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# TREATMENT STRATEGIES FOR THE MANAGEMENT OF RHEUMATOID ARTHRITIS

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Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by symmetric inflammation of the small joints of the hands and feet and other peripheral joints, with the potential—unless optimally controlled—to result in progressive destruction of articular and peri-articular structures.<sup>1</sup> RA is a systemic disorder and characteristically causes fatigue, anemia, and elevation of acute-phase reactants such as the erythrocyte sedimentation rate (ESR). In its most severe form, RA can lead to internal organ inflammation and damage in the lungs, blood vessels, and nerves. Of particular concern is the association of RA with cardiovascular disease (CVD) due to the “spillover effect” of the inflammation onto blood vessels. RA is an independent risk factor for increased coronary artery disease (CAD) severity. In a study by Warrington et al that compared CAD patients with CAD patients who also had RA, those with an RA diagnosis had a two-fold probability of having a

diseased vessel.<sup>2</sup> RA and CAD cases also tended to have increased all-cause mortality (32%) compared with CAD-only controls (18%). In addition, the risk of cardiovascular (CV) death was increased in RA and CAD cases (17%) compared with CAD-only controls (7%).

A study by Dessein et al reported that CVD risk factors in RA patients tended to cluster with those observed in the metabolic syndrome.<sup>3</sup> Abnormalities in C-reactive protein (CRP), high-density lipoprotein (HDL) cholesterol, and triglycerides, as well as insulin sensitivity and hypertension, are interrelated in RA patients, whereas none of these relationships were seen in osteoarthritis (OA) patients.

The rheumatologist must therefore remain vigilant about changes not only in the joints but other body systems as well, and direct treatment strategies accordingly. In much the same way as diabetes therapy has broadened to include that disease's collateral effects on the CV system, retina, kidney, and nerves, so too has

the treatment of RA become a global one, expanding to encompass other organs affected by RA. For this reason, treatment paradigms are shifting quickly. The physician must focus on both the optimal control of inflammation and on other CV risk factors such as cholesterol, blood pressure, diabetes, weight control, and smoking.

This article will demystify some of the cloudier issues surrounding RA, its etiology, and overall treatment. Does smoking impact the initiation and progression of RA? Are statins relevant as a treatment adjunct for RA itself or as adjunctive treatment to prevent collateral damage? In early RA, how soon should treatment be initiated and which agents should be used? Will combinations of biologic agents prove to be both effective and safe in the future? Is there still a role for methotrexate monotherapy in RA treatment? These and other questions will be explored as we discuss the epidemiology, etiology, symptoms, diagnosis, and evaluation of RA, as well as pharmacotherapy and other treatments.

## **EPIDEMIOLOGY AND ETIOLOGY**

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The incidence of RA varies by geographical region. The majority of studies carried out in North America and northern European regions approximate a prevalence of 0.5% to 1.1% of the population, and a mean annual incidence of 0.02% to 0.05%.<sup>4</sup> Native Americans have the world's highest prevalence of RA—five to six times greater than the general American population. The occurrence of the disease seems to be lower in other parts of the world, with South Americans, Asians, Africans, and Middle Easterners having relatively low rates. About 70% of

RA patients are women.<sup>5</sup> RA is associated with an increased mortality, and the disease generally reduces the patient's lifespan by three to 10 years.<sup>4</sup> Rate of disease onset appears to peak in the fifth decade of life.<sup>4</sup>

## **Genetics and Environment**

Epidemiological evidence exists to demonstrate that genetic factors are related to an increased risk of RA. However, RA is considered to be a multifactorial disease resulting from the interaction of both genetic and environmental factors, which contribute to its occurrence and expression. The main risk factors include genetic susceptibility, sex, age, smoking, and still-undefined infectious agents, as well as hormonal, dietary, socioeconomic, and ethnic factors. Most of these factors are likely to be associated with both disease occurrence and severity. A lower socioeconomic status, poor education, and poverty are linked to a poorer disease outcome.

RA has a genetic basis, which is thought to account for about 60% of disease susceptibility and expression.<sup>5</sup> The main genetic risk factor for RA is the shared epitope (SE) of the human class II histocompatibility antigen HLA-DR,<sup>6</sup> which can be found in antigen-presenting cells, B cells, monocytes, macrophages, and activated T cells. The main connection of the SE with RA occurrence and severity appears to be related to its linkage to autoantibodies to citrullinated peptides.

In addition, several non-HLA loci have been linked to RA, including the 18q21 region of the TNFRSF11A gene, which encodes the receptor activator of nuclear factor kappa  $\mu$ , essential in bone resorption in RA.<sup>5</sup> Pharmacogenetic factors are also

important in the treatment of RA.<sup>5</sup> This is because the activity of the enzymes needed to metabolize such anti-RA agents as methotrexate and azathioprine, including methylenetetrahydrofolate reductase (MTHFR) and thiopurine methyltransferase (TPMT), are in part genetically determined.

### **The Viral, TB, and Stress Connections**

Recent evidence implicates viral involvement in the manifestation of RA in genetically predisposed individuals. Epstein-Barr virus (EBV), a ubiquitous human virus, has generated tremendous interest as a potential trigger. Stimulating polyclonal lymphocyte expansion, this virus persists within B-cell lymphocytes for the life of the host, but is inhibited from reactivating by the immune response.<sup>7</sup> However, patients with RA may possess an impaired capacity to control EBV infection.<sup>8</sup> EBV has oncogenic potential and is involved in the development of some lymphomas. Histologic analysis shows that most lymphomas in RA patients are diffuse large B-cell lymphomas, a form of non-Hodgkin's lymphoma. Overall, RA patients have approximately a twofold heightened risk of developing lymphoma.<sup>8</sup> Some, but not all, of this increased risk reflects an increase in EBV-associated lymphomas. Indeed, one study that assessed RA patients who had lymphoma revealed that EBV was present in 12% of the tumors.<sup>9</sup> Lymphoma may be linked to the elevated EBV load found in RA patients and may reflect subtle injury to antiviral immunity in this group of patients. Recent evidence has ruled out that human retrovirus-5 proviral DNA exists in synovial tissue

and blood samples in RA patients,<sup>10</sup> contrary to earlier reports.<sup>11</sup>

Mobley has proposed that epidemiological and archaeological evidence suggests a link between RA and *Mycobacterium tuberculosis*.<sup>12</sup> Although the data that imply this connection are incomplete, a correlation exists between current rates of RA incidence among various ethnic populations and the death rates caused by tuberculosis among those populations 100 to 200 years ago. For example, RA is relatively non-existent in Africa, except in areas that were originally colonized by Europeans. The verification of this hypothesis may help us in more completely understanding the etiology of RA. Straub et al have suggested that psychological stress affecting hormones and nerve fibers may exacerbate RA. The reasoning: When chronic inflammation is present, inadequate cortisol secretion and decreased sympathetic tone occur. The result is functional loss of synovial sympathetic nerve fibers, a local beta-to-alpha-adrenergic shift, local uncoupling of cortisol and norepinephrine, and a disconnection of the body from the inflamed area that becomes the basis for the stress-induced provocation of RA.<sup>13</sup> The investigators concluded that patients could, if trained, control their stress, a hypothesis that requires further research.

### **Smoking**

As mentioned, the main genetic risk factor for RA is the SE gene, although it is also now known that smoking is an important environmental risk factor. Smoking may trigger in SE genes RA-specific antibodies to citrullinated proteins, the most specific autoimmunity known for RA.<sup>14</sup> Klareskog et al found that smoking can trigger HLA-DR SE gene-restricted immune

reactions in anticitrulline-positive RA, but not in anticitrulline-negative RA; the combination of smoking history and the presence of double copies of HLA-DR SE genes can raise the risk for RA 21-fold compared with the risk among nonsmokers who carry no SE genes.<sup>14</sup> The Epidemiological Investigation of Rheumatoid Arthritis (EIRA) group performed a population-based case-control study using incident cases of RA that quantified the hazard: It showed that the increased risk was only apparent among patients who had smoked for 20 years or longer years at a rate of six to nine cigarettes per day, with the risk remaining high and continuing for 10 to 19 years after smoking cessation.<sup>15</sup> The risk increased with escalating cumulative smoking. In time, other environmental provocations may be found to have a similar triggering effect, but at present, only smoking and its effect on RA has been studied intensely.

### **Breast-feeding**

Breast-feeding appears to lower the risk for RA. In a large cohort, cumulative breast-feeding for more than 12 months (relative risk 0.8) was inversely related to the development of RA.<sup>16</sup> This apparent effect showed a significant trend toward lower risk with longer duration of breast-feeding—20% lower if feeding by breast occurred for 12 to 23 months and 50% lower for breast-feeding of 24 months or longer. Irregular menstrual cycles and earlier age at menarche (10 years or younger) increased the risk of RA by 40% and 60%, respectively. The use of oral contraceptives does not seem to impact the incidence of RA.

