Rheumatoid Arthritis: Pathogenesis, Clinical Features, and Treatment

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1. Pathogenesis

Rheumatoid arthritis (RA) is a chronic, destructive, inflammatory arthropathy manifested by articular and extra-articular features. RA has profound effects on patient function and morbidity and exacts a substantial economic burden from affected persons. Although the pathology of the synovial inflammation and cartilage destruction that occurs in patients with RA has been described for decades, many important developments in the understanding of genetic influences and immunopathophysiologic mechanisms have recently been defined. Basic research delineating the molecular mechanisms of synovial inflammation has driven the development of innovative therapies for patients with RA. Hopefully, new genomic and proteomic information will allow further stratification identification of subsets of RA patients who respond better, longer, and with fewer adverse reactions to targeted therapies.

The pathobiology of RA involves a complex interaction of three different scientific domains: 1) a complex genetic predisposition to the disease plus some environmental stimulus; 2) a self-perpetuating, self-amplifying, intra-synovial immune response; and at the final stage, 3) tissue injury mediated by pro-inflammatory cells, inflammatory effector molecules, and degradative enzymes. In individuals with RA, this process is arthrotropic and produces a characteristic pathologic lesion in the synovium as well as the hallmark erosions of bone and destruction of cartilage at the joint margin.

The histopathology of RA synovium has been well described. The synovial lining, the interstitium, and the microvasculature are all involved. Early on in the process, the synovial lining, which includes both Type A (macrophage-like) and Type B (mesenchymal or fibroblast-like) cells, becomes proliferative. The synovial lining increases in cell number and mass. Likewise, a diffuse and nodular inflammatory cell infiltrate is observed in the interstitium. It includes CD4+ and CD8+ lymphocytes, dendritic cells, and other antigen presenting cells. In some patients, the histologic appearance is quite dramatic, showing focal aggregation of both T- and B-cells, as well as the presence of germinal centers similar to that which is seen in lymphoid tissues.

The synovium of the rheumatoid joint, although not malignant, often times behaves as a local invasive "tumor." The microvasculature initially reveals endothelial cell activation. As the process matures, plasma cells and multinucleated giant cells appear, and the vascular supply becomes exuberant. Finally, the growing synovium appears as granulation tissue as it advances to the hyaline cartilage at the margin of the joint. A local effect of degradative enzymes and activated osteoclasts produces the classic erosion at the bone and cartilage margin. These enzymes may also affect structures that are more distant, including the tendons, ligaments, and other musculoskeletal structures. Erosions are produced by bone and matrix protein resorbing osteoclasts, which may be induced and activated by cytokines released into the inflammatory milieu. Some of the scientific observations that explain these phenomena are noted below.

Genetics and Environmental Stimulus

Genetic contributions to the pathogenesis of rheumatoid arthritis (RA) are very complex. Genetic studies in families of patients with RA suggest that monozygotic twins have a concordance rate for RA of between 15%-30%. Thus, genetic factors contribute to susceptibility but are not the whole story. Obviously, there must also be some triggering mechanism. It is certain that RA is a polygenic disease in which some genes may drive the initiation of the disease while others may impact the response to therapy or define disease severity and prognosis.

Approximately 2 decades ago, certain alleles of the HLA-DR4 locus were found to be associated with RA in Caucasian patients. Most scientific evidence now suggests that certain genes within the major histocompatibility complex (MHC), located on the short end of chromosome 6 play the most significant role in the initiation of the rheumatoid disease process. Susceptibility to RA can be explained by the shared epitope hypothesis, ie, a 5-amino acid sequence found on several HLA-DR4 alleles defines a structural domain that confers susceptibility to RA. Recent studies suggest that the clinical phenotype of RA (ie, destructive joint disease and extraarticular manifestations) is also associated with certain genes within the MHC. Evidence also suggests that there are RA susceptibility genes on other chromosomes that appear to correlate with the phenotypic presentation of RA. Recently, allelic variations in PTPN22, a gene that encodes a tyrosine kinase involved in inhibition of T-cell activation, have been shown to be associated with RA.

There are several ways HLA-DR alleles could confer susceptibility to RA. In the simplest scenario, a peptide derived for example from a microbial protein could bind to HLA-DR, and via standard antigen presentation mechanisms trigger the proliferation of antigen-specific T-lymphocytes. If the inciting microbe selectively infects synovial cells and the resulting immune response is unable to clear the microbial infection, chronic synovial inflammation might ensue. Alternatively, antigen-specific T-cells activated in response to a microbial peptide could recognize a self-peptide derived from a protein that is selectively expressed in synoviocytes, a process known as molecular mimicry. However, although myriad organisms have been proposed to predispose to RA over the years, conclusive evidence for any single cause is lacking. Moreover, the dosage effect of HLA-DR in RA (ie, persons with 2 copies of the shared epitope containing MHC Class II allele are more likely to have RA than those with a single copy) argues against simple antigen presentation being the relevant mechanism. More likely, presence of disease associated HLA-DR alleles modifies the T-cell-receptor repertoire during thymic selection.

Other factors are also involved in the triggering of RA in susceptible persons. One factor (not entirely extragenetic) is female sex. Particularly at younger ages of onset, RA is more common in women than in men, with a ratio of about 3:1. Whether this difference reflects hormonal differences, genetic factors involved in the presence or absence of the Y chromosome, or genetic factors in the random inactivation of one X chromosome is not known. Another factor may be the microbial flora (both pathogenic and commensurate) to which persons are differentially exposed, as mentioned above. Finally, it is possible that stochastic processes involved in the formation of the T-cell–receptor repertoire can, in a genetically susceptible person, produce a propensity for disease, the inheritance of which does not follow the rules of Mendelian genetics. At some point, the susceptible host's genome, interacting perhaps with some exogenous factor, be it an infectious antigen or self-protein, induces the next phase in pathogenesis.

Intrasynovial Immune Response

The presence of activated T-cells, increased concentrations of pro-inflammatory mediators, and endothelial activation within the synovium appear to implicate an aberrant self-perpetuating and self-amplifying immune response central to the initiation and sustenance of rheumatoid synovitis. Animal models of autoimmunity strongly support a role for the T-cell–receptor recognition of MHC–peptide complexes in the initiation and propagation of autoimmune disease. In most animal models, the specific antigen responsible for the induction of autoimmunity is known (eg, type II collagen in collagen-induced arthritis) and the MHC molecules that bind the peptide antigen, as well as the T-cell receptors that recognize the resulting complex, can be determined experimentally. Under these experimental conditions, interventions that disrupt this quaternary complex (eg,

antibodies recognizing involved T-cell–receptor V regions or specific MHC alleles) ameliorate autoimmune disease. Both CD4+ and CD8+ T-cells can contribute to the initiation and propagation of autoimmune disease in animal models. Often both cell types are required to produce disease. Although it is likely that human autoimmune disease is also initiated by the recognition of self-MHC–peptide complexes by CD4+ or CD8+ T-cells, it is not yet possible to identify triggering antigens. The identification of such antigens would greatly facilitate the design of antigen-specific therapies for human autoimmune disease. Although the evidence implicating CD4+ T-cells in the initiation of RA is strong, an essential role for other cell types is certain. Activated macrophages found in synovial tissues are a major source of cytokines such as tumor necrosis factor-alpha (TNF-α), which suggests an important role for this inflammatory cytokine in this disease. Fibroblasts, mast cells and B-cells have also been shown to be capable of significantly contributing to the generation of rheumatoid inflammation.

Effector Molecules and Cartilage Damage

Once this biologic inflammatory process has matured, it appears to be regulated and amplified by inflammatory cells and their regulatory proteins, the most notable of which include the pro-inflammatory cytokines. T-cells and antigen presenting cells directly (by cell to cell contact) and indirectly (by other signals) stimulate macrophages to secrete interleukin-1 (IL-1) and tumor necrosis factor-alpha (TNF-α), among other inflammatory mediators. IL-1 and TNF-α or their mRNA have been identified in the serum, synovial fluid, and tissues of patients with RA. Both of these cytokines have broad biologic effects, including the induction by synoviocytes of matrix metalloproteinases as well as the inhibition of tissue inhibitors of metalloproteinases (TIMPs). In vivo and in vitro studies have documented that recombinant IL-1 and TNF-α injure normal hyaline cartilage. Chondrocytes, in particular, enter a catabolic phase when exposed to these cytokines, leading to an increase in collagenase production and a decrease in matrix protein synthesis. TNF-α also induces adhesion molecules, eg, the intracellular adhesion molecule 1 (ICAM-1), which may in turn affect the homing and trafficking of inflammatory cells into the synovium. The "proof of concept" that TNF is an important mediator in the pathobiology of

RA has been clearly shown by the profound clinical effects of the anti-TNF therapies (ie, infliximab, etanercept, and adalimumab), on the signs, symptoms and structural damage that characterizes RA. Finally, the invasive nature of the RA pannus has suggested to some observers that the tissue behaves like a locally invasive tumor. Indeed, growth factors such as TGF-β and FGF produced locally in the synovium by resident macrophages and fibroblasts may provide the drive for tissue expansion.

Certain autoantibodies are associated with RA. The most characteristic, certainly from a historical perspective is rheumatoid factor (RF). The landmark discovery of RF which is present in approximately 75%-85% of people with RA, marked the beginning of the understanding that RA is a systemic autoimmine disease. Although it is relevant to the diagnosis of RA, RF may be of greater value to the clinician in prognosis. Epidemiologic observations suggest that the presence of the RF is a marker that predicts more serious disease. Rheumatoid factors are autoreactive antibodies that bind to the Fc portion of IgG molecules. RF is not specific for rheumatoid arthritis, as it is observed in a host of other autoimmune disorders or infectious diseases. Also, by definition of how the test is performed, 5% of the normal population will have a positive test for RF. RF of isotypes indicative of class switching (ie, IgG and IgA, rather than IgM) may be more specific, as are higher titers. Although the potential contribution of RF to the pathogenesis of RA is unclear, it has been suggested that RF may induce tissue damage by acting as immune complexes. Over the years, a variety of other autoantibodies have been reported to be associated with RA, including antikeratin antibodies, antiperinuclear factor, and antifilaggrin antibody. It has been demonstrated that the antigen recognized in common by these antibodies is citrullinated protein. Citrulline is a nonstandard amino acid created by the de-amination of arginine residues in proteins by the enzyme peptidyl arginine deiminase (PADI). Interestingly, in some populations, allelic variations in the genes encoding PADI have been shown to correlate with RA. Tests for anti-CCP (cyclic citrullinated peptide) antibodies are as sensitive as RF for the diagnosis of RA and are more specific. Similarly, high titers of anti-CCP antibodies define patients with a more aggressive disease phenotype.

2. Epidemiology

RA occurs worldwide in virtually all ethnic groups, with a prevalence estimated between 0.5% and 1%. Notable exceptions include a prevalence of 5% or more in certain North American indigenous populations (eg, the Yakima and Pima tribes) and a very low prevalence in sub-Saharan Africa. It is significantly more common in females than in males (about 3:1 female: male ratio). Recently, an inception cohort study in Rochester, Minnesota established the annual incidence rate at 75.3 per 100,000 with a point prevalence of ~1%. There are some interesting epidemiologic trends from the Finnish Health Care system that suggest that over recent years the overall prevalence of RA may be dropping and that it also may be occurring later in life.

Mortality rates of a cohort of 75 patients with RA followed over 15 years in a university hospital outpatient clinic have been reported to be 1.5- to 2-fold higher than those of the United States population matched for age and gender. Similarly, an analysis of the Mayo Clinic and surrounding area population revealed that although the life expectancy had increased in the general population from 1955 to the present, it had not changed for those patients with RA. Death most often results from infection, heart disease, respiratory failure, renal failure, or gastrointestinal disease rather than from joint disease itself. Specifically, accelerated atherosclerotic disease may afflict RA patients. Whether this is due to an inflammatory pathobiology or to exposure to antirheumatic drugs (ie, glucocorticoids) or both is unclear. A recent cohort study found that greater number of involved joints, decreased functional status, presence of comorbid cardiovascular disease, older age, and fewer years of formal education were all significant predictors of mortality in RA. Five-year survival of those patients with the poorest functional status was 40%-60%, which is comparable to that of patients with three-vessel coronary artery disease or stage IV Hodgkin's disease. Notably, it seems that effective therapies may have a positive effect on this trend, and it has been shown that treatment with methotrexate and TNF-inhibitors may positively impact survival among RA patients.

