of Rheumatology. Preliminary definition of improvement in rheumatoid arthritis. *Arthritis Rheum.* 1995;3896:727-735.

29. Hirano Y, Oishi Y, Yamauchi K. A comparative study of clinical composite measures (DSA28, SDAI, CDAI, Boolean) using patients with rheumatoid arthritis treated with anti-TNF agents. *Ann Rheum Dis.* 2012;71(suppl 3):372.

30. Somers K, Geusens P, Elewaut D, et al. Novel autoantibody markers for early and seronegative rheumatoid arthritis. *J Autoimmun.* 2011;36(1):33-46.

31. Felson DT, Smolen JS, Wells G, et al; American College of Rheumatology; European League Against Rheumatism. American College of Rheumatology/European League Against Rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. *Arthritis Rheum.* 2011;63(3):573-586.

32. Singh JA, Furst DE, Bharat A, et al. 2012 update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. *Arthritis Care Res (Hoboken).* 2012;64(5):625-639.

33. Saag KG, Teng GG, Patkar NM, et al; American College of Rheumatology. American College of Rheumatology 2008 recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis. *Arthritis Rheum.* 2008;59(6):762-784.