### **Higher Weight, Lower RA Mortality**

In RA, body mass has a paradoxical effect on mortality. RA patients with high body mass indices (BMI) have lower mortality than thinner patients, probably because low weight in an RA patient may reflect a catabolic effect of unbridled systemic inflammation. Escalante et al showed that patients with BMIs of 30 and higher had a much lower mortality (1.7 deaths/100 person-years) compared with those whose BMI was under 20 (15.0 deaths/person-years).<sup>17</sup> The investigators also observed an interaction between BMI and ESR where the BMI protective influence occurred only if the ESR was low, leading them to conclude that the effect of body mass on mortality appeared to be modified by the level of systemic inflammation. Other risk factors for RA are presented in **Table 1**.

## **SYMPTOMS AND DIAGNOSIS**

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RA is diagnosed by recognizing a clinical pattern of joint and constitutional signs and symptoms. The classification criteria listed in **Table 2** can aid in classifying patients for the purpose of clinical research studies, but may not absolutely establish the diagnosis in any individual patient, especially those with early disease. While the characteristic persistent symmetric polyarthritis of the small joints of the hands and feet are telltale manifestations, no two people with RA have exactly the same illness profile. The disease evolution, course, and speed of onset and advancement differ from patient to patient. It is this heterogeneity that demands careful follow-up and assessment, as well as careful measurement

of disease activity, response to treatment, and progression.

The typical RA patient presents with a history that includes prolonged morning stiffness (ie, for longer than one hour), which may subside with activity,

as well as complaints of polyarthralgias and/or polyarthritis, joint gelling, and fatigue. Examination findings suggest that RA includes symmetric polyarthritis of the wrists, the metacarpophalangeal and proximal interphalangeal

**Table 1. Additional Risk Factors and Their Impact on RA**

| Risk Factor  | Impact  |
|--|---|
| Exposure to environmental toxicants <sup>96</sup>        | <ul style="list-style-type: none"> <li>• Silica exposure: 3.4-fold RR* increase for all persons; 4.5-fold risk increase for males</li> <li>• Male farmers: 40% RR* increase</li> <li>• Pesticide exposure: 29% increase</li> <li>• Hair dressers: 52% increase</li> </ul>   |
| Coffee, tea, caffeine consumption in women <sup>97</sup> | <ul style="list-style-type: none"> <li>• Decaffeinated coffee: ≥4 cups/day produced a 2.6-fold increased risk compared with those who reported no use</li> <li>• Tea: &gt;3 cups/day of tea displayed a 39% decreased risk compared with women who never drank tea</li> <li>• Caffeinated coffee and daily caffeine intake were not associated with the development of RA</li> </ul>  |
| High vitamin D intake <sup>98</sup>                      | <ul style="list-style-type: none"> <li>• Greater intake of vitamin D was associated with a 33% decrease in risk of RA (<i>P</i> for trend=0.05)</li> <li>• Dietary intake: 28% decrease (<i>P</i> for trend=0.16)</li> <li>• Supplemental intake: 34% decrease (<i>P</i> for trend=0.03) vitamin D</li> <li>• Findings are hypothetical at this time</li> </ul>   |
| During and after pregnancy                               | <ul style="list-style-type: none"> <li>• Disease development of RA is mitigated by estrogen and pregnancy, whereas SLE<sup>†</sup> tends to flare during pregnancy and in response to estrogen<sup>99</sup></li> <li>• 3 in 4 women with RA experience significant improvement in symptoms when pregnant, but almost all relapse within 4 months postpartum<sup>99</sup></li> <li>• Pregnancy causes a shift from TH1 to TH2 immune response, increasing the cytokines IL-4 and IL-10, which may add to gestational improvement of RA<sup>99</sup></li> <li>• RA is 5 times more likely to develop after delivery than at any other time<sup>100</sup></li> </ul> |

\*RR, relative risk; †SLE, systemic lupus erythematosus

**Table 2. Classification Criteria for the Acute Arthritis of Rheumatoid Arthritis\*<sup>101</sup>**

| Criterion  | Definition  |
|--|---|
| 1. Morning stiffness   | Morning stiffness in and around the joints, lasting at least 1 hour before maximal improvement  |
| 2. Arthritis of $\geq 3$ joint areas   | 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, <sup>†</sup> MCP, <sup>‡</sup> wrist, elbow, knee, ankle, and MTP <sup>††</sup> joints |
| 3. Arthritis of hand joints  | At least 1 area swollen (as defined above) in a wrist, MCP, <sup>‡</sup> or PIP <sup>†</sup> joint  |
| 4. Symmetric arthritis   | Simultaneous involvement of the same joint areas (as defined in 2, above) on both sides of the body (bilateral involvement of PIPs, <sup>†</sup> MCPs, <sup>‡</sup> or MTPs <sup>††</sup> is acceptable without absolute symmetry)                                    |
| 5. Rheumatoid nodules  | Subcutaneous nodules over bony prominences or extensor surfaces, or in juxta-articular regions, observed by a physician   |
| 6. Serum rheumatoid factor   | Demonstration of abnormal amounts of serum rheumatoid factor by any method for which the result has been positive in <5% of normal control subjects   |
| 7. Radiographic changes  | Radiographic changes typical of RA 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)           |
| <p>*For classification purposes, a patient shall be said to have RA if at least 4 of these 7 criteria have been satisfied. Criteria 1-4 must have been present for at least 6 weeks. Patients with two clinical diagnoses are not excluded. Designation as classic, definite, or probable RA is <i>not</i> to be made.</p> <p><sup>†</sup>PIP, proximal interphalangeal; <sup>‡</sup>MCP, metacarpophalangeal; <sup>††</sup>MTP, metatarsophalangeal</p> |   |

joints of the hands, and the similar joints of the feet, as well as rheumatoid nodules. Serologic and imaging studies may be helpful in ruling out RA mimics and in confirming the diagnosis. Arthrocentesis, although not diagnostic,

is useful in excluding infection. Radiographic changes include periarticular osteopenia, joint space narrowing due to cartilage damage, and erosions due to bony damage. The presence of autoantibodies to cyclic citrullinated

peptides (anti-CCP antibodies) has been demonstrated to have 93% specificity for RA.<sup>18</sup> Anti-CCP antibodies may be valuable in confirming a diagnosis of RA in patients with an atypical presentation or when another diagnosis is equally likely, such as Lyme disease. The presence of a combination of both rheumatoid factor and anti-CCP in the serum of a patient has great specificity for RA and also augurs poorly for the eventual development of joint damage, limitation in function, and extra-articular disease manifestations.

### Differential Diagnosis

The list of RA mimics is extensive. RA can resemble any disorder causing acute or chronic polyarthritis. A thorough history and examination are often helpful in narrowing the differential diagnosis in the individual patient. Joint inflammation is the hallmark of a number of rheumatic diseases, including RA, juvenile idiopathic arthritis, gout and pseudogout, and the spondyloarthropathies—psoriatic arthritis (PsA), ankylosing spondylitis, reactive arthritis, and inflammatory bowel disease-associated arthropathy. Although some mechanisms of joint or soft tissue damage are communal among these diseases, each condition has a unique impact on articular bone and cartilage or on the axial or appendicular skeleton.<sup>19</sup> For this reason, the clinician must diagnose by differentiating among the extensive list of inflammatory arthropathies.

### Rheumatoid Arthritis vs Osteoarthritis

OA is best differentiated from RA by a thorough history and examination. The absence of systemic inflammatory signs

and symptoms in OA, as well as onset in later life and the pattern of joint involvement, are often enough to differentiate these two disorders. Erosive OA may have an inflammatory appearance on examination, but OA tends to involve the proximal interphalangeal (PIP), digital interphalangeal (DIP), and first carpometacarpal joints, and does not involve the wrists or metacarpophalangeal joints.<sup>10</sup> OA is not associated with proliferative synovitis, is not rheumatoid factor-positive, and has a distinct radiographic appearance. Its character of swelling differs from that of RA in that it is bony, with irregular spurs and occasional soft cysts, whereas the swelling of RA is characterized as synovial and affects soft tissues, becoming bony only in its late stages due to secondary OA.

### Spondyloarthropathies

These disorders include psoriatic arthritis, reactive arthritis, the arthritis associated with inflammatory bowel disease, and ankylosing spondylitis. Such disorders can mimic RA because they can cause significant peripheral joint inflammation. However, there are particular characteristics that distinguish them from RA: Joint inflammation is uncommonly symmetric and usually large joint, lower extremity, and asymmetric in type; there may be a rash; accompanying eye inflammation is represented by uveitis, not scleritis; bowel inflammation may exist; and the spine is commonly involved, as are the sacroiliac joints. The genetic link of these disorders is with HLA-B27, not the shared epitope of RA. PsA usually presents with a scaly rash, but the joint inflammation may occur prior to the rash and can mimic RA signs and symptoms.

Sacroiliac or DIP involvement of the hands may identify a PsA diagnosis. Treatments for both diseases overlap.

### Systemic Lupus Erythematosus

Patients with systemic lupus erythematosus (SLE) may have a similar distribution of joint involvement but rarely have erosive disease.<sup>1,20</sup> SLE has characteristic skin lesions on areas exposed to sunlight and a fixed erythema over the malar eminences, which tends to spare the nasolabial folds. Compared with RA, SLE affects females more often, as much as 90%.<sup>1</sup> SLE is the archetypal systemic disease and can commonly involve the kidneys, nervous system, lungs, heart, and skin, altogether or one at a time.<sup>1,20</sup> SLE is a febrile disease; RA is not. Unlike RA, leukopenia and/or thrombocytopenia are characteristic of SLE. As in RA, serologic tests are employed in supporting the diagnosis and helping to follow disease activity and severity. The antinuclear antibody test is a good screening test because of its excellent sensitivity. Treatment is with non-steroidal anti-inflammatory drugs (NSAIDs), antimalarials, immunosuppressive treatments, and corticosteroids.