3. Clinical Features

RA is characterized by symmetrical synovitis involving multiple diarthrodial joints as well as extra-articular features. Recent investigations have clarified the severe effects that RA can have on a person's function and mortality. Epidemiologic and genetic studies have identified specific markers that correlate with disease severity and prognosis. With the more widespread use of aggressive therapeutic regimens, including accelerated doses of methotrexate, combination DMARD therapy, new DMARDs such as leflunomide, and the use of new biologic response modifiers (etanercept, infliximab, adalimumab, and anakinra, abatacept and rituximab), some of the manifestations of RA appear to be changing. For example, it has been suggested that features classically associated with very aggressive disease, such as rheumatoid vasculitis, are less commonly observed currently.

In 1987, the criteria for the classification of RA were revised by a committee of the American College of Rheumatology (ACR). These diagnostic criteria were not intended to establish a diagnosis clinically. Rather, they were designed to define homogeneous cohorts of patients for clinical research (Table 1). Likewise, in 1991 the Steinbrocker criteria for the classification of functional capacity in RA were revised by another committee of the ACR (Table 2). These criteria were designed to define the level of clinical disability in RA patients, which is rapidly becoming an important clinical endpoint and stratification variable in RA drug trials.

Clinical Presentation

Most patients with RA note a gradual onset of joint inflammation over weeks to months; however, 10%-20% may develop the classic joint stiffness, pain, and swelling of RA acutely. Some patients have a waxing and waning course sometimes referred to as "palindromic rheumatism"; it may be several years before the chronic, persistent features of RA become evident. Systemic symptoms, such as malaise, fatigue, and weakness often accompany the signs and symptoms of joint inflammation.

Based on cross-sectional studies of patients with RA, elderly-onset RA with onset at age 60 years or older has been considered to be a clinical entity distinct from younger-onset RA. However, the evidence from

Table 1

**1987 American College of Rheumatology Criteria for
the Classification of Rheumatoid Arthritis***

1. Morning stiffness in and around the joints lasting at least 1 hour before maximal improvement

2. At least 3 joint areas simultaneously have had soft tissue swelling or fluid (not bony overgrowth alone) observed by a physician. The 14 possible areas are: right or left PIP, MCP, wrist, elbow, knee, ankle, and MTP joints

3. At least 1 area swollen (as defined above) in a wrist, MCP, or PIP joint

4. Simultaneous involvement of the same joint areas (as defined in 2) on both sides of the body (bilateral involvement of PIPs, MCPs, or MTPs is acceptable without absolute symmetry)

5. Subcutaneous nodules over bony prominences, extensor surfaces, or in juxta-articular regions, observed by a physician

6. Demonstration of abnormal amounts of serum rheumatoid factor by any method for which the result has been positive in less than 5% of normal control subjects

7. Radiographic changes typical of rheumatoid arthritis on posteroanterior hand and wrist radiographs, which must include erosions or unequivocal bony decalcification localized in or most marked adjacent to the involved joints (osteoarthritis changes alone do not qualify)

* For the diagnosis of RA, 4 of the 7 criteria are required.
MCP = metacarpophalangeal; MTP = metatarsophalangeal; PIP = proximal interphalangeal

Table 2

**1991 American College of Rheumatology Revised Criteria
for Classification of Functional Status in Rheumatoid Arthritis***

Class I	Completely able to perform usual activities of daily living (self-care, vocational, and avocational)
Class II	Able to perform usual self-care and vocational activities, but limited in avocational activities
Class III	Able to perform usual self-care activities, but limited in vocational and avocational activities
Class IV	Limited in ability to perform usual self-care, vocational, and avocational activities

* Usual self-care activities include dressing, feeding, bathing, grooming, and toileting. Avocational (recreational and/or leisure) and vocational (work, school, homemaking) activities are patient-desired and age- and sex-specific.

observational studies has been conflicting. The clinical presentation of elderly-onset RA may be similar to that of polymyalgia rheumatica, with an abrupt onset of shoulder and hip joint inflammation. Other studies have found the anatomic distribution of joint inflammation in patients with elderly-onset RA to be similar to that of patients with younger-onset RA. Rheumatoid nodules and serum rheumatoid factor have been observed less often in patients with elderly-onset RA than in those with younger-onset RA. Some authorities believe that elderly-onset RA usually follows a relatively benign course and generally responds well to treatment. However, a recent study of consecutive patients who presented to a university hospital rheumatology clinic found few significant differences between elderly-onset RA and younger-onset RA at the time of disease onset.

Joint Manifestations

Morning gel describes a peculiar stiffness that is pronounced in the morning or after periods of inactivity. It plagues most patients with active inflammatory arthritis, including those with RA. Its duration and quality oftentimes provide the clues to early diagnosis of an inflammatory arthropathy. The clinical hallmark of RA is a symmetrical polyarthritis involving the proximal interphalangeal joints (PIPs), metacarpophalangeal joints (MCPs), wrists, elbows, shoulders, hips, knees, ankles, and metatarsophalangeal joints (MTPs). Although fully expressed RA may involve multiple joints, it normally begins in one or a few joints and typically evolves in an additive fashion. The hands and wrists are affected in approximately 90% of RA patients, and these joints may show unique changes over time. Early in RA, joint tenderness and subtle swelling are observed, but after months to years the synovitis becomes proliferative and destructive. The tissue within the joint becomes boggy to the touch, then typical joint deformities appear, including ulnar drift at the MCPs, rotatory subluxation at the wrist (ulnar styloid), and the "swan-neck" (flexion of DIP, hyperextension of PIP) and "boutonniere" (hyperextension of DIP, flexion of PIP) deformities.

Although over 70% of patients with RA display radiographic evidence of erosions adjacent to small joints of the hands and feet within the first 2 years after diagnosis, about 25% of patients with early RA may not develop erosive damage even after 8 years or more of follow-up. Most studies involving an inception cohort of patients suggest an overall, relatively linear rate of joint damage progression. The development of erosions correlates with the persistence of inflammation, as evidenced by clinical measures of morning stiffness, synovial swelling, and elevation of erythrocyte sedimentation rate and other acute phase reactants. Magnetic resonance imaging (MRI) visualizes and quantifies tissue or "synovial load" and also detects early invasion of pannus into hyaline cartilage and sub-chondral bone. There is also increasing interest in the use of ultrasonography, which can visualize bony erosions, joint fluid, and synovial hypertrophy.

A syndrome of "pseudo-thrombophlebitis" can be seen in RA patients with active synovitis of the knee. Typically, a swollen, warm, tender calf causes problems with weight bearing, and the physical examination findings clearly mimic that of deep venous thrombophlebitis. The cause is typically a large, draining popliteal cyst, and for this reason, noninvasive lower extremity studies of the deep venous system are typically negative.

The cervical spine is a common site of involvement in RA. In autopsy studies, up to 50% of patients with RA show some cervical spine involvement. There is a direct relationship between cervical spine disease and the presence of erosive peripheral joint disease. Proliferative synovitis can damage the ligaments and articular cartilage of the cervical spine, causing several types of cervical spine instability. These include: 1) atlantoaxial subluxation in 50%-70% of patients; 2) subaxial subluxation in 20%-25% of patients; and 3) basilar invagination into the foramen magnum alone or in combination with atlantoaxial subluxation in approximately 20% of patients. Symptoms of cervical spine involvement in RA include neck pain, occipital headache, and paresthesias in the extremities. Basilar invagination may cause symptoms of vertebrobasilar insufficiency, such as tinnitus, vertigo, visual disturbances, and dysphagia. Spinal cord compression may cause weakness or paralysis. Assessment of the potential for neurologic injury is especially important in patients with advanced RA requiring general anesthesia because of the risk of cervical cord compression during intubation. Plain lateral radiographs of the cervical spine with gentle flexion and extension views are used to quantify the degree of instability.

Pleuropulmonary Manifestations

Abnormalities of the pleura and lungs have been detected by high-resolution computed tomography (HRCT) in up to 75% of patients with RA. However, pleura inflammation is often asymptomatic and may not be detected until chest radiographs are done for other reasons. The prevalence of pleural effusion in RA is only about 5%. In some patients the pleural fluid glucose may be dramatically low compared to serum levels. Although it may present rarely before arthritis is manifested, pleural effusion usually occurs in individuals with active established RA. About one-third of patients with RA with pleural effusions have coexisting interstitial lung disease.

Interstitial pulmonary fibrosis occurs in 20%-40% of patients with RA, more commonly in patients with rheumatoid nodules and serum rheumatoid factor. It can be asymptomatic in its early stages because the decreased physical activity of patients with RA may be insufficient to induce dyspnea. The early radiographic changes of interstitial pulmonary fibrosis, consisting of ground-glass opacities predominantly in the lower lungs, may not be evident on conventional plain radiographs but appear as high-attenuation lesions at the periphery of the lungs on HRCT. Compared to HRCT, pulmonary function testing, especially assessment of residual volume, is a more sensitive but relatively nonspecific indicator of interstitial pulmonary fibrosis in RA. Increased numbers of activated T-lymphocytes, predominantly T-helper (CD4+) cells, are evident in the bronchoalveolar fluid of patients with RA with interstitial pulmonary fibrosis, compared to patients with RA without lung disease and healthy persons. Interstitial lung disease in patients with RA may also be a complication of gold or methotrexate therapy, and there have also been anecdotal reports associated with the TNF inhibitors.

Because transbronchial biopsies do not provide enough tissue for reliable diagnosis, the pattern of lung disease in patients with RA for whom treatment for pulmonary symptoms is being contemplated is best determined by open-lung biopsy. Various histologic patterns have been described, including pulmonary rheumatoid nodules, usual interstitial pneumonitis (UIP), bronchiolitis obliterans with patchy organizing pneumonia (BOOP), lymphoid hyperplasia, and cellular interstitial infiltrates. Patients with rheumatoid nodules, lymphoid hyperplasia, or non-specific cellular interstitial infiltrates have a better prognosis than patients with UIP.

Pulmonary rheumatoid nodules may occasionally be visualized on routine radiographs and confused with malignancy. Occasionally, these nodules may cavitate. The unique entity of Caplan's syndrome defines multiple pulmonary nodules with cavitation in coal miners exposed to dust and other inhalants.

Cardiac Manifestations

Symptomatic cardiac involvement is rare in patients with RA; however, echocardiography has shown the prevalence of asymptomatic cardiac involvement to be higher than previously reported in autopsy studies. In a study of patients with RA and no cardiac symptoms, there was a significantly increased prevalence of posterior pericardial effusion (57.1%), mitral valve prolapse (34.3%), mitral valve thickening (22.9%), aortic root dilatation (34.3%), and aortic valve thickening (20.0%) compared to healthy persons. Myocarditis and endocarditis are not commonly seen in patients with RA. Areas of focal myocarditis are seen at autopsy but are clinically insignificant. Arrhythmias secondary to involvement of the conduction system by myocarditis, vasculitis, or nodules can occur but are exceedingly rare. Endocardial disease in the form of nonspecific valvulitis has been observed in up to 70% of autopsied cases but is usually asymptomatic and generally goes unrecognized during life. Rarely, valvular dysfunction may be caused by rheumatoid nodules. Aortitis, most commonly involving the thoracic aorta, was identified in 10 of 188 consecutive autopsied cases of patients with RA and was associated with the presence of serum rheumatoid factor, subcutaneous nodules, and rheumatoid vasculitis involving vessels other than the aorta.

Felty's Syndrome and Pseudo-Felty's Syndrome

Felty's syndrome, which was reported in previous years in as many as 1% of patients with RA, was originally described as the association of RA with leukopenia and splenomegaly. It was frequently associated with the presence of rheumatoid nodules, Sjögren's disease, and other extra-articular manifes-

tations. Felty's syndrome typically occurred in older patients with advanced erosive RA of at least 10 to 20 years' duration. Almost all Caucasian patients with Felty's syndrome were positive for HLA-DR4. Serum rheumatoid factor is almost always present, usually in high titer, and antinuclear antibodies (most commonly antihistone antibodies) are present in 47%-100% of patients with Felty's syndrome. The prevalence of Felty's syndrome and some other severe extra-articular manifestations of RA appear to be decreasing over recent years, possibly in conjunction with the more common use of highly effective treatment regimens.

Large granular lymphocytes (LGLs) normally comprise 10%-15% of circulating peripheral blood mononuclear cells. These LGLs contain azurophilic granules scattered in the cytoplasm and can be divided into two subgroups: natural killer cells (CD3-, CD16+, CD56+) and CD3+ LGLs (CD3+, CD16+, CD56+), which are a subpopulation of T-cells. Both subgroups of LGL are capable of non-MHC-restricted cytotoxicity and can secrete a variety of cytokines. Patients with clonal or polyclonal proliferations of LGL, more commonly of CD3+ LGL, are considered to have a form of chronic lymphoproliferative disease called the *large granular lymphocyte syndrome.* Many of these patients' cells display restricted T-cell–receptor gene rearrangements, but a specific common pattern of variable (V), diversity (D), and joining (J) region T-cell receptor b-chain gene usage is not observed when different patients are compared.

RA is the disease most frequently associated with the LGL syndrome (up to 39% of patients). Patients with the LGL syndrome and RA exhibit idiopathic neutropenia and splenomegaly, a condition called pseudo-Felty's syndrome. Because of an increased number of LGLs, the total leukocyte count may be normal in patients with pseudo-Felty's syndrome. Similar to patients with Felty's syndrome, patients with pseudo-Felty's syndrome have serum rheumatoid factor and other autoantibodies and are susceptible to frequent infections. However, extra-articular manifestations and severe erosive arthritis are less common among patients with pseudo-Felty's syndrome.

Rheumatoid Nodules

Rheumatoid nodules occur in approximately 15% to 40% of patients with RA and are associated with the presence of serum rheumatoid factor, erosive joint destruction, necrotizing vasculitis, and other extra-articular manifestations of RA. They usually occur in areas that are repeatedly subjected to friction or pressure, such as the extensor surface of the forearm or the Achilles tendon; however, nodules may also develop in viscera such as the heart and lungs. Histologically, rheumatoid nodules contain a central area of necrosis encircled by palisading histiocytes, which are surrounded by granulomatous tissue infiltrated with lymphocytes.

Patients receiving low-dose methotrexate therapy for RA may develop accelerated rheumatoid nodule formation despite good control of joint inflammation. These nodules are usually smaller than 5 mm and are located on the fingers, although they may be present at other sites.

Malignancy

The overall incidence of cancer in patients with RA is not increased; however, patients with RA have an increased risk of developing lymphomas and lung cancer, and a decreased risk for developing cancers of the colon, rectum, and stomach. The low risk of colorectal cancer among RA patients may be related to their common use of nonsteroidal anti-inflammatory drugs (NSAIDs).

Patients receiving methotrexate therapy for RA have developed non-Hodgkin's lymphoma, which may regress with the discontinuation of methotrexate therapy, as occurs with lymphomas in patients receiving immunosuppressive drugs after organ transplantation. These reversible lymphomas are usually diffuse, large-cell lymphomas of B-cell lineage. Epstein-Barr virus genome and latent membrane protein have been detected in lymphomas of patients with RA who were treated with methotrexate alone or with cyclosporin A, suggesting that immunosuppression may have contributed to the development of these lymphoid neoplasms. Recently, there has been some concern as to whether patients treated with TNF inhibitors may be at greater risk of developing lymphomas, particularly

non-Hodgkin's lymphoma (NHL). Analysis of any increased risk attributable to therapy is compounded by the fact that patients with severe RA are at greater risk of developing NHL than the general population, and the risk correlates with the severity and activity of disease. Of note, this has been the subset of RA patients for whom TNF inhibitor therapy has been most widely utilized. At present, it seems that much of the increased risk observed among patients treated with TNF inhibitors relates to the activity and severity of RA, but this bears close observation.

4. Prognosis

The clinical expression of RA is usually established in the first 2 years, although the disability measures almost always get worse with time. As mentioned previously, mortality studies suggest that patients with severe RA die at an accelerated rate due to infection, cardiopulmonary disease, and gastrointestinal bleeding. Results from a recent observational study suggest that patients who are unresponsive to methotrexate may have a significantly higher mortality risk compared to those patients who do respond to methotrexate. The presence of serum rheumatoid factor in patients appears to best predict the subsequent development of RA for patients presenting with undifferentiated polyarthritis. Patients who have elevated titers of serum rheumatoid factor and anti-CCP antibodies early in the course of disease more often develop erosive joint disease than patients who are seronegative. High titers of rheumatoid factor are also associated with the appearance of extra-articular manifestations. Likewise, RA patients who have the HLA-DR4 haplotype usually have a poorer clinical outcome.

Most patients with RA have a slowly progressive course characterized by exacerbations and improvements. Long-term studies have shown that fewer than 10% of patients with RA ever go into a prolonged remission. Greater number of tender or swollen joints at disease onset has been correlated with increased disease activity and joint erosion. Lower socioeconomic status and fewer years of formal education, which is a component of or a surrogate marker for lower socioeconomic status, have been associated with higher morbidity and mortality in RA.

Defining markers of a bad prognosis early on in RA facilitates therapeutic decision-making. Historically, second-line therapy was reserved for severe refractory patients who had unremitting disease for years. With recent evidence suggesting that erosions appear early, there is a new emphasis on treating RA patients earlier with second-line agents. Bad prognostic features include: RF and anti-CCP seropositivity; evaluated markers of inflammation (ESR and CRP); rheumatoid nodules; extra-articular features; larger numbers of active joints; early functional impairment; and early appearance of erosions. These features should trigger the instinct to treat more aggressively. However, as always, the patient must be educated about the risks and benefits of such approaches and participate actively in the deci-

sion-making. Also, the above associations, while certainly true for large groups of patients, may not be applicable for a single patient: The exceptions can prove the rule.

5. Therapy

Background

RA is a chronic progressive disease, punctuated by periods of exacerbation and remission. Over 5 to 10 years, this "saw tooth" natural history leads to structural joint damage and deteriorating musculoskeletal function. One subset of RA patients progress early and inexorably to functional disability and total joint replacement despite aggressive treatment. On the other end of the clinical spectrum, some individuals have mild RA with long periods of inactivity, a pauci-articular disease expression, or a short course of active arthritis followed by total remission. Although those remitting patients have clinical findings that satisfy published criteria for the diagnosis of RA during periods of active disease, many experts believe that they may in fact not have RA but some other reactive, inflammatory, self-limited arthropathy. Complicating this clinical heterogeneity is a lack of simple surrogate markers that indisputably predict long-term outcome in every single patient; therefore, in practice, customizing therapy by risk and benefit is difficult.

The history of anti-inflammatory drug development dates to the early part of the 20th century, when bed rest, painkillers, salicylates, and homeopathic remedies were standard practice. In the late 1940s and early 1950s, corticosteroids were discovered. When administered to patients with RA, the dramatic improvements they induced caused them to be considered "miracle drugs." Soon thereafter, appreciation of the adverse effects related to their use tempered enthusiasm. Other than acetylsalicylic acid (aspirin), the first of many NSAIDs, phenylbutazone, was developed and also proved to be effective for patients with arthritis. Interestingly, it was during this same time that aminopterin, the parent compound of methotrexate, was initially identified and administered successfully to patients with RA. Soon thereafter, gold salts were proven to be effective in the first prototype of a well-designed trial of a disease-modifying antirheumatic drug (DMARDs). Most recently, biologic drugs specifically targeted to components of the immune system have been introduced into the clinic.

Table 3

Clinical Evaluation of Rheumatoid Arthritis

	Classification of Disease Activity	
	Slowly Progressive	**Aggressive**
Swollen joints	Few	Many
ESR or CRP	Normal or modestly elevated	Markedly elevated
Radiographic erosions	Absent	May be present
Rheumatoid nodules	Absent	May be present
Extra-articular manifestations	Absent	May be present
Rheumatoid factor or anti-CCP	Normal or modestly elevated	Markedly elevated
Functional status	Preserved	Impaired

CRP = C-reactive protein; ESR = erythrocyte sedimentation rate.
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Dallas, Tex: The University of Texas Southwestern Medical Center at Dallas; 1996.

General Approach to Treatment

Although RA treatment approaches are highly individualized, according to practitioner experience and patient preference, several trends deserve mention. Controlling pain is a critical objective, but RA with active inflammation needs to be differentiated from the mechanical pain that can arise with joint deformity, because management strategies will differ. Specifically, pain from end-stage mechanical joint problems may not necessarily require the use of potentially toxic immunosuppressive drugs. The level of intensity of the therapeutic approach needs to be developed with the cooperation of the patient. Treatment algorithms should always be used as a guideline to be modified by the actual clinical circumstances—not as a rigid treatment protocol. The critical step in determining treatment guidelines involves differentiating slowly progressive from aggressive disease as outlined in Table 3.

Before 1989, when the early and widespread use of methotrexate became commonplace, the treatment pyramid of RA was popularized. During this period, overly aggressive treatment with corticosteroids and other second-line drugs was eschewed because of the concern for toxicity and because the disease was regarded as nonfatal and only modestly disabling. Initial drug therapy included months to years of high-dose salicylates or NSAIDs superimposed on a broad base of patient education, rest, modest exercise, and the use of assistive devices. Only with the widespread appearance of erosions on radiographs would second-line drugs be prescribed. During the 1980s, mean disease duration for many second-line drug trials was in the 5- to 7-year range.

Traditional Treatment Pyramid

Prior to 1990, standard rheumatologic practice involved a step-wise, conservative approach in the early phases of the disease termed the RA treatment pyramid. For the purpose of future discussion of RA

treatment algorithms, this pyramid will be described here. The driving philosophy was that more toxic, but perhaps more effective, drugs would only be used after a prolonged period of persistent inflammation, often after patients had developed erosive disease. At the base of the pyramid lay the broad platform of physical medicine modalities, pain management, patient education, and "watchful waiting." The next level involved prescribing salicylates and non-steroidal anti-inflammatory drugs (NSAIDs) to reduce pain and suffering while optimizing exercise and physical therapy approaches and awaiting (hopefully) spontaneous disease remission. After a period of unremitting disease (often lasting for years) followed by structural damage, the disease modifying antirheumatic drugs (DMARDs) might be added as the third tier of the pyramid. The rationale for the delay here was that DMARDs (including intramuscular gold, methotrexate, and immunosuppressive drugs) were only worth the risk of adverse events in patients with chronic, progressive disease who were at risk of joint destruction. For the unfortunate patient who did not respond to these modalities, the fourth level of treatment would include experimental therapies (usually under scientific protocol). Finally, glucocorticoids (both systemic and intra-articular) could be used at all levels of the treatment pyramid for patients at the early, middle, or later stages of disease.
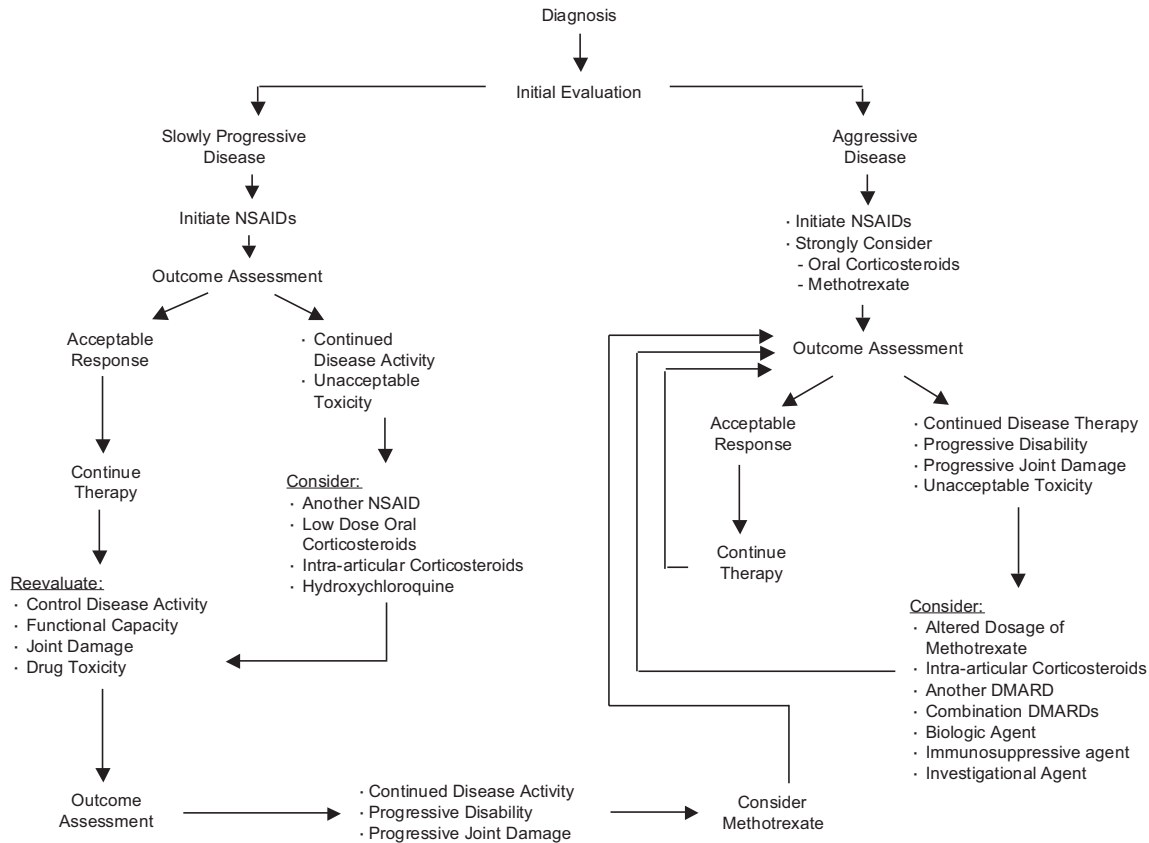
Early Aggressive Therapy