### Fibromyalgia Syndrome

Fibromyalgia syndrome (FMS) may present with diffuse, symmetric myalgias, arthralgias and stiffness at rest, with aching pain, tenderness, and areas of tendon insertions.<sup>1</sup> However, the absence of synovitis, the presence of multiple musculoskeletal tender points throughout the body, the lack of pain in joint range of motion, and normal laboratory and imaging studies confirm the diagnosis of FMS. FMS is present in 5%

of patients with SLE<sup>21</sup> and 17% of patients with RA<sup>22</sup>; thus, its diagnosis does not exclude other concomitant disease. Treatment includes aerobic exercises and the use of medications that control the pain that is thought to be due to central sensitization in the brain.

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## EVALUATION

There are three sets of tests or clinical scales used to evaluate disease severity and activity and define the prognosis in a patient with RA: serologic markers, radiologic markers, and disease activity scales. One assessment tool in each set must be part of the ongoing patient assessment in order to assure optimal disease control and avoidance of irretrievable joint damage.

### Serologic Markers

Because RA diagnosis is largely based on clinical signs and symptoms, identifying the disease in its early stages is often challenging. Thus, disease-specific autoantibodies that could be used as serological markers would be valuable.

#### *Rheumatoid factor*

Rheumatoid factor (RF) is the traditional serologic marker for RA. RF has a sensitivity of 70% to 75% in patients who fulfill the American College of Rheumatology (ACR) criteria for diagnosis.<sup>23</sup> However, because RF is also present in other diseases (**Table 3**), diagnosis based on RF alone can lead to misdiagnosis and subsequent inappropriate treatment. Since the presence of RF is an ACR criterion for RA, the test is performed on a routine basis in most clinical laboratories.

**Table 3. Diseases Associated with a Positive Rheumatoid Factor<sup>102</sup>**

| Disease Class       | Diseases   |
|---------------------|--|
| Rheumatic diseases  | <ul style="list-style-type: none"> <li>• Polymyositis/dermatomyositis</li> <li>• Progressive systemic sclerosis</li> <li>• Rheumatoid arthritis</li> <li>• Sjögren's syndrome (with or without arthritis)</li> <li>• Systemic lupus erythematosus</li> </ul> |
| Infectious diseases | <ul style="list-style-type: none"> <li>• Bacterial endocarditis</li> <li>• Infectious hepatitis</li> <li>• Infectious mononucleosis</li> <li>• Hansen's disease</li> <li>• Syphilis</li> <li>• Tuberculosis</li> </ul>                                       |
| Others              | <ul style="list-style-type: none"> <li>• Chronic active hepatitis</li> <li>• Cirrhosis of the liver</li> <li>• Interstitial pulmonary fibrosis</li> <li>• Sarcoidosis</li> </ul>   |

### *Anti-cyclic citrullinated peptide antibodies*

The only autoantibody known to date that offers good sensitivity with superior specificity for RA is one that targets citrullinated epitopes.<sup>24</sup> Second-generation diagnostic marker tests that measure anti-CCP antibodies have been evaluated over the last decade, with some large cohort studies showing a combination of RF-like sensitivity and an almost absolute specificity for RA.<sup>25</sup> In one such study, 120 out of 150 RA patients evaluated were found to have anti-CCP antibodies (with a sensitivity of 80%), and a strong correlation was noted between the presence of anti-CCP antibodies and disease activity score ( $r=0.82$ ).<sup>25</sup>

In another study, anti-CCP2 kits showed a sensitivity of 65% and a specificity of 96%.<sup>26</sup> Of the 140 RA patients who participated, 21 patients had a short disease duration (less than six months) and an anti-CCP2 sensitivity of approximately 50% was

demonstrated. While the anti-CCP2 sensitivity was less than in the larger study population, it was but nonetheless useful for identifying early disease.

In a third study, RF and anti-CCP antibodies were evaluated as prediction models for persistent disease. Erosive arthritis was particularly associated with the presence of anti-CCP antibodies.<sup>27</sup> RA patients positive for anti-CCP develop significantly more radiological damage than anti-CCP-negative patients,<sup>28</sup> although anti-CCP testing may be valuable if used concomitantly with an RF assay to diagnose patients with suspected early RA. This was shown in an analysis of serum samples; when the two antibodies were used together, the specificity was 99.6%.<sup>29</sup> The presence of either RF or anti-CCP antibodies are predictive of more severe disease, a greater propensity for early and progressive joint damage, functional limitations, and a shorter life span.

### *Erythrocyte sedimentation rate and C-reactive protein*

ESR and CRP have been demonstrated to strongly correlate with radiographic damage and long-term functional disability.<sup>30,31</sup> ESR correlated robustly with disease progression when plotted over periods of up to 20 years.<sup>30</sup> Elevated CRP provides a suitable short-term correlation with functional outcome and can be used as a guide for therapy.<sup>31</sup>

### **Radiologic Markers**

Erosion is a sentinel event for RA patients because erosions do not heal, even with the most aggressive or earliest treatment onset. Therefore, the ability to identify erosions as early as possible can conceivably reduce disability. Although erosions can be visualized early in RA, their appearance is usually delayed from six months to one year before they become clear on a plain radiograph. Use of newer techniques, such as magnetic resonance imaging (MRI), may allow erosive RA to be detected two years earlier than plain imaging; however, this technique has not been validated in RA. Such scans have been reported to detect erosions as early as four months after the onset of disease when plain radiography is frequently normal<sup>32</sup> and appear to provide a more precise three-dimensional picture of how RA impacts the joints, as bone marrow edema, synovitis, tendonitis, and erosions can be seen in much greater detail. However, the use of MRI in the field is controversial. Despite its advantages in early diagnosis, the procedure is expensive and may not be more useful than plain radiographs for following response to therapy.

Ultrasonography has been found to be superior to MRI and radiography in detecting early RA damage. In a study that used MRI as the reference method, ultrasonography had higher sensitivity and accuracy in detecting signs of inflammation and destruction in RA finger joints than did clinical and radiographic examinations, without loss of specificity.<sup>33</sup> Ultrasonography is noninvasive, lacks nonionizing radiation, and is less expensive, making it a practical means to assess joint inflammation and damage. It has disadvantages, too, however: Extensive training is needed to read ultrasonograms; even then, skill in using the technique and ultrasonogram interpretation are greatly operator-dependent.

### **Disease Activity Scales**

While serologic and radiologic markers provide quantifiable and visual evidence of disease progression or remission, simple, objective, standardized tools are needed to compare the clinician's RA patients individually and as a group with national standards.

#### *Disease Activity Score*

The Disease Activity Score (DAS) is widely used in clinical trials. A DAS of 5.1 defines the level of severe RA and in some countries is the criterion for the initiation of anti-tumor necrosis factor (TNF) therapy. A study of 669 RA patients was performed to evaluate the concordance between DAS scores and physicians' assessments of RA activity, and to assess the suitability of using the DAS in individual patients.<sup>34</sup> The results showed that DAS and physician global assessment had substantially different distributions of values. The level

of agreement between DAS scores and physician global assessments was 0.62 (using Lin's coefficient of concordance), suggesting poor-to-moderate concordance between the two measures of disease activity.

The results of the DAS and the DAS28 (Disease Activity Score including a 28-joint count) are not directly interchangeable: The DAS ranges from 1 to 9; the DAS28 ranges from 2 to 10. The original DAS included the Ritchie articular index, the 44-swollen-joint count, the ESR, and a general health assessment on a visual analog scale (VAS). After validation of the 28-non-graded-joint count for tenderness and swelling, a DAS28 including only these 28-joint counts came into use.<sup>35</sup> Along with both tender- and swollen-joint counts, it includes a physician global assessment and ESR. Because it demands the use of a complex equation and a calculator, as well as a blood test that may not be available at the time of the clinical assessment, it has not been universally used or accepted for routine care. Simpler scoring tools that do not demand such calculation or an ESR have been developed, correlate well with the DAS, and are currently in use.

### *Health Assessment Questionnaire*

Developed in 1978, the Health Assessment Questionnaire (HAQ) was one of the first self-report functional-status measures and has become the dominant instrument in many disease areas, including RA. The HAQ Disability Index and Pain Scale (HAQ-DI), also called the Modified HAQ (mHAQ) has been widely used for research purposes in both experimental and observational studies, as well as in clinical settings. The additional

domains included in the full HAQ (eg, demographics and health-care utilization) have primarily been used for research purposes.

The HAQ is typically used in one of two formats. The full five-dimension HAQ collects data on five generic patient-centered health dimensions, to: (1) avoid disability, (2) be free of pain and discomfort, (3) avoid adverse treatment effects, (4) keep dollar costs of treatment low, and (5) postpone death.<sup>36</sup> However, the version that is most frequently used is the "short" or "two-page" HAQ. The two-page HAQ contains the HAQ-DI, the HAQ visual analog pain scale (VAS), and the VAS patient global health scale. The self-reporting HAQ-DI can be completed in approximately five minutes; the full HAQ takes 20 to 30 minutes to complete. HAQ scores of 0 to 1 correspond to mild-to-moderate disability, 1 to 2 to moderate-to-severe disability, and 2 to 3 to severe-to-very-severe disability. Average scores in RA and OA patients are 1.2 and 0.8, respectively.<sup>36</sup> HAQ-DI asks patients to rate the amount of difficulty they experience performing eight activities (dressing, getting out of bed, lifting a cup, walking, bathing, bending, turning faucets, and getting in and out of a car), on a scale ranging from 0 to 3 (without difficulty, with some difficulty, with much difficulty, and unable).

HAQ and HAQ-DI scores are not interchangeable. A study that compared the HAQ with the HAQ-DI shows that the correlations between adjusted/unadjusted HAQ and MHAQ scores were 0.85/0.88.<sup>37</sup> A divergence in HAQ and MHAQ scores was observed in patients with high levels of disability, especially when MHAQ was compared with the adjusted final HAQ score. Adjustment of HAQ by using

devices that can help with daily activities increased the final score by an average of 0.15, and both adjusted and unadjusted HAQ scores were numerically clearly higher (mean 0.45 and 0.30, respectively) than the MHAQ score. Thus, MHAQ and HAQ may be valid as measures of physical capacity in RA patients, but clinicians should select the appropriate instrument for the setting and be cognizant of differences in scores, particularly at different disability levels.

## PHARMACOTHERAPY

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The pharmacotherapeutic agents used in patients with RA are divided into analgesics, anti-inflammatory drugs, disease-modifying antirheumatic drugs (DMARDs), and adjunctive global supportive drugs. Disease modification is defined as a medication that has been shown in randomized, controlled trials to limit or stop the development of joint-space narrowing or erosions. Analgesic and anti-inflammatory medications are important in arthritis pain management but should be used concurrently with nutritional, physical, educational, and cognitive-behavioral interventions. For the person with active RA, DMARDs are the first choice of pharmacotherapy.<sup>38</sup> These agents will be discussed according to their use as monotherapy, in combination regimens, in early RA, and in later RA. Adjunctive global supportive drugs include agents that can control osteoporosis, CVD, and other sequelae associated with RA.

### Analgesics and Anti-inflammatories

For the patient who is prescribed DMARDs, acetaminophen may be

used as a concomitant medication for mild pain.<sup>38</sup> NSAIDs and even some opioids are used in severe pain, although caution must be used when narcotics are prescribed because of the risk of dependence. Morphine, oxycodone, hydrocodone, or another mu-opioid agonist opioid, when prescribed either as a single agent or combined with an NSAID or acetaminophen, should be used for moderate to severe RA pain that has not responded to other treatments.

However, because RA is an inflammatory disease, patients will benefit more from concomitant therapy with an anti-inflammatory medication. As a class, NSAIDs are highly effective in treating the pain and inflammation associated with RA, but their reputation is qualified by their potential for significant gastrointestinal (GI) toxicity. Patients with one or more risk factors for NSAID-associated ulcers—advancing age, history of peptic ulcer, and/or concomitant use of corticosteroids and anticoagulants—should either avoid NSAIDs or be treated concomitantly with prophylactic anti-ulcer treatment. However, approximately 80% of such patients may not receive an appropriate therapeutic intervention.<sup>39</sup> To lower the risk of NSAID-associated GI injury: 1) use the minimum effective dose of the NSAID or avoid NSAIDs completely; 2) prescribe a proton-pump inhibitor or misoprostol (Cytotec®) for patients at highest risk; or 3) consider a cyclo-oxygenase-2 (COX-2) inhibitor because of its greater GI safety.

The COX-2 inhibitor celecoxib (Celebrex®) can be used as an adjunct medication for the patient with moderate-to-severe pain with or without inflammation, unless exacerbation of renal disease is a clear concern. If the

anti-inflammatory medication and the DMARD provide inadequate pain relief, then acetaminophen should be added.<sup>38</sup>

The COX-2 inhibitor celecoxib, considered to be a selective NSAID, is as effective as nonselective NSAIDs in reducing pain and inflammation and improving of joint function for patients with RA when compared with nonselective NSAIDs, as shown in a meta-analysis of randomized trials.<sup>40</sup> However, with recent growing concern about the cardiovascular safety of COX-2 inhibitors, which has prompted the removal of two of these agents from the market, the physician must select an appropriate patient by considering the risk-benefit ratio, which includes serious GI bleeding, history of intolerance to nonselective NSAIDs, CVD or associated risks, renal disease, patient preference, and cost. Both patient and physician must also remember that RA patients may have occult CVD that could be exacerbated by such a medication.

Low-dose oral glucocorticosteroids (less than 15 mg/day of prednisone or the equivalent as a single dose) should be considered for short-term (ie, one-to-two-week) use in patients with RA, especially those with severe, active disease and in whom the physician is waiting for a DMARD response.<sup>38</sup> These agents have been proven to decrease erosion progression for the first two years. A 2005 study has confirmed that low-dose (7.5 mg/day) prednisolone as an adjunct to DMARDs in early active RA retarded the progression of radiographic damage after two years in patients with early RA, generated a high remission rate, and was well tolerated.<sup>41</sup> Compared with patients in the non-prednisolone group, those in the prednisolone group experienced fewer

newly eroded joints per patient after two years ( $P=0.007$ ) and less radiographic progression beyond the smallest detectable difference (25.9% vs 39.3%;  $P=0.033$ ); more patients in the prednisolone group achieved disease remission at two years (55.5% vs 32.8%;  $P=.0005$ ). These findings thus support the use of low-dose prednisolone as an adjunct to DMARDs in early active RA. While such studies are interesting, long-term corticosteroids, even at low doses, do have the potential for cumulative side effects such as osteoporosis, osteonecrosis, diabetes, and infection risk.

### **DMARDs as Monotherapy in Early RA**

Early DMARD use after RA-symptom onset clearly results in a better clinical and radiologic outcome (**Table 4**).<sup>42</sup> This is felt to be a therapeutic window of opportunity in which DMARD therapy can significantly alter the disease outcome; thus, the earliest diagnosis and DMARD administration is essential.

The conventional DMARDs—methotrexate (MTX; Rheumatrex<sup>®</sup>, Trexall<sup>®</sup>), sulfasalazine (SSZ; Azulfidine<sup>®</sup>), hydroxychloroquine (HCQ; Plaquenil<sup>®</sup>), cyclosporine (CYC; Neoral<sup>®</sup>), and gold therapy—have been proven in clinical studies to be effective in improving the signs and symptoms of early RA; they can improve joint function, may delay or prevent disability, may reduce radiographic progression, and are cost-effective, having been on the market for many years.

In a placebo-controlled study, SSZ was shown to improve the clinical outcome over 48 weeks and to retard the development of erosions.<sup>43</sup> However, its ability to induce remission is inadequate. HCQ is moderately effective in

**Table 4. Treating RA Early is a Window of Therapeutic Opportunity**<sup>\*42</sup>

| The time when DMARDs are started | Good clinical response (% of patients) <sup>†</sup> |
|----------------------------------|---|
| Within first year                | 53%   |
| After 1 to 2 years               | 44%   |
| After 5 to 10 years              | 38%   |
| More than 10 years               | 35%   |

\*Primary data from 14 diverse, randomized, controlled trials of second-line drugs or devices in one trial; a total of 435 RA patients were analyzed. The data set included 11 methotrexate trials (five placebo-controlled trials and six comparative trials, of which two trials were unpublished), one combination trial of cyclosporine plus methotrexate, one induction trial of a combination treatment in early RA (the COBRA trial), and one placebo-controlled trial of a new device called the ProSORBA Column. This immunoabsorption column is an apheresis-based treatment containing *Staphylococcus* protein A.