Because patients treated by the pyramid approach frequently suffered through years of smoldering disease, a more aggressive approach has been embraced recently. Although the rationale for this aggressive treatment paradigm is being presently debated, emerging practice patterns suggest that rheumatologists are adopting this approach. Several events have forced a reevaluation of the traditional treatment pyramid. First, the toxicities (especially gastrointestinal and renal) of the traditional NSAIDs and salicylates are now more apparent. Large databases of patients with RA and other musculoskeletal diseases suggest an excessive rate of gastroduodenal ulcers, GI perforation, or GI bleeding in individuals exposed chronically to these drugs. So, the notion that these agents (used early and often in RA patients) have a "benign" toxicity profile is under increased scrutiny. Second, newer, more effective DMARD drugs are used earlier in patients with RA. Specifically, methotrexate shed

its negative aura as a cancer chemotherapy agent and randomized, controlled trials showed impressive efficacy. As observational studies suggested, due to continued long-term effectiveness and an acceptable toxicity profile in the real world of rheumatology practice, methotrexate became the gold standard treatment for patients with moderate RA. Third, long-term epidemiologic studies now suggest that the conservative, step-wise pyramid treatment approach leaves many patients with smoldering disease for long periods of time, resulting in poor long-term functional outcome. In addition, several studies have documented initiation and significant progression of structural damage early in the course of RA. Specifically, imaging techniques (especially MRI) have identified the presence of early erosions and marrow effects of pannus in the absence of radiographic abnormalities, suggesting that irreversible damage may occur long before traditional outcome parameters are able to detect it. Fourth, several simple prognostic clinical measures have been linked to poor outcome. These include: 1) persistent joint inflammation or multiple affected joints; 2) elevated titers of rheumatoid factor or anti-CCP antibodies; 3) radiographic erosions; 4) extra-articular features; and 5) early functional impairment. Finally and most importantly, the advances in molecular and genetic medicine have elucidated a new understanding of RA pathogenesis that has now reached clinical practice. In the last decade, 6 new biologic therapies that have revolutionized the RA treatment scheme have been approved by regulatory authorities and introduced into the clinic. These include: the p75-soluble TNF-α receptor-Ig Fc piece fusion protein (etanercept); a chimeric monoclonal antibody to TNF-α ligand (infliximab); a human anti-TNF-α antibody (adalimumab); an interleukin-1 receptor antagonist (anakinra), an inhibitor of T-cell costimulation (CTLA-4Ig; abatacept); and a chimeric monoclonal antibody to the B-cell molecule CD20.

These recent trends in rheumatology practice have driven the concept of "inversion of the pyramid," ie, DMARDs and the newer drugs are instituted early in disease and in novel combinations in RA patients having poor prognostic features. Concomitantly, the use of NSAIDs would be used for "breakthrough" pain, general palliation, or perhaps not at all (if pain is well managed). NSAID drug holidays, therefore, are more frequent, and hopefully, GI toxicity will be minimized. Likewise, COX-2 specific inhibitors, which

Figure 1

Medical management of rheumatoid arthritis

Diagnosis
→
Initial Evaluation

Slowly Progressive Disease
↓
Initiate NSAIDs
↓
Outcome Assessment
→ Acceptable Response / · Continued Disease Activity · Unacceptable Toxicity

Acceptable Response
↓
Continue Therapy
↓
Reevaluate:
· Control Disease Activity
· Functional Capacity
· Joint Damage
· Drug Toxicity
↓
Outcome Assessment
→ · Continued Disease Activity · Progressive Disability · Progressive Joint Damage
→ Consider Methotrexate

Consider:
· Another NSAID
· Low Dose Oral Corticosteroids
· Intra-articular Corticosteroids
· Hydroxychloroquine

Aggressive Disease
↓
· Initiate NSAIDs
· Strongly Consider
  - Oral Corticosteroids
  - Methotrexate
↓
Outcome Assessment
→ Acceptable Response / · Continued Disease Therapy · Progressive Disability · Progressive Joint Damage · Unacceptable Toxicity

Acceptable Response
↓
Continue Therapy

Consider:
· Altered Dosage of Methotrexate
· Intra-articular Corticosteroids
· Another DMARD
· Combination DMARDs
· Biologic Agent
· Immunosuppressive agent
· Investigational Agent

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show an improved safety profile, are now widely used. It has been theorized that this new approach would both maximize benefit and minimize toxicity. Recent observations involving drug retention rate in rheumatology practice suggests that this practice pattern is finding its way into clinics. Based on published evidence, the medical management of RA is schematized in Figure 1. Critical to therapeutic success is constant vigilance and systematic follow-up to evaluate effectiveness and toxicity. In this scheme, methotrexate is central. The newer drugs, anti-TNF agents, and other biologic agents may eventually be used in a different niche as post-marketing surveillance information becomes available.

Specific Therapeutic Approaches

Most rheumatologists agree that the judicious use of NSAIDs or COX-2 specific drugs are still the useful adjuncts, particularly during the early stages of active RA for both slowly progressive and aggressive disease. Full doses should be used and careful follow-up arranged so that second-line drugs can be prescribed when appropriate. Full doses of aspirin are acceptable but infrequently used because of poor patient compliance and significant long-term tolerability problems. Chronic NSAID use in RA has never been shown to retard radiographic progression, and in addition, NSAIDs may cause gastropathic side effects in high-risk patients. These drugs do, however, partially reduce the pain and suffering that are the hallmark of the disease.

Table 4

Rheumatoid Arthritis: Medical Management of Rheumatoid Arthritis with Disease-Modifying Antirheumatic Drugs

Slowly Progressive Disease	Aggressive Disease
Consider in NSAID-nonresponsive patients	**Consider early in course of disease**
Hydroxychloroquine	Methotrexate, leflunomide
Sulfasalazine*	Intramuscular gold (rarely used now)
Minocycline*	Hydroxychloroquine
	Sulfasalazine*
	For patients refractory to the above, consider:
	Etanercept, infliximab, or adalimumab
	Combinations of DMARDs*
	Cyclosporine*
	Anakinra
	For patients refractory to TNF inhibitors, consider:
	Abatacept
	Rituximab

Not approved by the FDA for use in rheumatoid arthritis.
DMARD = disease-modifying antirheumatic drug; NSAID = nonsteroidal anti-inflammatory drug.
Reprinted with permission from Lipsky, PE. Algorithms for the Diagnosis and Management of Musculoskeletal Complaints. Dallas, Tex: The University of Texas Southwestern Medical Center at Dallas; 1996.

If erosions appear early or if the disease shows aggressive features that are unabated despite NSAID use, then a decision to use a single second-line drug should be made within 3 months or less (Table 4). Thus careful follow-up is crucial. Consideration should be given to use hydroxychloroquine or sulfasalazine if the disease is slowly progressive. On the other hand, if aggressive clinical features are obvious (erosions, sustained disease activity with multiple joint involvement, or extra-articular features), then methotrexate alone or perhaps in combination with hydroxychloroquine or sulfasalazine might be a favored approach. Prednisone or equivalent is typically used during periods of very active disease as "bridge therapy" and then tapered as the disease comes under control with drug treatment. The early use of low-dose corticosteroids was shown to retard radiographic progression; however, no long-term effect was observed on other key clinical parameters such as functional status, and the long-term sequelae are still of concern. In most practices in the United States, certain older DMARDs have become uncommon. Thus, because of adverse effects related to their use, the introduction of newer agents and other factors, rheumatologists infrequently use parenteral gold, oral gold, azathioprine and D-penicillamine.

The biggest change in RA treatment in the last 5 years involves the use of multiple second-line agents concurrently. Until recently this approach had been considered overly aggressive and highly toxic. However, several well-designed, randomized, controlled trials of combination chemotherapy have shown improved outcomes. Almost all effective combination regimens use methotrexate as the cornerstone. Combinations of methotrexate plus sulfasalazine and hydroxychloroquine (or leflunomide, or cyclosporine) have all proven more efficacious than monotherapy. Most importantly, adverse effects with the combination approaches were comparable to those of monotherapy. The new TNF-α inhibitors have profound rapid effects on the clinical signs and symptoms of RA as well as on mood and constitutional symptoms. In addition, they also retard structural damage and improve quality of life. While there has been a marked trend towards increasing use of these agents, eg, patients with earlier stages of disease, their ultimate practice niche is still evolving. At present, etanercept, infliximab, and adalimumab are most widely used for patients who fail to respond to methotrexate or who cannot take it because of comorbid diseases. Interestingly, recent data suggests that patients failing one TNF inhibitor, whether due to loss of efficacy or adverse effects, can still achieve meaningful clinical responses when switched to another TNF inhibitor. For patients failing TNF inhibitors or perhaps for those with contraindications to their use, the new biologic agents abatacept and rituximab may be tried.

A study in early RA from the Netherlands has provided some insight as to the relative efficacy of various treatment approaches. In this study, known as the BeSt trial, 508 patients with early RA (defined as < 2 years of arthritis) were randomized to one of 4 treatment arms: 1) sequential monotherapy (beginning with methotrexate [MTX]); 2) step-up combination therapy (also beginning with MTX); 3) initial combination therapy with MTX, sulfasalazine (SSZ) and high dose prednisone (as was used in the earlier COBRA study); and 4) initial combination therapy with MTX plus TNF-inhibitor (infliximab). In all arms, the goal was low levels of disease activity. At their 3 monthly follow-up visits, patients not achieving this goal, defined by a disease activity score (DAS) of 2.4 or less, were required to have their treatment altered according to an algorithm specific for each group. Eventually, groups 1, 2, and 3 could end up on MTX plus TNF inhibitor. If

patients did achieve low disease activity on 2 successive visits, treatment was tapered (to a minimum of MTX 10 mg/week over the first 2 years, and off all therapy after the second year). Data from the 1 year and 2 years of follow-up showed that patients in groups 3 and 4 achieved low disease activity and even remission quicker than did those in groups 1 and 2, although as might have been expected given the study design with its mandatory changes in therapies, clinical efficacy was comparable across all groups by 2 years. However, the progression of joint damage measured radiographically was less in groups 3 and 4 through the first 2 years of the study. Preliminary assessment at year 3 has suggested that a substantial number of patients can have their therapy tapered or even discontinued while maintaining low levels of disease activity. This suggests that early aggressive therapy may be able to change the course of RA.

Surgery

Appropriately timed reconstructive orthopedic surgery is an invaluable treatment strategy for selected patients with RA. Generally, surgery is most effective for patients with RA with the following conditions: impending tendon rupture in the hand and wrist (tendon repair); functional limitation due to end-stage arthritis in large or weight-bearing joints (total joint replacement of hip, knee, shoulder); joint instability or intractable pain with routine use (fusion of thumb, wrist, ankle, cervical spine).

Outcome Assessment

The optimal method for measuring outcome in the treatment of patients with RA has always been an area of discussion. Standard outcome parameters in RA treatment trials include: tender and swollen joint counts; global assessments of disease activity; assessment of pain by the patient; measurement of the acute phase response (eg, with the erythrocytsedimentation rate [ESR] or C-reactive protein [CRP]); assessment of functional status (eg, using the Health Assessment Questionnaire [HAQ]) and assessment of joint damage; quantifying periarticular erosions; and joint space narrowing on radiographs.

Because individual measures are inexact, a trend has been to use composite measures that incorporate several aspects of disease activity, and require important

improvements in a majority for a "response" to be achieved. The most commonly used are the response criteria developed by the ACR which require 20% or more improvement in a variety of measures (commonly called "ACR20 response") and the disease activity score (DAS) and its modifications (eg, DAS28). These composite indices are standard in clinical trials and are increasingly becoming more widely used in practice.

This issue of quantifying outcome is important, because if measures are insensitive to change or do not describe clinically relevant conditions, then evaluations of therapies both in practice and in rigidly designed trials will be extremely difficult. It may be that treatment in RA will follow the treatment paradigm in oncology, such as induction of remission/maintenance and relapse/reinduction strategy. One might then envision the newer, emerging biologic therapies to be used in conjunction with established synthetic drugs. Emerging data suggest that this indeed may be the case.

Because the TNF inhibitors have been shown to be capable of stopping the progression of radiographic joint damage—a level of disease control previously considered unachievable—this has become increasingly utilized. Indeed, measures of radiographic damage are standard in clinical trials now, and arresting such damage has become a goal in the treatment of RA.

6. Specific Antirheumatic Drugs

NSAIDs and Salicylates

Mechanisms of action. Prostaglandins increase vascular permeability and sensitivity to bradykinins, thereby enhancing inflammation and increasing sensitivity to pain. NSAIDs inhibit the production of prostaglandins of the E series, including the formation of prostacyclin and thromboxane, resulting in complex effects on vascular permeability and platelet aggregation. In the inflammatory cascade, polyunsaturated fatty acids (including arachidonic acid), which are constituents of all cell membranes and exist in ester linkage with glycerols of phospholipids, are converted to prostaglandins or leukotrienes through the action of phospholipase A2 or phospholipase C. Free arachidonic acid acts as a substrate for the prostaglandin H (PGH) synthetase complex (PGHS), which includes both cyclooxygenase and peroxidase. These catalyze the conversion of arachidonic acid to the unstable cyclic-endoperoxide intermediates, PGG2 and PGH2, which then are converted to the more stable PGE2 and PGF2 compounds by specific synthetases that exist in specific tissues. NSAIDs specifically inhibit cyclooxygenase activity and thereby reduce the conversion of arachidonic acid to PGG2.

One of the most important advances in the area of inflammation involves recent elucidation of cyclooxygenase (COX) biology. Accumulated evidence now suggests that there are at least 2 related isoforms of the cyclooxygenase enzymes. They possess significant homology in those amino acid sequences considered important for catalysis of arachidonic acid. The most important differences between the two isoforms are in their regulation and expression of the enzymatic activity. To date, a constitutive form has been described, prostaglandin synthetase H1 (PGHS-1 or COX-1), which is inhibited by all of the available NSAIDs to varying degrees (depending on the applied experimental model system used to measure the drug effects). COX-1 is expressed variably in most tissues; it has been described as a "housekeeping enzyme" that regulates normal cellular processes and is stimulated by hormones or growth factors. It is thought to be important in maintaining the integrity of the gastric and duodenal mucosa, and its inhibition is considered the basic cause of many of the toxic effects of the NSAIDs. The other isoform is an inducible, highly regulated enzyme, prostaglandin synthetase H2 (PGHS-2 or COX-2), which is usually undetectable.

The expression of COX-2 is increased during states of inflammation or experimentally in response to mitogenic stimuli. For example, in fibroblasts, various growth factors, phorbol esters, and interleukin-1 (IL-1) stimulate the expression of COX-2; in monocyte–macrophage systems, endotoxin stimulates it. The expression of COX-2 is inhibited by glucocorticoids. Orally active NSAIDs and salicylates inhibit both isoforms of cyclo-oxygenase, thereby reducing the synthesis of prostanoids at sites of inflammation as well as the "housekeeping" arachidonate mediators in renal parenchyma and gastric mucosa.

Arachidonic acid can also serve as a substrate for 5- or 12-lipoxygenase. These enzymes catalyze the conversion of arachidonic acid to biologically active leukotriene and hydroperoxyeicosatetraenoic acids (HETEs). Although none of the currently available NSAIDs inhibit 5-lipoxygenase directly, several NSAIDs may indirectly reduce leukotriene levels by shunting arachidonic acid back into the triglyceride pool. Several new compounds may have inhibitory effects on both cyclooxygenase and lipoxygenase. It remains to be seen whether these effects will be biologically important at the clinical level.

Data suggest that NSAIDs have other effects that may be pertinent to their clinical effects; they inhibit activation and chemotaxis of neutrophils as well as reduce the elaboration of toxic oxygen radicals from stimulated neutrophils. There is also evidence that several NSAIDs scavenge superoxide radicals. NSAIDs are lipophilic, becoming incorporated in the lipid bilayer of cell membranes and thereby interrupting protein-protein interactions that are important for signal transduction. Specific NSAIDs have been shown to inhibit proteoglycan synthesis by chondrocytes in vitro. There are in vitro data and a few case reports to suggest that the use of some NSAIDs accelerates cartilage damage in OA, although few investigators believe the data to be compelling enough to preclude the use of NSAIDs as standard therapy for OA. Some NSAIDs have been shown to affect T-lymphocyte function experimentally. Another newly described biologic effect of NSAIDs not directly related to prostaglandin synthesis involves the interference with neutrophil-endothelial cell adherence, which is a critical step in the inflammation pathway. The effects of the NSAIDs on nitric oxide metabolism have also been described. Nitric oxide synthetase, once induced by cytokines and other pro-inflammatory mediators, produces nitric oxide in large amounts, leading to increased signs of inflammation such as vasocongestion, increased cytotoxicity, and increased vascular permeability.

There is interesting evidence about the effects of prostaglandins on cellular function. It has recently been described that prostaglandins inhibit apoptosis (programmed cell death) and that NSAIDs, through inhibition of prostaglandin synthesis, reestablish the return to a more normal cell cycle in some cell systems. Thus, the suggestion is that in vitro prostaglandins are important modulators of apoptosis and that NSAIDs may alter this mechanism, thus altering cell-cycle changes.

In summary, the literature is replete with reports of purported biologic efforts of NSAIDs; however, the role and importance of these prostaglandin- and non-prostaglandin-mediated processes in clinical inflammation are not entirely clear.

Pharmacology. All NSAIDs are well absorbed from the gastrointestinal tract, and because they are weakly acidic, they become tightly bound to serum proteins. Therefore, alterations of circulating free drugs may occur when NSAIDs are co-administered with other protein-bound drugs or in patients with hypoalbuminemia. In general, most NSAIDs are metabolized in the liver and by-products excreted in the urine. Some NSAIDs are excreted in the bile and the urine. Others have prominent enterohepatic circulation. NSAIDs should be used with caution and vigilance in the patient with liver or renal dysfunction.

Plasma half-life of the NSAIDs is highly variable; this pharmacokinetic heterogeneity reflects the wide variability in dosing regimens. In general, the NSAIDs (and COX-2 specific anti-inflammatory drugs) with the longest half-lives (eg, piroxicam, nabumetone, oxaprozin, and rofecoxib) are administered once daily; others (eg, ibuprofen) have short half-lives, and are administered 4 times per day in order to achieve a biologic and clinical effect. Some NSAIDs are lipid soluble, readily penetrate the CNS, and occasionally cause side effects like HA, mentation difficulties, and mood alterations.

Table 5

Nonsteroidal Anti-Inflammatory Drugs and Dose Ranges by Chemical Classification

Chemical Category	Drug (trade name)	Daily Recommended Adult Dose (mg)	Plasma Half-Life (hrs)
Carboxylic acids	Acetylsalicylic acid (aspirin)	1300-5000	4-15
	Choline magnesium Salicylate (Trilisate®)	1500-3000	4-15
	Salsalate (Disalcid®)	1500-3000	4-15
	Diflunisal (Dolobid®)	500-1500	7-15
Propionic acids	Ibuprofen (Motrin®)	1600-3200	2
	Naproxen (Naprosyn®)	500-1000	13
	Fenoprofen (Nalfon®)	1200-3200	3
	Ketoprofen (Orudis®)	150-300	2
	Flurbiprofen (Ansaid®)	200-300	3-9
	Oxaprozin (Daypro®)	600-1800	40-50
Acetic acids	Indomethacin (Indocin®)	75-200	3-11
	Tolmetin (Tolectin®)	800-1600	1
	Sulindac (Clinoril®)	300-400	16
	Diclofenac (Voltaren®)	100-200	1-2
	Etodolac (Lodine®)	600-1200	2-4
	Ketorolac (Toradol®)*	20-40	2
Fenamic acids	Mefenamic acid (Ponstel®)†	500-1000	2
	Meclofenamic acid (Meclomen®)	200-400	2-3
Enolic acids	Roxicam (Feldene®)	10-20	30-86
Naphthylkanones	Nabumetone (Relafen®)	500-1000	19-30
COX 2 inhibitors	Celecoxib (Celebrex®)	200-400	
	Rofecoxib (Vioxx®)	12.5-25	
	Valdecoxib (Bextra®)	10-20	

Used for management of acute pain (not recommended for use for more than 21 days).
†Used for management of pain or dysmenorrhea (not recommended for more than 7 days).*

Clinical use. Overall, the magnitude of therapeutic effects of NSAIDs is similar when studied in populations of arthritis patients in clinical trials. However, wide variability in response to particular NSAIDs has been observed in individual patients. These drugs do not appear to retard the development or progression of chondral erosions. However, NSAIDs do offer palliation with respect to pain and suffering, as attested to by the "flare" phenomena frequently observed in clinical trials when these drugs are withdrawn from patients with active RA. Despite the recent philosophical change regarding the traditional treatment pyramid, NSAIDs are routinely used in RA patients to reduce the symptoms of pain. Most practitioners now recognize that they are purely soothing for musculoskeletal symptoms, but do not provide a "disease-modifying" biologic effect, and have significant attendant toxicity. Thus, there is increasing vigilance regarding their use. As a class of drug, NSAIDs, especially over-the-counter NSAID preparations, are used routinely in primary care practice. The NSAIDs and typical dosages and regimens are outlined in Table 5.

Adverse effects. Adverse effects of traditional COX-1 inhibiting NSAIDs are a major issue, especially in patients at high risk for toxicity. GI side effects in particular are a major reason for discontinuing NSAIDs. Large databases suggest a hierarchy of toxicity, with tolmetin and indomethacin exhibiting the most toxicity and ibuprofen and nonacetylated salicylates the least. Large population-based epidemiologic studies suggest that patients exposed to NSAIDs exhibit a 3-10 fold higher risk of GI toxicity and death than those who are not exposed. GI side effects range in severity from mild dyspepsia and flatulence to death from massive GI blood loss or visceral perforation. Complicating the surveillance issue for side effects is the observation that up to 40% of patients with documented gastroduodenal erosive disease may not complain of symptoms. Although observations gleaned from randomized controlled trials may not reflect the true natural history in large populations, endoscopic studies in short-term trials have identified gastroduodenal ulcers with a frequency of 15%-30%. Risk factors for GI adverse events in the RA population include age, concomitant use of NSAIDs, prior NSAID related side effects, and level of disability.

Two strategies presently exist to prevent GI ulceration. The first involves the concomitant use of misoprostol, a methylated, orally-active prostanoid. Randomized controlled trials and large post-marketing, population-based outcomes studies have proven that misoprostol reduces the risk of serious GI complications including perforation, ulcers, and bleeding by up to 50%. However misoprostol at high doses itself produces annoying GI side effects including abdominal pain and diarrhea. Recently, a combination of diclofenac (an NSAID) and misoprostol (in daily doses lower than label suggestion) reduced the frequency of NSAID-induced ulcers by 60%-80%, while showing significant symptomatic efficacy. The second strategy builds upon the elucidation of the 2 separate isoforms of cyclo-oxygenase, COX-1 and COX-2. Specific inhibitors of COX-2, the isoform induced by biologic mediators of inflammation, have been developed into anti-inflammatory drugs that are selective, and do not inhibit COX-1, when used in physiologic doses.

Three COX-2 specific inhibitors, celecoxib, rofecoxib, and valdecoxib, had been approved by various regulatory agencies both in the United States and around the world. Several other COX-2 inhibitors, including etoricoxib and lumaricoxib, progressed through late phases of the drug development pathway and were even approved in a number of countries. In clinical trials and in the clinic, all the COX-3 inhibitors successfully achieved their main clinical advantage, namely the control of signs and symptoms of arthritis while reducing gastrointestinal complications typical of nonselective NSAIDs, particularly NSAID gastropathy. However, the use of COX-2 inhibitors was dramatically altered when it was shown that patients treated with rofecoxib experienced significant complications of atherosclerotic cardiovascular disease more often than patients treated with older NSAIDs. Subsequently, rofecoxib was removed from the market worldwide, valdecoxib was withdrawn by its manufacturer, and drugs in development had their plans put on hold. At present, celecoxib remains the only COX-2 inhibitor approved for use in the US and many other countries. Analysis of this area is dynamic and evolving.