<sup>†</sup>Defined by the ACR core criteria

early RA and shows a clinically and statistically significant improvement over placebo in joint score, pain, grip strength, and patient acceptance, but has not been shown to reduce radiological damage when compared with placebo.<sup>44</sup> When the use of intramuscular gold was compared at different stages of disease, early use produced the most improvement in functional status.<sup>45</sup>

In a double-blind trial, SSZ was shown to significantly reduce radiographic progression when compared with HCQ over 48 weeks ( $P < 0.05$ ),<sup>46</sup> and demonstrated significant differences in clinical outcome measures such as grip strength and morning stiffness at 48 weeks.<sup>47</sup> CYC was comparable to parenteral gold in retarding radiographic progression of joint damage and was better tolerated in terms of adherence to therapy.<sup>48</sup> In a study that compared MTX with gold over 36 months, treatment with either drug induced remission of early and erosive RA in about one-third of patients and at least marked improvement in 80% of patients; tolerability was significantly better in the MTX arm.<sup>49</sup>

Leflunomide (Arava<sup>®</sup>), an inhibitor of pyrimidine synthesis that inhibits the activation and proliferation of T lymphocytes, has demonstrated efficacy and tolerability similar to MTX, as well as significant functional improvement over MTX, in a 52-week study of 482 patients.<sup>50</sup> When compared with SSZ over 24 weeks in a study of 358 patients (41% with less than two-year disease duration), leflunomide demonstrated a more rapid rate of onset (7.3 weeks vs 8.3 weeks) and significantly greater reduction in function disability compared with placebo.<sup>51</sup>

### DMARDs Used in Combination in Early RA

Several important trials were conducted to compare combination therapies to monotherapies or other combination regimens. In the FIN-RACo (Finnish Rheumatoid Arthritis Combination therapy) trial, 195 patients with recent-onset RA (median duration: six months) were randomized to receive either a combination of DMARDs (SSZ, MTX, HCQ, and prednisolone) or a

single DMARD with or without prednisolone.<sup>52</sup> The frequency of achieving remission in the combination-DMARD group after two years was similar in patients with short (four months or less) and long (greater than four months) delay periods—that is, approximately 42% in each group—whereas the corresponding frequencies in the single-DMARD group were 35% and 11%, respectively ( $P=0.021$ ). Recent five-year data show that, of the 160 patients (78 in the combination group and 82 in the single group) who completed the study, at five years, 28% of the patients in the combination-DMARD group and 22% in the single-DMARD group had achieved remission ( $P$ =not significant).<sup>53</sup> These results confirm that therapy with combinations of DMARDs contributes to an improved long-term radiologic outcome in patients with early and clinically active RA.

In the 56-week Combinatietherapie Bij Reumatoïde Artritis (COBRA) trial, which demonstrated that step-down combination therapy with prednisolone, MTX, and SSZ was superior to SSZ monotherapy for suppressing disease activity and radiologic progression of RA, patients were followed in an open study for a total of five years to investigate whether the benefits of COBRA therapy were sustained over time.<sup>54</sup> At five years, no statistically or clinically significant differences between the combination and SSZ monotherapy treatment arms were observed. At the beginning of follow-up, patients in the combination group had a significantly lower mean DAS28 and a lower median radiologic damage (Sharp) score compared with those in the SSZ monotherapy group. The HAQ was similar in both groups. During four to five years of follow-up,

the DAS28 decreased 0.17 points per year in the SSZ group and 0.07 in the COBRA group. Thus, these findings indicate that while aggressive use of intensive, short-term DMARD combination therapy results in a sustained decrease in the rate of radiologic joint damage, the benefits of such therapy dissipate over time unless aggressive therapy is maintained.

In the Tight Control of Rheumatoid Arthritis (TICORA) study, researchers tested the hypothesis that tight control of RA symptoms—a concept borrowed from diabetes treatment—can be attained using standard DMARDs, which in turn leads to improved clinical and radiologic outcomes in patients with early RA compared with routine care.<sup>55</sup> Patients with RA less than five years in duration were placed either in an intensive-management group (for tight control) or in a routine-management group. The tight-control group was seen monthly so that participants could have their disease reviewed and measured. If at three months the DAS was greater than 2.4 after the patient received a new DMARD, then a structured escalation of therapy by protocol was administered. The DMARD therapy included SSZ, then MTX plus SSZ plus HCQ, then MTX 25 mg/week, then SSZ 5 g/day. At that point, prednisone was added at 7.5 mg/day, then MTX plus CYC, then leflunomide. The routine group was seen every three months, but the DAS score of participants was not measured, and they were managed at the discretion of their rheumatologist. The results showed that the mean decrease in DAS was greater in the intensive group than in the routine group (-3.5 vs -1.9, a difference of 1.6;  $P<0.0001$ ). Compared with routine care, patients

treated intensively were more likely to have a good response (ACR 70 response—71% vs 18%;  $P<0.0001$ ) or be in remission (DAS $<1.6$ ; 65% vs 16%;  $P<0.0001$ ). This study showed that an approach using intensive outpatient management of RA significantly improved disease activity, radiographic disease progression, physical function, and quality of life at no additional cost. The researchers employed the DAS as a “glycosylated hemoglobin equivalent” score, as would be used in a diabetic patient, and demonstrated that aiming for a clinically desired goal afforded better disease control.

The BeST trial, a randomized, single-blind Dutch study of 508 patients with fewer than two years of RA, was conducted to assess the clinical and radiologic outcomes in four treatment groups.<sup>56</sup> Patients in all groups were started on a single therapy that was changed according to protocol if they

did not reach a DAS remission. Presented in more detail in **Table 5**, the patient groups were: 1) sequential monotherapy (typically MTX, SSZ, or leflunomide); 2) step-up combination therapy (MTX, then SSZ, HCQ, then prednisone); 3) step-down combination therapy (COBRA); 4) initial therapy with MTX plus infliximab, which is an anti-tumor necrosis factor agent that will be discussed later. According to the protocol, patients in group 4 had to discontinue infliximab if they reached and maintained DAS remission at three months.

Treatment adjustments were made every three months to monitor for low disease activity (DAS in 44 joints of  $\leq 2.4$ ). The results showed that initial combination therapy including either prednisone (group 3) or infliximab (group 4) resulted in earlier functional improvement than did sequential monotherapy (group 1) and step-up combination therapy (group 2), with

**Table 5. Design of the BeST Trial<sup>56</sup>**

| Group 1<br>Sequential<br>monotherapy<br>(N=126)              | Group 2<br>Step-up<br>combination<br>(N=121)                     | Group 3<br>Initial combination<br>(N=133)   | Group 4<br>Initial<br>infliximab+MTX*   |
|--|--|---|---|
| MTX 15 mg<br>↓<br>MTX 25 mg<br>↓<br>SSZ†<br>↓<br>Leflunomide | MTX 15 mg<br>↓<br>MTX 25 mg<br>↓<br>MTX+SSZ<br>↓<br>MTX+SSZ+HCQ‡ | MTX 7.5 mg/wk<br>+SSZ+prednisone<br><br>60 → 7.5 mg/day<br>↓<br>MTX 25 mg<br>+SSZ+prednisone<br>↓<br>MTX+CYC††+prednisone | MTX 25 mg+<br>infliximab 3 mg/kg<br>↓<br>MTX+infliximab<br>10 mg/kg<br>↓<br>SSZ |

\*MTX, methotrexate; †SSZ, sulfasalazine; ‡HCQ, hydroxychloroquine; ††CYC, cyclosporine

mean scores at three months on the Dutch version of the HAQ (D-HAQ)<sup>57</sup> of 1.0 in groups 1 and 2 and 0.6 in groups 3 and 4 ( $P<0.001$ ).<sup>56</sup> After one year, mean D-HAQ scores were 0.7 in groups 1 and 2 and 0.5 in groups 3 and 4 ( $P=0.01$  for groups 1 vs 3;  $P=0.003$  for groups 1 vs 4). Thus, in patients with early RA, initial combination therapy resulted in earlier functional improvement and less radiographic damage after one year than did sequential monotherapy or step-up combination therapy.

### Anti-TNF $\alpha$ Agents in Early RA

Thus far, we have learned that we can see improved clinical and radiological outcomes in RA with early intervention and combination therapy. We know that a number of features exist that are related to poor outcomes, such as high RF titers, positive anti-CCP antibodies, involvement of multiple joints, and evidence of radiographic erosion. Yet we have failed to identify even a single characteristic of RA that tells us that a particular patient will experience either a poor or excellent outcome. The factors that can predict such information have eluded researchers at this juncture. Certainly with the emergence of the tumor necrosis factor-alpha (TNF $\alpha$ ) antagonists—infliximab, etanercept, and adalimumab—and combination-treatment studies that involve anti-TNF $\alpha$  agents plus MTX, we have a significant armamentarium for treating aggressive RA that will effectively stop or at least dramatically retard joint damage.

Infliximab neutralizes the biological activity of TNF $\alpha$  by binding with high affinity to the soluble and transmembrane forms of TNF $\alpha$  and inhibiting binding of TNF $\alpha$  with its receptors.<sup>58,59</sup> Adalimumab binds specifically to

TNF $\alpha$  and blocks its interaction with the p55- and p75-cell-surface TNF receptors; it also lyses surface TNF-expressing cells in vitro in the presence of a complement.<sup>60</sup> Etanercept is a human fusion protein that combines two extracellular binding domains of the p75 form of the TNF receptor to the Fc portion of a human IgG1 antibody molecule.<sup>61</sup> As will be discussed in this section, these drugs are effective in the majority of patients who have not responded to MTX therapy and are considered by many clinicians to be the gold standard of RA treatment. However, while they work quicker than MTX, these drugs also have the potential to increase infections (including unusual infections such as tuberculosis), they must be administered parenterally, and they can be very expensive.

### *Etanercept (Enbrel®)*

In the Early Rheumatoid Arthritis (ERA) trial, patients with active RA and a median disease duration of 11 months were treated with aggressively dosed MTX up to a maximum of 20 mg/week, etanercept monotherapy 10 mg SC twice weekly, or etanercept monotherapy 25 mg SC twice a week.<sup>62</sup> The groups receiving etanercept responded more quickly than the MTX group. At two years, 55% of the etanercept 25 mg group had improved HAQ scores by at least 0.5 units compared with 37% of patients in the MTX group ( $P<0.001$ ). The mean changes in total Sharp scores and erosion scores in the etanercept 25 mg group (1.3 units and 0.7 units, respectively) were significantly lower than those in the MTX group (3.2 units and 1.9 units, respectively;  $P=0.001$ ). Thus, etanercept as monotherapy was

safe and superior to MTX in reducing disease activity, stopping structural damage, and decreasing disability over two years in patients with early, aggressive RA.