Glucocorticoids

Since their discovery in the late 1940s by Hench and colleagues at the Mayo Clinic, glucocorticoids have been used to treat patients with RA. Although early observations suggested that these compounds exhibited profound clinical effects in patients with RA, the long-term adverse event profile severely limited the widespread and prolonged usage of these drugs. Because of the disastrous side effects observed in the early 1950s, some academic centers and private rheumatologists avoided the use of these drugs for any patient with RA. What followed was a profound antipathy on the part of rheumatologists to use glucocorticoids for nonfatal inflammatory diseases. Gradually, these agents were accepted as short- or intermediate-term "bridge therapy" for active RA while awaiting disease amelioration by second-line agents. In addition, several studies have now shown that treatment with corticosteroids can slow the progression of radiographic joint damage in RA.

Since those early days, the practice pendulum has swung back, and glucocorticoids are now routinely but cautiously prescribed for patients with active RA.

Mechanism of action. The mode of action of glucocorticoids is complex. They bind specifically to a cytoplasmic receptor, which belongs to a super family of regulatory proteins (including the estrogen and vitamin D receptors). The glucocorticoid-receptor complex migrates to the nucleus and then affects gene transcription. Glucocorticoids have profound and protean anti-inflammatory effects caused by the suppression of immunomodulating proteins, including IL-1, IL-6, TNF-α, interferon-gamma, and GMCSF. In addition, glucocorticoids inhibit the production and expression of pro-inflammatory prostaglandins and leukotrienes, inducible nitric oxide synthase, plasminogen activator, and adhesion molecules (ICAM-1). Glucocorticoids also modulate cellular physiology by reducing neutrophils at sites of inflammation; decreasing the number and function of monocytes/macrophages (perhaps by affecting chemokine physiology); suppressing antigen presenting cells; and inhibiting the number of circulating lymphocytes and their functions, including the proliferative response to mitogens, cytokine production, and immunoglobulin production. In addition, glucocorticoids also produce significant metabolic effects elsewhere. Generally speaking, they are catabolic and induce breakdown of protein, diminished utilization of glucose, and alterations in lipids, thereby facilitating premature atherosclerosis.

Pharmacology. Glucocorticoids are well-absorbed from the gastrointestinal tract. Once absorbed, the drug binds to corticosteroid binding globulin (CBG) and albumin. Glucocorticoids are metabolized largely by the liver, where they are hydroxylated, conjugated, and then excreted in the urine. Prednisone is an inactive steroid, but once absorbed it is converted in the liver to prednisolone. The half-life and biologic effects of various glucocorticoid preparations are highly variable. Differences in plasma half-life and other factors contribute to significant differences in clinical potency. Most practitioners divide glucocorticoids into 3 groups according to their duration of action. Short-acting glucocorticoids (8-12 hours) include cortisol and cortisone; intermediate-acting glucocorticoids (12-36 hours) include prednisone, prednisolone, and methylprednisolone; and finally, long-acting glucocorticoids (36-72 hours) include dexamethasone.

Clinical use. Low dosages of glucocorticoids co-administered with NSAIDs and DMARDs are used routinely as "bridge therapy" for some patients with very active RA. In that setting, the plan is to first quickly extinguish the signs and symptoms of the "flare" phenomena, but then to always taper glucocorticoid treatment once the DMARD takes effect. In some patients with chronic progressive disease, long-term low-dose glucocorticoid treatment is required to maintain the disease at a certain level of control and to secure a reasonable quality of life. Glucocorticoids are also used intermittently over 1-2 weeks in doses tapering rapidly from 20 mg per day for patients experiencing a "flare" of RA.

New information now exists regarding the magnitude and durability of these effects as well as the potential for retarding cartilage damage and structural deterioration of the joint. In 1995, Kirwan showed that low-dose glucocorticoids resulted in a reduction of progression of a joint damage in patients with RA who were taking second-line antirheumatic drugs. One hundred and twenty-eight RA patients with average disease duration of less than 2 years were randomized

in double-blind fashion to either placebo or low-dose prednisolone. All patients were receiving stable doses of NSAIDs or second-line antirheumatic agents. Clinical improvement of the signs and symptoms of RA in the prednisolone group was greater than in the placebo group after the first year of therapy but disappeared at 2 years. However, at 2 years, the erosion scores were significantly better in the prednisolone group compared to the placebo group. Kirwan's observations were the first to define a potential "disease modifying" capability of glucocorticoids.

Building upon that evidence, a recent 2-year double-blind randomized placebo-controlled trial was completed in patients with early RA who were not concurrently exposed to second-line antirheumatic drugs. Similar to the Kirwan study, the glucocorticoid group showed more clinical improvement than the placebo group early on in the observation period, but the difference between the groups was insignificant at 6 and 12 months. However, radiologic outcome showed significant reduction in erosion and joint space narrowing scores in the prednisone group versus the placebo group. These observations suggest that glucocorticoids may have "structure-modifying" effects despite the potential for long-term toxicity.

Given the recent additions to the pharmacologic armamentarium to treat glucocorticoid-induced osteoporosis and glucocorticoid-associated gastrointestinal side effects, the concern about long-term side effects has been mitigated to some extent. However, given all of the other potential adverse effects of glucocorticoids, these agents should always be used judiciously. A thorough discussion of risk benefit and appropriate concern for patient expectations should be part of the decision-making process when using these drugs.

Adverse effects. The adverse effects of glucocorticoids are legion and are noted in Table 6. For the most part, these side effects are dose- and duration-dependent. Of particular importance in the rheumatic disease population are immune suppression, and osteoporosis. Other side effects may also be seen in RA patients, including aggravated hypertension, glucose intolerance, stimulation of cataract growth, difficulties with wound healing and, occasionally, CNS effects ranging from mild emotional lability to frank psychosis.

Table 6

Side Effects of Corticosteroid Therapy

Very common, should be considered in all patients

Osteoporosis
Increased appetite
Centripetal obesity
Impaired wound healing
Increased risk of infection
Suppression of hypothalamic-pituitary axis
Arrest of normal growth in children

Frequently seen

Myopathy
Osteonecrosis
Hypertension
Thin fragile skin, striae, purpura
Edema
Hyperlipidemia
Psychiatric symptoms, particularly euphoria
Diabetes mellitus
Posterior subcapsular cataracts

Uncommon, but important to recognize early

Glaucoma
Silent intestinal perforation
Peptic ulcer disease
Gastric hemorrhage
Hypokalemic alkalosis
Hyperosmolar nonketotic coma

Rare

Hirsutism
Panniculitis
Secondary amenorrhea
Impotence
Epidural lipomatosis

Modified from Behrens TW, Goodwin JS. Glucocorticoids. In: McCarty D, Koopman W, eds. Arthritis and Allied Conditions. *11th ed. Philadelphia, Pa: Lea & Febiger; 1989:604-21.*

The effect of glucocorticoids on bone mineral density is probably the most vexing complication for RA patients exposed to these compounds, especially because many of these patients are post-menopausal women. Bone mineral density loss in these patients can range from 4%-10% per year, and even low-dose glucocorticoid therapy may cause significant osteoporosis in some patients. Most of the bone loss occurs early. Glucocorticoids cause osteoporosis via several mechanisms, including stimulation of osteoclastic bone resorption, reduction of calcium absorption, reduction in sex hormone production, and finally, a direct negative effect on bone formation.

Strategies to minimize glucocorticoid-associated osteoporosis have been developed recently and include calcium supplementation as a base with vitamin D. In addition, drugs that reduce osteoclastic bone resorption, (eg, the biphosphonates, calci-tonin ((intranasal and parenteral)), PTH hormone, estrogen replacement for women, and testosterone replacement for hypogonadal men), are the key therapeutic agents that may reduce bone mineral density loss.

Acetaminophen

Acetaminophen has analgesic and antipyretic properties. The exact mechanism of action is unknown, but it may have both peripheral and central actions. This medication is well absorbed after oral administration and may be effective within 30 to 60 minutes. The half-life and duration of action is approximately 4 hours. This drug is metabolized in the liver and excreted in the urine. Overall, it is safe and produces less gastrointestinal dyspepsia and bleeding than the NSAIDs. Acetaminophen is used routinely in RA patients to manage pain due to mechanical joint problems. This agent may cause hepatotoxicity in patients

Table 7

Monitoring Drug Therapy in Rheumatoid Arthritis

Recommended monitoring strategies for drug treatment of rheumatoid arthritis*

Drugs	Toxicities Requiring Monitoring†	Baseline Evaluation	Monitoring System Review/ Examination	Laboratory
Salicylates, nonsteroidal anti-inflammatory drugs	Gastrointestinal ulceration and bleeding	CBC, creatinine, AST, ALT	Dark/black stool, dyspepsia, nausea or vomiting, abdominal pain, edema, shortness of breath	CBC yearly, LFTs, creatinine testing may be required‡
Hydroxy-chloroquine	Macular damage	None unless patient is over age 40 or has previous eye disease	Visual changes, consider funduscopic and visual fields every 12 months	
Sulfasalazine	Myelosuppression	CBC, and AST or ALT in patients at risk, consider G6PD	Symptoms of myelosuppression§, photosensitivity, rash	CBC every 2-4 weeks for first 3 months, then every 3 months

Table 7 *(continued)*

Monitoring Drug Therapy in Rheumatoid Arthritis

Drugs	Toxicities Requiring Monitoring†	Baseline Evaluation	Monitoring System Review/ Examination	Laboratory
Methotrexate	Myelosuppression, hepatic fibrosis, cirrhosis, pulmonary infiltrates or fibrosis	CBC, chest radiography within past year, hepatitis B and C serology in high-risk patients, AST or ALT, albumin, alkaline phosphatase, and creatinine	Symptoms of myelosuppression§, shortness of breath, nausea/vomiting, lymph node swelling	CBC, platelet count, AST albumin, creatinine every 4-8 weeks
Leflunomide	Hepatoxicity, myelosuppression, diarrhea (same as methotrexate for last 3 columns)			
Gold, intramuscular	Myelosuppression, proteinuria	CBC, platelet count, creatine, urine dipstick for protein	Symptoms of myelosuppression§, edema, rash, oral ulcers, diarrhea	CBC, platelet count, urine dipstick every 1-2 weeks for first 20 weeks, then at the time of each (or every other) injection
Gold, oral	Myelosuppression, proteinuria	CBC, platelet count, urine dipstick for protein	Symptoms of myelosuppression§, edema, rash, diarrhea	CBC, platelet count, urine dipstick for protein every 4-12 weeks
Corticosteroids (oral <10 mg of prednisone or equivalent)	Hypertension, hyperglycemia	BP, chemistry panel, bone densitometry in high-risk patients	BP at each visit, polyuria, polydipsia, edema, shortness of breath, visual changes, weight gain	Urinalysis for glucose yearly

*CBC = complete blood cell count (hematocrit, hemoglobin, white blood cell count) including differential cell and platelet counts; ALT = alanine aminotransferase; AST = aspartate aminotransferase; LFTs = liver function tests; BP = blood pressure.

† Potential serious toxicities that may be detected by monitoring before they have become clinically apparent or harmful to the patient. This list mentions toxicities that occur frequently enough to justify monitoring. Patients with comorbidity, concurrent medications, and other specific risk factors may need further studies to monitor for specific toxicity.

‡ Package insert for diclofenac (Voltaren®) recommends that AST and ALT be monitored within the first 8 weeks of treatment and periodically thereafter. Monitoring of serum creatinine should be performed weekly for at least 3 weeks in patients receiving concomitant angiotensin-converting enzyme inhibitors or diuretics.

§ Symptoms of myelosuppression include fever, symptoms of infection, easy bruisability, and bleeding.

American College of Rheumatology Ad Hoc Committee on Clinical Guidelines: Guidelines for monitoring drug therapy in rheumatoid arthritis. Arthritis Rheum. *1996;39:723-31. Reprinted with permission of the American College of Rheumatology.*

with preexisting liver dysfunction. The issue of renal dysfunction secondary to acetaminophen has received significant attention. A case-control study (telephone sampling method) examining 716 patients with end stage renal disease from all causes and 361 age-similar controls from the same geographic area suggested that an average intake of acetaminophen of more than one pill per day and a cumulative intake of 1000 or more pills in a lifetime were associated with an increased risk of end stage renal disease. This study should be interpreted with caution due to potential limitations, including recall bias, confounding factors associated with acetaminophen use in the cases that were not examined in the study, and the lack of control over accuracy of the information reported by telephone interview. The true risk of acetaminophen use in the development of end stage renal disease remains unknown.