### *Infliximab (Remicade®)*

The Active-Controlled Study of Patients Receiving Infliximab for Treatment of Rheumatoid Arthritis of Early Onset (ASPIRE) compared the efficacy of combination therapy with MTX and infliximab with MTX monotherapy in patients with early RA (median RA duration in MTX group, 0.8 years; infliximab group, 0.9 years).<sup>63</sup> Patients were randomized into three treatment groups: MTX plus placebo, MTX plus infliximab 3 mg/kg, and MTX plus infliximab 6 mg/kg. The MTX dose was increased rapidly to 20 mg/wk. At week 54, 31% of the patients in the 6 mg/kg group reached DAS remission compared with 15% in the MTX monotherapy group ( $P<0.001$ ). HAQ-score improvements from weeks 30 to 54 were also statistically superior in both groups receiving infliximab (3 mg/kg group,  $P=0.03$ ; 6 mg/kg group,  $P=0.001$ ). The ASPIRE study was the first to demonstrate that an anti-TNF $\alpha$  combination with aggressively dosed MTX is superior to aggressively dosed MTX monotherapy in MTX-naïve RA patients with respect to clinical symptoms, radiographic progression, and maintenance of function. It was also the first study to show that an aggressive MTX dose coupled with an effective dose of an anti-TNF $\alpha$  significantly retarded radiographic progression when compared with aggressively dosed MTX monotherapy in early RA.

### *Adalimumab (Humira®)*

The PREMIER trial was conducted to compare the efficacy and safety of adalimumab plus MTX vs MTX monotherapy or adalimumab monotherapy in patients with early, aggressive RA who were MTX-naïve.<sup>64</sup> The results showed that combination therapy was superior to both MTX and adalimumab monotherapy in all outcomes measured, with significantly less radiographic progression ( $P\leq 0.002$ ) among patients in the combination treatment arm at one year. At year 1, more patients receiving combination therapy exhibited an ACR50 response (62%) than did patients who received MTX or adalimumab monotherapy (46% and 41%, respectively; both  $P<0.001$ ). After two years of treatment, 49% of patients receiving combination therapy exhibited disease remission (DAS28 $<2.6$ ), and 49% showed a major clinical response (ACR70 response for at least six continuous months), rates approximately twofold greater than those seen among patients receiving either monotherapy ( $P<0.001$ ).

## **Anti-TNF $\alpha$ Agents in Later RA**

### *Anti-TNF $\alpha$ agents used as monotherapy*

While the previously discussed studies coupled the anti-TNF $\alpha$  agents with MTX, each anti-TNF $\alpha$  agent has also showed efficacy as monotherapy in patients with later-stage RA who were refractory to DMARD therapy. For example, twice-weekly SC injections of etanercept 10 mg or 25 mg, or placebo, were given for six months to 234 patients with active RA who had an inadequate response to DMARDS.<sup>65</sup> Etanercept monotherapy significantly reduced disease activity. The respective mean percentage reduction in the

number of tender and swollen joints at six months was 56% and 44% in the 25 mg group and 10 mg group, respectively, and 6% in the placebo group ( $P<0.05$ ). Also at six months, 59% of the 25 mg group and 11% of the placebo group experienced an ACR20 response ( $P<0.001$ ); 40% and 5%, respectively, achieved an ACR50 response ( $P<0.001$ ).

A single phase-three, placebo-controlled trial involving repeated treatment cycles of infliximab monotherapy or infliximab plus MTX confirmed the efficacy and safety of the combination of infliximab and MTX.<sup>66</sup> At 30 weeks, ACR20 scores were achieved in 53%, 50%, 58%, and 52% of patients receiving 3 mg/kg every four weeks or eight weeks or 10 mg/kg every four weeks or eight weeks, respectively, compared with 20% of patients receiving placebo plus MTX ( $P<0.001$  for each of the four infliximab regimens vs placebo).

In a 12-week, phase-two, double-blind, placebo-controlled study, 284 patients with DMARD-refractory RA were randomized to receive weekly SC injections of adalimumab 20 mg ( $n=72$ ), 40 mg ( $n=70$ ), 80 mg ( $n=72$ ), or placebo ( $n=70$ ) without concomitant DMARDs.<sup>67</sup> At week 12 for adalimumab 20 mg, 40 mg, and 80 mg, ACR20 response rates were 36%, 40%, and 39%, respectively, vs 7% for placebo ( $P<0.001$  for all comparisons), with statistically significant improved ACR50 and ACR 70 rates ( $P\leq 0.001$  and  $P\leq 0.05$  for all comparisons, respectively).

#### *Etanercept plus MTX*

The Trial of Etanercept and Methotrexate with Radiographic Patients Outcomes (TEMPO) compared the effects of MTX monotherapy, etanercept monotherapy, and a combination

of the two agents on clinical symptoms, radiographic progression, and function in patients with active RA.<sup>68</sup> In the trial, 686 patients with active RA were randomized to receive etanercept 25 mg SC twice weekly, MTX up to 20 mg/week, or MTX plus etanercept. The combination was more efficacious than either MTX or etanercept in slowing joint damage (mean difference in total Sharp score was -3.34 ( $P<0.001$ )). Thus, the combination of etanercept and MTX was significantly more effective in reducing disease activity, improving functional disability, and slowing radiographic progression than MTX or etanercept alone.

#### *Infliximab plus MTX*

The Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy (ATTRACT) study was designed to evaluate the efficacy and safety of repeated administration of infliximab plus MTX over a two-year period in RA patients who previously experienced an incomplete response to MTX.<sup>69</sup> The 428 patients were randomized to receive MTX plus placebo or infliximab at a dose of 3 mg/kg or 10 mg/kg plus MTX for 54 weeks, with an additional year of follow-up and/or continued treatment. Of 259 patients who entered the second year of treatment, 216 (83%) continued to receive infliximab plus MTX for 102 weeks. The infliximab plus MTX regimens resulted in significantly greater improvement in HAQ scores ( $P\leq 0.006$ ) compared with the MTX-only group. From baseline to week 102, median changes in the total radiographic score were 4.25 for patients who received the MTX-only regimen and 0.50 for patients who received the

infliximab plus MTX regimen. Overall, throughout 102 weeks of therapy, infliximab plus MTX provided significant, clinically positive outcomes in physical function and quality of life, accompanied by a slowing of joint damage among later-stage RA patients who previously had an incomplete response to MTX alone.

### *Adalimumab plus MTX*

In a multicenter, 52-week, double-blind, placebo-controlled study conducted by Keystone et al, 619 patients with active RA who had an inadequate response to MTX were randomized to receive adalimumab 40 mg SC every other week (n=207), adalimumab 20 mg SC every week (n=212), or placebo (n=200) plus concomitant MTX.<sup>70</sup> At week 52, a statistically significant decrease in radiographic progression was observed in the patients receiving adalimumab 40 mg every other week or 20 mg weekly compared with that in the placebo group ( $P \leq 0.001$  for each comparison). Also at week 52, HAQ scores were significantly improved with adalimumab 40 mg every other week and 20 mg weekly compared with placebo (the mean change in HAQ scores for the patients receiving adalimumab were -0.59 and -0.61, respectively, vs -0.25 for the patients receiving placebo;  $P \leq 0.001$  for each comparison). These findings confirm that adalimumab was more effective than placebo at slowing the progression of structural joint damage and improving physical function in patients with active RA who had failed on MTX therapy.

### *Issues involving anti-TNF $\alpha$ agents*

The use of anti-TNF $\alpha$  agents is associated with some potentially severe side

effects. Analysis of a Swedish database revealed that RA inpatients have a twofold increased risk of developing tuberculosis (TB) compared with the general population, while RA patients taking an anti-TNF $\alpha$  agent have a fourfold increased risk of developing TB.<sup>71</sup> Thus, patients should be screened for TB using five tuberculin units of purified protein derivative (PPD) prior to the initiation of anti-TNF $\alpha$  therapy.<sup>72</sup> Those patients with a positive PPD should have a chest x-ray; those patients showing no abnormality can be treated with both the anti-TNF agent and nine months of isoniazid and vitamin B6 therapy.

In anti-TNF $\alpha$  trials, patients treated with these agents had a heightened risk of infection, including fungal and other opportunistic infections.<sup>73</sup> This risk necessitates increased surveillance for infection in such patients, as well as influenza immunizations each year and pneumococcal immunization every five years.<sup>74</sup>

Whether or not lymphoma risk is increased when anti-TNF $\alpha$  agents are used is still a matter of debate. In a prospective study of 18,572 RA patients, lymphoma risk increased if the patient had RA (by a factor of 1.9), if the patient received MTX (by a factor of 1.7), infliximab (by a factor of 2.6), and etanercept (by a factor of 3.8).<sup>75</sup> The investigators remarked that the increased lymphoma rates observed with anti-TNF $\alpha$  therapy may have reflected channeling bias, whereby patients with the highest risk of lymphoma preferentially received anti-TNF $\alpha$  therapy. Thus, these data are not sufficient to establish a causal relationship between RA therapies and lymphoma development.

Anti-TNF $\alpha$  agents can be expensive, depending on the patient's insurance

coverage. Based on average U.S. wholesale prices in 2003, the approximate annual cost of adalimumab 40 mg SC every other week is \$15,679, etanercept 25 mg SC twice weekly is also \$15,679, and infliximab for a 70 kg person at 3 mg/kg (initially administered at zero, two, and six weeks, and then taken every eight weeks thereafter) is \$16,598.<sup>76</sup> Moreover, these price estimates do not include the cost of pre-therapy TB testing or monitoring for treatment complications.

Can a patient who fails on one anti-TNF $\alpha$  agent be switched to another one? Limited data from the Stockholm TNF $\alpha$  follow-up registry (STURE) demonstrate that switching agents may be an option.<sup>77</sup> Of the 18 patients who initially received etanercept, for example, discontinuation of that therapy was mostly due to lack of efficacy. When the patients were then switched to infliximab, the mean best DAS28 was significantly better than the previous result ( $P < 0.05$ ). Of the 13 patients who received infliximab first, discontinuation was mainly due to adverse events. After switching to etanercept, clinical efficacy was similar but fewer side effects were experienced. Despite these results, there is a lack of randomized, prospective trials that would generate more substantial long-term outcome data.

## Newer Agents

### *Abatacept (Orencia®)*

Abatacept is a novel fusion protein designed to modulate the T cell costimulatory signal mediated through the CD28 to CD80/86 pathway; it inhibits T-cell activation and interrupts the process leading to inflammation in RA.<sup>78,79</sup> Abatacept is approved for use in

patients who have had an inadequate response to MTX or a TNF $\alpha$  antagonist.<sup>79</sup> It is not recommended for use concomitantly with either the interleukin-1 receptor antagonist anakinra or the TNF $\alpha$  agents because of an increased rate of infections with biologic combination treatments. In a 12-month, multicenter, randomized, double-blind, placebo-controlled, phase-three clinical trial, the safety and effectiveness of abatacept was evaluated in patients in whom RA remained active despite MTX therapy.<sup>80</sup> Patients were randomly assigned to either 10 mg/kg abatacept ( $n=433$ ), or placebo ( $n=219$ ). At 12 months, more patients treated with the 10 mg/kg dose achieved ACR50 responses (48.3% vs 18.2%;  $P < 0.001$ ) and ACR70 responses (28.8% vs 6.1%;  $P < 0.001$ ) compared with patients who received placebo. More patients treated with abatacept had DAS28 remission compared with placebo patients at 12 months (23.8% vs 1.9%;  $P < 0.001$ ). Thus, abatacept was associated with significant reductions in disease activity and improvements in physical function maintained over the course of 12 months in patients with RA that had remained active despite MTX treatment. In a study that included patients who had an inadequate response to a TNF $\alpha$  antagonist, abatacept was started (dose for patients weighing  $< 60$  kg: 500 mg; 60-100 kg: 750 mg;  $> 100$  kg: 1 g).<sup>80</sup> At the study's end at six months, ACR20, ACR50, and ACR70 scores, as compared to placebo, were 50% vs 20% ( $P < 0.001$ ), 20% vs 4% ( $P < 0.001$ ); and 10% vs 2% ( $P < 0.01$ ), respectively.

The adverse reactions of greatest concern in abatacept therapy are serious infections and malignancies. Serious infections (eg, pneumonia, cellulitis, UTIs, bronchitis, diverticulitis, acute pyelonephritis) were reported in 3.0% of

patients treated with abatacept versus 1.9% of placebo patients.<sup>80</sup> More cases of lung carcinoma were observed in abatacept-treated patients (0.2%) than in placebo-treated patients (0%). The rate observed for lymphoma is approximately 3.5-fold higher in patients who took abatacept in pivotal clinical trials than in the general population.<sup>80</sup>

### *Anakinra (Kineret®)*

Anakinra blocks the biologic activity of IL-1 by competitively inhibiting IL-1 binding to the interleukin-1 type I receptor (IL-1RI).<sup>81</sup> Anakinra is indicated for the reduction in signs and symptoms and slowing the progression of structural damage in moderately to severely active RA in adult patients who have failed on one or more DMARDs.<sup>82</sup> In a double-blind, randomized, placebo-controlled study that assessed 506 patients with active RA despite current treatment with MTX, patients remained on MTX but also received anakinra 100 mg/day SC or placebo.<sup>83</sup> The results showed that, compared with placebo, significantly greater proportions of patients treated with anakinra achieved ACR20 (38% vs 22%;  $P < 0.001$ ), ACR50 (17% vs 8%;  $P < 0.01$ ), and ACR70 (6% vs 2%;  $P < 0.05$ ) responses. The response to anakinra was rapid; the number of patients with an ACR20 response at week four was twice as high with anakinra as with placebo ( $P < 0.005$ ). Thus, anakinra can be useful in patients who have not succeeded on MTX monotherapy. Anakinra is associated with an increased risk of infections, particularly if the patient is also receiving an anti-TNF $\alpha$  agent. Problems related to this medication include the fact that it is given as a daily SC injection and that its clinical

effectiveness in the “real world” has not been impressive. Thus, its use has been relegated to those patients in whom anti-TNF $\alpha$  agents have failed.

### *Rituximab (Rituxan®)*

Rituximab is a genetically engineered chimeric murine/human monoclonal antibody directed against the CD20 antigen found on the surface of normal and malignant B lymphocytes.<sup>84</sup> It is indicated for use in combination with MTX to reduce signs and symptoms in adult patients with moderate to severe active RA who have had an inadequate response to one or more anti-TNF $\alpha$  agents.

The REFLEX study was performed to assess the efficacy and safety of rituximab in combination with methotrexate to reduce signs and symptoms in adult patients with moderately-to-severely-active RA who have had an inadequate response to one or more TNF antagonist therapies.<sup>85</sup> In this study, rituximab 1000 mg, given as two infusions two weeks apart along with weekly MTX, was effective in decreasing signs and symptoms of active RA in patients who have experienced an inadequate response to TNF antagonists.<sup>85</sup> Patients on a background regimen of MTX (10 mg/week to 25 mg/week) were randomized to a single course of either rituximab 1000 mg (N=311) or placebo via IV infusion on days 1 and 15. Mean baseline data were: RA duration, 12 years; DAS28, 6.9; percentage of patients who had an insufficient response to two or three anti-TNF blockers, 40%. The patients enrolled in REFLEX had either an inadequate response or intolerance to at least one TNF $\alpha$  blocker. At 24 weeks, the proportion of patients with an ACR20 response was significantly higher

( $P < 0.0001$ ) for rituximab-treated patients compared with placebo-treated patients (51% vs 18%;  $P < 0.0001$ ).<sup>85</sup> The proportions of patients achieving ACR50 and ACR70 responses at week 24 (**Table 6**) were also significantly higher for rituximab-treated patients than for those receiving placebo (ACR50: 27% rituximab vs 5% placebo; ACR70: 12% rituximab vs 1% placebo;  $P < 0.0001$  for both comparisons). ACR20 response rates over time showed a statistically significant ( $P < .0001$ ) difference between rituximab and placebo by treatment week 8; ACR50 and ACR70 responses over time showed a statistically significant ( $P < 0.0001$ ) separation by weeks 12 and 16 of treatment, respectively.

More serious adverse events were reported in the placebo arm than in the rituximab arm (10% vs 7%).<sup>85</sup> As expected, exacerbation of RA was reported twice as frequently in placebo patients as in rituximab patients (42% vs 21%).<sup>85</sup> The frequencies of adverse events reported with <10% incidence were similar between the respective placebo and rituximab arms: urinary tract infections (UTIs; 8% and 3%), headache (9% vs 8%), upper respiratory tract infection (URIs; 7% vs 8%) and nasopharyngitis (6% vs 7%) and nau-

sea (2% vs 7%). Any AEs during or within 24 hours of infusion of rituximab occurred in a higher proportion of rituximab-treated patients during or following the first infusion (29%) compared with placebo-treated patients (23%). The most common AE was headache, affecting 5% of patients in both treatment groups following the first infusion but decreasing to less than 1% in both groups after the second infusion.<sup>85</sup> The incidence of infections was higher in patients treated with rituximab (41%) than in patients who received placebo (38%), but the overall infection rate per 100 patient years was higher in placebo-treated patients (154.6) than rituximab-treated patients (138.2).<sup>85</sup> The most common infections in both groups were URIs, UTIs, nasopharyngitis, bronchitis, and sinusitis.