DMARDs

Antimalarial Drugs

Mechanism of action and pharmacology. The antimalarial drugs, chloroquine and hydroxychloroquine, are 4-aminoquinolones. Quinine, a related compound, has been used since the 1800s to treat rheumatic diseases. These drugs are well absorbed from the gastrointestinal tract; hydroxychloroquine is excreted in the feces and chloroquine in the urine. Although the exact mechanisms of action have not been completely elucidated, the antimalarial drugs have been shown to inhibit the release of IL-1 by monocytes. They inhibit lysosomal enzyme release by stabilizing lysosomal enzymes, and they retard phagocyte chemotaxis and lymphocyte blastogenesis. They have also been shown to inhibit phospholipase A2, a critical enzyme in the prostaglandin cascade.

Clinical use. Although antimalarial drugs fell out of favor for the treatment of rheumatic diseases in the 1950s because of the retinal toxicity that was observed with long-term and high-dose therapy, these drugs have made a comeback in recent years. Several controlled trials have proven hydroxychloroquine to be effective for patients with mild SLE whose manifestations are primarily dermatitis and arthritis. These drugs are also used in early RA (usually before methotrexate, parenteral gold, and anticytokine therapy), or in more aggressive RA as combination chemotherapy with methotrexate. A recent controlled trial of hydroxychloroquine showed it to be significantly more effective than placebo in patients with early RA. Clinical effects are usually observed at 8 to 12 weeks; starting dosage is 400 mg/d in divided doses, with a dose reduction to 200 mg/d at 8 to 12 weeks if a good response is observed.

Adverse effects. Adverse events are common and probably dose related, thus providing some rationale for the lower doses presently in use. Gastrointestinal intolerance with dyspepsia, diarrhea, and nausea are common; however, gastrointestinal bleeding is not a usual sequelae of these symptoms. Peripheral neuropathic symptoms, myopathy, and skin rashes (including exfoliative dermatitis) have also been reported. Of most concern is the potential for ocular toxicity, which includes central effects on visual accommodation, corneal deposits, and retinopathy. The latter is associated with permanent visual loss, but at the doses prescribed today, this side effect is very rare in clinical practice. Symptoms include central scotomata, peripheral field deficits, or frank blindness. Regular ophthalmologic examination (according to American Academy of Ophthalmology Guidelines), which should include visualization of the macula for pigmented stippling as well as peripheral field testing to a red test object, may define a state of premaculopathy that predicts the eventual irreversible changes (Table 7).

Sulfasalazine

Sulfasalazine is 5-aminosalicylic acid linked by a diazo bond to the antibacterial sulfonamide, sulfapyridine. In Western Europe, it has been used since the 1940s for patients with RA. Because of its favorable effects and relative lack of toxicity, it is now more widely used in the United States, especially in early mild RA.

Mechanism of action. The exact mechanism of action of sulfasalazine is poorly understood and is complicated by the fact that the metabolites, 5-aminosalicylic acid and sulfapyridine, are also biologically active. Most compelling is the fact that the parent molecule, sulfasalazine, can inhibit 5-lipoxygenase, thus reducing production of leukotrienes. It has also been shown to inhibit lymphocyte mitogenesis and nuclear factor kappa B, a transcription factor important in the genetic regulation of inflammatory pathways.

Pharmacology. Because of its insolubility, sulfasalazine is poorly absorbed in the stomach and small bowel. In the colon, the diazo bond is reduced by bacteria, thus liberating 5-aminosalicylic acid, most of which remains in the colon and is excreted in the feces. Sulfapyridine is absorbed, metabolized in the liver, and excreted in the urine.

Clinical use. Sulfasalazine is widely used in patients with early mild RA, and most long-term studies suggest a favorable efficacy profile. Most recently, sulfasalazine has also been shown to be marginally effective in patients with the seronegative spondyloarthropathies, especially in those with psoriatic arthritis. It apparently has little effect on axial spine disease. It is commonly prescribed as part of a combination chemotherapy protocol with hydroxychloroquine and methotrexate. The starting dosage is usually 500 mg twice a day, with gradual escalation to a total of 3 g/d in two divided doses.

Adverse effects. Adverse effects are common but usually minor in magnitude or severity. Most long-term RA studies of sulfasalazine have recorded very few serious adverse events. Previous sulfa allergy precludes its use, and glucose-6-phosphate dehydrogenase (G6PD) screens may be considered in appropriate patients. Gastrointestinal intolerance, including nausea and abdominal discomfort, are usually seen in the first 2 to 3 months of therapy and may be minimized by gradually increasing the dose. Cutaneous adverse events include urticaria, pruritus, maculopapular rash, and photosensitive eruption. As with any sulfa drug, serum sickness or toxic epidermal necrolysis rarely can be seen. Leukopenia and neutropenia, which are usually clinically insignificant, are observed in 1% to 5% of exposed patients; therefore, periodic hemogram screening is suggested (Table 7).

Methotrexate

Methotrexate is a methylated analogue of tetrahydrofolate and inhibits dihydrofolate reductase. Its history as an antirheumatic drug dates to 1950, when a case series of patients with inflammatory arthritis improved significantly after taking aminopterin, a drug related to methotrexate. Although it remained in use for psoriasis, methotrexate was largely abandoned as a treatment for RA until the 1970s, when it began to see limited use by individual practitioners. Subsequently, it was systematically evaluated and proven efficacious in several large, randomized, controlled trials in the 1980s. Today, its clinical utility in the treatment of patients with RA is undisputed, and it stands alone as the gold standard second-line antirheumatic drug against which others are compared. Even the new TNF inhibitors are typically added to methotrexate "partial responders" or after methotrexate has failed or caused toxicity.

Mechanism of action. At the cellular level, methotrexate is transported across the cell membrane, binds to dihydrofolate reductase, reduces intracellular folate pools, and inhibits purine synthesis. Intracellular methotrexate is metabolized to polyglutamates, which serve to amplify inhibition of dihydrofolate reductase. The antimetabolic effects of methotrexate can be reversed with exogenously applied reduced folates, such as leucovorin (folinic acid).

In patients with RA, methotrexate may not function as it does in cancer patients receiving antimetabolite chemotherapy. Indeed, its prompt clinical effects suggest inhibition of inflammation as a possible mechanism of action. However, methotrexate does not inhibit cyclooxygenase. It does inhibit IL-1 and leukotriene-4 (LTB4), and reduces levels of proteolytic enzymes. Methotrexate, by virtue of the biologic effects of intracellular polyglutamates, may induce extracellular expression of adenosine, which in turn may have an inhibitory effect upon cells that participate in inflammation.

Pharmacology. Unlike most other second-line antirheumatic drugs, methotrexate's pharmacokinetic profile and mechanisms of action have been well studied. In low oral doses, the drug is well absorbed, with peak plasma levels occurring in 1 to 2 hours; at higher doses, however, the fraction of drug absorbed actually decreases because of saturation of carrier-mediated gastrointestinal absorption. In addition, the presence of food may decrease bioavailability. When the drug is given parenterally, its pharmacokinetic profile is somewhat different. Methotrexate is protein bound and may be displaced by other protein-bound drugs, including NSAIDs. Methotrexate is excreted in the urine by a process of filtration, reabsorption, and tubular secretion, and thus blood levels might be affected by drugs that interfere with these processes.

Clinical use. Widely utilized in many connective tissue and autoimmune diseases, methotrexate has been shown to be an excellent steroid-sparing agent. It is effective in the spondyloarthropathies, psoriatic arthritis, inflammatory myopathies, systemic vasculitis, and nonrenal SLE. However, it has been most extensively studied in patients with RA. Multiple short-term and long-term studies have shown superior clinical efficacy. Patients with RA take methotrexate for years, attesting to its favorable efficacy-to-toxicity profile. In most studies, methotrexate produces a predictable response at 6 to 8 weeks, which peaks at 6 months and then requires gradually increasing dosages of the drug in order to maintain the improvement. Although methotrexate may not produce remission in many patients, it may retard radiographic progression. Dosing usually begins at 7.5 to 10 mg orally per week, with gradual increases up to maximum dosage of 20 to 25 mg orally per week depending on clinical response. If the clinical effect is suboptimal or if gastrointestinal adverse effects occur, methotrexate at similar doses can be given parenterally. Most recently it has been tested in combination with other antirheumatic drugs, such as hydroxychloroquine and sulfasalazine in combination, and with cyclosporine alone.

Adverse effects. Adverse events may be classified as minor and major. Minor adverse effects, which are common, include stomatitis, gastrointestinal upset, headache or minor central nervous system disturbance, and elevations of levels of liver transaminases. All of these minor adverse effects may be averted by concomitant use of folic acid. Alternatively, changing dose, dose regimen, or route of administration may also reduce these annoying side effects.

The more serious or major side effects include liver toxicity, which is especially well described in the past among patients with psoriasis. In patients with RA, mild transient elevation of liver function tests is commonly observed, but serious liver disease, including cirrhosis, is extremely rare. Risk factors for serious liver disease may include other contributors to liver dysfunction, such as alcohol, diabetes mellitus, non-alcoholic fatty liver disease, and other medications. Briefly, complete blood count, renal function, liver function, and serum albumin are monitored every 1 to 2 months during therapy with methotrexate (Table 7). A significant fall in serum albumin or persistent elevation of liver function tests may warrant a liver biopsy if therapy is to be continued. Dosages must be lowered for patients with renal insufficiency.

Bone marrow suppression manifested as pancytopenia is an infrequent but clinically significant adverse event in patients with RA. Macrocytosis may be a harbinger of this toxicity, and concomitant renal insufficiency resulting in increased levels of and prolonged exposure to methotrexate may predispose to marrow toxicity. Folinic acid (leucovorin rescue) effectively reverses this.

An acute hypersensitivity to pneumonitis has been observed in approximately 1%-2% of patients and at times may be severe or even fatal. Clinical characteristics include dry cough, fever, dyspnea, and severe hypoxemia. Radiographs show diffuse interstitial prominence or frank infiltrates and occasional adenopathy. Because methotrexate may predispose patients to opportunistic organisms, infection must be ruled out and the drug stopped. Patients usually respond to symptomatic support and drug withdrawal.

Finally, methotrexate is a known teratogen, and the characteristic fetal abnormalities in babies of mothers exposed to this drug have been termed "aminopterin syndrome." The children exhibit craniofacial dysplasias, mental retardation, and cardiovascular anomalies. Methotrexate is also a potent abortifacient; in combination with misoprostol, it was shown to be an effective abortion-inducing therapy. Thus, methotrexate should never be given to pregnant or lactating mothers. Although there exists little consensus regarding an algorithm to discontinue methotrexate if a pregnancy is desired, conventional wisdom suggests that the drug should be discontinued in women for at least 3 months (to include at least two ovulatory cycles) before conception. Methotrexate in doses used for RA probably does not have significant effect on fertility or sterility, although this is poorly studied.

Cyclosporine

Mechanism of action. Cyclosporine, a metabolic product of fungal organisms, has immunologic activity affecting calcium-associated signaling events in the regulation of cytokine gene expression. Cyclosporine inhibits T-cell interaction with macrophages, reduces IL-2 synthesis, prevents production of IL-1 receptor, and suppresses synthesis and release of IL-2 by CD4+ cells. Recent studies also indicate that cyclosporine increases insulin–like growth factor and bone GLA (gamma-carboxyglutamic acid) protein and may stimulate the androgen axis. Growth of bone marrow-derived B-lymphocytes, myeloid, and erythroid cell lines are not inhibited by cyclosporine.

Pharmacology. Cyclosporine is lipophilic and may be given orally or intravenously. Absorption of oral doses of cyclosporine is variable. It is bound to plasma proteins, lipoproteins, and erythrocytes. Volume of distribution includes tissues that accumulate higher concentrations than serum, such as body fat, liver, spleen, pancreas, kidneys, lungs, and lymph nodes. The drug is metabolized in the liver to multiple metabolites (some of which have immunosuppressive activity) by cytochrome P450 mixed function oxidase. Drug interactions may occur, and grapefruit juice may increase cyclosporin A serum levels. Ketoconazole and diltiazem raise cyclosporine levels, whereas phenytoin, phenobarbital, and rifampin may lower drug levels. The drug must be carefully administered in patients with renal dysfunction, and combination with other potentially nephrotoxic medications such as NSAIDs are discouraged or done with considerable caution and monitoring.

Clinical use. Use of cyclosporin A in rheumatologic conditions has thus far included RA, Sjögren's disease, Behçet's-related inflammatory eye disease, SLE, scleroderma, polymyositis, and systemic vasculitis. Dosages of <5 mg/kg daily reduce potential for side effects. A number of combination therapy studies have been reported, among them a study comparing the use of cyclosporin A to placebo in RA patients who were inadequately controlled with low-dose weekly oral methotrexate. This study showed a significant drug effect compared to placebo, although concerns about this continue. However, because of the potential for adverse reactions (see below) even at the lower doses, cyclosporin A use is decreasing as the anti-TNF inhibitors penetrate routine practice.

Adverse effects. Toxic effects of cyclosporin A include: nausea; anorexia; flushing; headaches; tremors; sleep disturbance; hypertrichosis; gingival hyperplasia; hypertension; and hyperuricemia. Renal insufficiency may result from reversible acute toxicity likely to be due to vasoconstriction or from chronic nephropathy with findings of interstitial fibrosis, tubular atrophy, and vasculopathy. Baseline renal insufficiency, age above 30 years, and higher dosing place the patient at increased risk for these side effects. Potassium-sparing diuretics should be avoided, because cyclosporine may cause hyperkalemia. Frequent monitoring of blood pressure, blood chemistries, and leukocyte counts, as well as urinalysis should be done. Because the potential for malignancy exists in patients treated with cyclosporin A, appropriate long-term monitoring of these patients is important.

Leflunomide

Leflunomide was initially developed to prevent transplant rejection; it was developed clinically for RA patients as an alternative to methotrexate and sulfasalazine. It was approved by regulatory authorities for use in patients with active RA.

Mechanism of action. The active metabolite of leflunomide inhibits dihydroorotate dehydrogenase, thereby interfering with pyrimidine synthesis. The down-stream is inhibition of activated lymphocytes (T-cells and B-cells) and other cells that participate in the inflammatory process. In animal models, it inhibits the expression of adjuvant and collagen-induced arthritis and allograft rejection. It inhibits T-cell proliferation and B-cell antibody formation. Leflunomide also inhibits tyrosine kinases, although the in vivo clinical effect of this action is not completely elucidated.

Pharmacology. Leflunomide is orally administered, shows good bioavailability, and has a long plasma half-life of roughly 2 weeks. It is highly protein bound, metabolized in the liver, exhibits significant enterohepatic circulation, and is excreted by the kidney and gut.

Clinical use. In 3 12-month phase III controlled clinical trials involving 1839 patients, leflunomide was found to be significantly superior to placebo, and equivalent to methotrexate and sulfasalazine in reducing the signs and symptoms of active RA. The onset of action of leflunomide appeared to be earlier than with the other active comparator treatments. Importantly, in these same trials, leflunomide retarded the progression of radiographic erosions, but this structural modification effect was similar in magnitude to that observed in both methotrexate and sulfasalazine treatment groups. It has also been shown to improve quality of life.

In practice, the use of leflunomide increased after its introduction, particularly among patients who failed methotrexate or who were not considered candidates for the anticytokine treatments. A loading dose of 100 mg po qd for 3 days was recommended in the past, but its use has decreased as a means to minimize side effects. Some people begin with the maintenance dose of 20 mg po qd. Dosage reduction to 10 mg po qd is occasionally a useful strategy when adverse effects are encountered. Individual practitioners are now experimenting with leflunomide in combination with other second-line agents.

Adverse effects. Side effects seen with leflunomide include reversible alopecia, skin rash, diarrhea, and liver transaminase elevations. The pivotal trials of leflunomide for RA showed that approximately 15% of patients had mild elevations of liver transaminases (1.2-2.0 x upper limit of normal). Severe elevations (ie, >3 times the upper limit of normal) were only seen in approximately 1%-4 % of patients in these trials. Many of the hepatic adverse events occurred early in the treatment phase (usually within the first 6 months). Many of the patients who had severe hepatic reactions to leflunomide were taking other medications that may have been hepatotoxic or had significant comorbid diseases that might have contributed to the outcome.

The general recommendations for monitoring liver function in patients taking leflunomide are similar to the guidelines developed for monitoring RA patients taking methotrexate therapy. It is now recommended that ALT and AST be measured prior to drug initiation, monthly for 6 months, and finally, every 1 to 3 months thereafter if the drug is well tolerated. More frequent monitoring should be done if the patient shows elevations of liver transaminases. If elevations are observed, the dose should be reduced or stopped and liver function tests should be repeated until they are normal. Persistently abnormal or any severe elevation of liver transaminases (ie, >3 x upper level of normal) should prompt withdrawal of the drug. In the early trials, infections were infrequent and were equally prevalent across methotrexate and sulfasalazine treatment groups. Leflunomide is teratogenic and contraindicated for pregnant women; thus, it should be used with great caution in women of childbearing potential.

Tumor Necrosis Factor Inhibitors: Etanercept, Infliximab and Adalimumab

In many animal models of arthritis, and in in vitro and ex vivo experiments assessing human rheumatoid tissue, TNF-α has been proven to be of profound importance in driving inflammation in the RA synovium. Transgenic mice transected with the human TNF-α gene develop chronic arthritis, and the treatment of these animals with either the TNF-α receptor fusion proteins or the monoclonal antibody to TNF-α have abrogated the disease in vivo. TNF-α induces other pro-inflammatory cytokines, (including IL-1 and IL-6), stimulates production of matrix metalloproteinases (eg, collagenase), and increases expression of adhesion molecules.

Etanercept

Etanercept is a dimeric fusion protein of the extracellular p75 soluble TNF-α receptor linked to IgG1. It specifically binds to TNF-α and prevents its interaction with the TNF-α receptor.

Pharmacology. It is administered subcutaneously, either 25 mg twice per week or 50 mg once a week. After a single 25 mg injection, the median half-life is 115 hours.

Clinical use. Etanercept has shown profound efficacy in a number of double-blind randomized controlled trials. In the first Phase III trial of 234 patients with active RA, an impressive reduction of clinical signs and symptoms was observed in the etanercept group compared to placebo. In another Phase III study of 6 months duration, RA patients who were inadequately controlled with methotrexate were randomized to either etanercept or placebo. The addition of

etanercept markedly improved the clinical status of RA patients compared to those who received placebo.

Adverse effects. As with all TNF inhibitors, there there is concern regarding the potential for immune suppression and increased risk of infection. In clinical trials, while overall infections were observed more commonly, there was no increase in the frequency of severe infections. As with all TNF inhibitors, the development of autoantibodies, in particular ANA and anti-dsDNA, was observed in higher frequency in etanercept-treated patients compared with placebo. However, development of clinical lupus is rare.

Infliximab

Infliximab is a chimeric IgG1 monoclonal antibody to TNF-α, thereby inhibiting its biologic effects in the synovium.

Pharmacology. It is administered intravenously, and after a single intravenous administration of 3 mg/kg, the half-life is 8 to 9.5 days. Infliximab is approved for use, in conjunction with concomitant methotrexate, at doses of 3 to 10 mg/kg given every 4 to 8 weeks.

Clinical use. Infliximab was initially approved by FDA for treating patients with active Crohn's disease. The efficacy of infliximab in patients with active RA despite concomitant therapy with methotrexate was evaluated in several randomized placebo-controlled trials. Infliximab at 3 mg/kg was profoundly superior to placebo in reducing the signs and symptoms of RA. The usual dose regimen is 3 mg/kg by intravenous infusion at 0, 2, and 6 weeks, followed by 3 mg/kg intravenously every 8 weeks. Infliximab should be given to RA patients taking methotrexate, and dosage adjustment of up to 10 mg/kg can be made if there is insufficient clinical response.

Adverse effects. As with all TNF inhibitors, there is a concern regarding the potential for immune suppression and increased risk of infection. In clinical trials, while overall infections were observed more commonly, there was no increase in the frequency of severe infections. As with all TNF inhibitors, the development of autoantibodies, in particular ANA and anti-dsDNA, was observed in higher frequency in etanercept-treated patients compared with placebo. Development of clinical lupus is rare.

Adalimumab

Adalimumab is a human IgG1 monoclonal antibody to TNF-α that specifically binds to circulating and cell-bound TNF, thereby inhibiting its biologic effects.

Pharmacology. Adalimumab is given subcutaneously and has a half-life of approximately 13 days. It is given at dose of 40 mg every other week, with the potential to increase weekly doses.

Clinical use. The efficacy of adalimumab in patients with active RA has been shown in several randomized placebo controlled trials, both in conjunction with methotrexate and as monotherapy.

Adverse effects. As with all TNF inhibitors, there is a concern regarding the potential for immune suppression and increased risk of infection. In clinical trials, while overall infections were observed more commonly, there was no increase in the frequency of severe infections. As with all TNF inhibitors, the development of autoantibodies, in particular ANA and anti-dsDNA, was observed in higher frequency in etanercept-treated patients compared with placebo. Development of clinic lupus is rare.

Interleukin-1 Receptor Antagonist Anakinra

Interleukin-1 (IL-1) is a pro-inflammatory cytokine that contributes to synovial inflammation, in part by the induction of other inflammatory cytokines and protein-degrading enzymes such as collagenase. Anakinra (IL-1ra) is a homologue of the naturally occurring IL-1 receptor antagonist (IL-Rra) that competes with IL-1 for binding to type 1 IL-1 receptors.

Pharmacology. Anakinra, which is given typically as a daily subcutaneous injection, has a half-life of approximately 4-6 hours.

Clinical uses. Anakinra has been shown to be effective in several double blind placebo controlled trials. In general, the extent of responses observed with anakinra is less than that seen with TNF inhibitors.

Adverse events. The overall safety profile of this agent seems to be acceptable with the most frequent adverse events being injection site reactions. Infec-

tions are always a concern because of the active pro-inflammatory nature of IL-1; however, significant increase in frequencies of opportunistic infections were not seen in the clinical studies. In a study in which anakinra was used in combination with the TNF inhibitor etanercept, a significantly greater number of serious infections developed; therefore, combination therapy is not recommended.

T-cell Costimulation Inhibitor Abatacept

Abatacept, previously known as CTLA-4-Ig, is a fusion protein consisting of the extracellular portion of the T-cell molecule CTLA-4 linked with the Fc piece of human IgG1 that has been modified so as to not activate complement. CTLA-4 is a natural inhibitor of the interaction between CD28, a key stimulatory molecule on T-cells, and its ligands CD80 and CD86 on antigen presenting cells.

Pharmacology. Abatacept is given as an intravenous infusion over 30 minutes once a month, after an initiation phase of treatment at weeks 0, 2 and 4. The dose is weight based, approximating 10 mg/kg.

Clinical use. The efficacy of abatacept has been shown in RA patients who had active disease despite concomitant MTX or who have failed previous treatment with TNF inhibitors.

Adverse effects. As with all immunomodulatory agents, patients treated with abatacept should be observed for signs and symptoms of infection, although in clinical trials these occurred only slightly more commonly than in the comparison arms. In a study in which abatacept was used in combination with the TNF inhibitor etanercept, a significantly greater number of serious infections developed; therefore, combination therapy is not recommended.

β-cell Inhibitor Rituximab

Rituximab is a chimeric monoclonal antibody directed against CD20, a molecule whose expression is limited to β-cells. Rituximab was approved as a treatment for non-Hodgkin's lymphoma in 1997. Because of the role of β-cells in various autoimmune diseases, it has been under study in several rheumatic diseases.

Pharmacology. In RA, rituximab is typically given as 2 intravenous infusions of 1,000 mg, given 2 weeks apart over 3-4 hours. Preinfusion corticosteroids (eg, 100 mg methylprednisolone) are commonly used and seem to increase the tolerability of the first dose particularly. Following treatment with rituximab, there is a profound and long-lasting depletion of circulating β-cells. Because not all patients respond, this cannot be used as a marker of efficacy.

Clinical use. The efficacy of rituximab has been shown in several studies in RA. Its initial approval in RA was for patients who had failed previous treatment with TNF inhibitors.

Adverse effects. As with all immunomodulatory agents, patients treated with rituximab should be observed for signs and symptoms of infection, although in clinical trials these occurred only slightly more commonly than in the comparison arms. While infusions of rituximab appear to be better tolerated in RA as compared to lymphoma, infusion related side effects can occur and can be severe.

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