In the earlier DANCER study, RA patients 18 to 80 years with inadequate response to MTX were continued on MTX (10 mg/week to 25 mg/week).<sup>86</sup> The current data do not show breakdown by corticosteroid or glucocorticoid use, although that data will be presented in the future. Assuming there is no difference in corticosteroid dose, as implied by the investigators, these high corticosteroid doses may not

**Table 6. Results at Week 24 for the REFLEX Study<sup>86</sup>**

| <b>Efficacy at Week 24</b>        | <b>Placebo<br/>(n=209)</b> | <b>Rituximab<br/>1000 mg<br/>(n=311)</b> |
|-----------------------------------|----------------------------|--|
| ACR20 (%)                         | 18                         | 51                                       |
| ACR50 (%)                         | 5                          | 27                                       |
| ACR70 (%)                         | 1                          | 12                                       |
| Moderate-good EULAR responses (%) | 22                         | 65                                       |

\* $P < .0001$   
EULAR, European League Against Rheumatism

be necessary for the efficacy of rituximab, although they were beneficial in suppressing infusion-related reactions. Thus, the patient will probably continue corticosteroid use in conjunction with rituximab, at least for the first infusion; after the first infusion, however, the frequency of infusion reactions, and therefore the need for corticosteroids, decreases with rituximab administration.

In another supportive, randomized double-blind, placebo-controlled trial of rituximab in 161 patients with active RA despite treatment with MTX, patients received one of four treatments: oral MTX, rituximab, rituximab plus cyclophosphamide (Cytoxan®), or rituximab plus MTX.<sup>87</sup> Patients received a single course of two rituximab infusions. At week 24, the proportion of patients with ACR50 rates was significantly greater with the rituximab-MTX combination (43%;  $P=0.005$ ) and the rituximab-cyclophosphamide combination (41%;  $P=0.005$ ) than with MTX alone (13%). In all groups treated with rituximab, a significantly higher proportion of patients had ACR20 rates (65% to 76% vs 38%;  $P<0.025$ ). All ACR responses were maintained at week 48 in the rituximab-MTX group. At week 24, serious infections occurred in one patient (2.5%) in the control group and in four patients (3.3%) in the rituximab groups. Peripheral-blood-immunoglobulin concentrations remained within normal ranges. The investigators concluded that for patients with active RA despite MTX treatment, a single course of two infusions of rituximab, alone or in combination with either cyclophosphamide or continued MTX, provided significant improvement in disease symptoms at 24 weeks.

## Global Approach to Therapy

Improving the outcomes of RA patients involves a global approach, much the same way diabetes and hypertension therapies involve a combination of exercise, diet, polypharmacotherapy, and other appropriate lifestyle modifications. These goals and their specifics are presented in **Table 7**.

### *Cardiovascular disease*

The patient with RA is at risk for a number of non-joint-related diseases. For instance, RA patients have a high prevalence of preclinical atherosclerosis independent of traditional risk factors, suggesting that chronic inflammation and possibly disease severity are atherogenic in this population. In a study by Roman et al of 98 consecutive outpatients with RA, 44% had preclinical atherosclerosis compared with 15% of 98 controls matched for age, sex, and ethnicity ( $P<0.001$ ).<sup>88</sup> The relationship between RA and carotid atherosclerotic plaque remained after accounting for age, serum cholesterol levels, smoking history, and hypertensive status; adjusted predicted prevalence was 38.5% for the RA group and 7.4% for the control group. Age ( $P<0.001$ ) and current cigarette use ( $P<0.014$ ) were also associated with carotid atherosclerotic plaque. Among RA patients, atherosclerosis was related to age, hypertension status, and use of TNF $\alpha$  inhibitors, a possible marker of disease severity. Thus, the person at risk for a CV event should be given a regular low dose of aspirin (between 75 mg/day and 160 mg/day) whether treated with a nonselective or a COX-2 selective NSAID.<sup>38</sup> Also, DMARD treatment can actually improve the outcome in RA. Choi et al demonstrated that MTX-treated

**Table 7. Improving the Outcome of Patients with RA: A Global Approach\***

| Goals  | Specifics  |
|--|--|
| Make the earliest possible diagnosis and initiate therapy as soon as possible.   | Send patient to Early Arthritis Center to allow for better and faster treatment of joint problems.   |
| Use markers that predict outcomes and which define treatment and response.   | Use RF, anti-CCP, imaging modalities, HAQ, DAS, pain scales, shared epitopes for optimal disease control.  |
| Limit collateral damage such as that caused by myocardial infarction, atherosclerosis, coronary artery disease, infection, malignancy, osteoporosis, amyloidosis.  | Use the diabetes paradigm: control lipids, take aspirin therapy, stop smoking; monitor for osteoporosis and prescribe bone-preserving medications as needed; avoid comorbid diseases and, thus, advise screening for cancer, sexually transmitted diseases, TB, etc. |
| *Paget SA. Rheumatoid arthritis—A profound paradigm shift in diagnosis and treatment: Initiating early treatment to optimize long-term response. Presented at: The European League Against Rheumatism (EULAR) 2005 Annual Meeting; June 8-11, 2005; Vienna, Austria. |  |

patients had a 70% reduction in CV mortality compared with those who did not receive disease-modifying therapy.<sup>89</sup> Other DMARDs, such as SSZ, HCQ, and gold did not provide this protection.

HMG-CoA reductase inhibitors, the statins, have been used of late in patients with RA. In the aforementioned study by Roman et al, the investigators advised rigorous control of RA activity because chronic inflammation is likely a driving force for premature atherosclerosis.<sup>88</sup> In another study by Roman et al, arterial stiffness was increased in patients with RA.<sup>90</sup> In that study, the researchers concluded that arterial stiffness is increased in chronic inflammatory disorders independent of the presence of atherosclerosis and is related to disease duration, cholesterol, and CRP, as well as the cytokine that stimulates its production, interleukin-6 (IL-6).

Clearly, the optimal approach to prevention of atherosclerosis in RA

patients includes a combined effect of control of inflammation and such known risk factors for atherosclerosis as obesity, smoking, diabetes, hypertension, hypercholesterolemia, and hyperhomocysteinemia. The addition of a daily baby aspirin (81 mg) is also appropriate, with appreciation of potential GI problems if used along with corticosteroids and NSAIDs.

### *Osteoporosis*

As discussed earlier, RA patients are frequently prescribed corticosteroids to reduce joint inflammation. They are therefore at risk for developing corticosteroid-induced osteoporosis. In a retrospective cohort study of 3,031 patients, in which 17% had a diagnosis of RA and the mean daily dose of corticosteroids was 20 mg of prednisone equivalents, fewer than 10% of the patients received a bone-mineral density measurement, 38% were dispensed osteoporosis medications, and

fewer than 15% received treatment with antiresorptive medications other than hormone replacement therapy.<sup>91</sup> Thus, when oral corticosteroids are used, prophylaxis with a bisphosphonate, as well as daily calcium and vitamin D supplementation, should be considered to lower the risk of corticosteroid-induced osteoporosis.<sup>38</sup> The lowest dose of corticosteroid for the shortest period of time leads to better bone health. Since the inflammatory process itself leads to osteoporosis due to the bathing of bones with TNF $\alpha$ , IL-1, and IL-6, optimal disease control also improves bone health.

## DIET AND EXERCISE

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The huge advances made in the last decade in controlling the systemic inflammation of RA could be substantially weakened if the nutritional, metabolic, and functional consequences of even well-treated RA are not addressed. Physical and occupational therapy should be a centrally important part of the care of an RA patient in all phases of the illness.

In one analysis of the literature in which 198 publications were reviewed, five recommendations for nonpharmacologic treatments of early RA were validated by the authors of the analysis:<sup>92</sup>

- Clinicians may opt to provide joint protection education to patients with potentially severe early RA, with the knowledge that structured joint protection programs have not been found effective
- Physical exercise and sports can be suggested to patients with early RA; muscle strength exercises are suitable
- In patients with early RA, meta-

tarsal pain and/or foot alignment abnormalities should be monitored periodically, with insoles recommended as needed

- Dietary measures and nutritional supplements are not indicated as part of the treatment of early RA
- Elimination diets, particularly those with low intakes of dairy products, should be discouraged in patients with early RA

## ALTERNATIVE THERAPIES

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Alternative therapies are a popular option or adjunct to pharmacotherapy in a variety of disease states, including rheumatic diseases. However, the perceived efficacy of alternative therapies, particularly acupuncture and homeopathy, may be less than satisfactory in patients with RA than in patients with OA or spondyloarthropathies, as was shown in a cross-sectional survey of patients with a variety of rheumatic diseases.<sup>93</sup> A literature review that focused on RA patients treated with and without acupuncture found that there was no statistically significant difference between groups for ESR, CRP, VAS, number of swollen and/or tender joints, or MDAS, or for the decrease in analgesic intake.<sup>94</sup> The same review looked at patients who received electroacupuncture and found that a significant decrease in knee pain was reported in the experimental group 24 hours post-treatment compared with the placebo group, with a significant decrease also observed at four months post-treatment, although these studies were too small for the investigators to make a recommendation on this technique.

## SURGERY

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The current surgical techniques used in RA patients include:<sup>95</sup>

- Arthroscopy, used principally for small repairs, such as removal of debris and cartilage
- Synovectomy, usually of the knee and the elbow, although the procedure does not prevent cartilage loss.
- Osteotomy, a realignment of a joint to restore pain-free mobility
- Arthrodesis, a technique used today to fuse ankles, wrists, vertebrae, and failed knee replacements
- Total joint replacement, involving the complete removal of the abnormal joint and replacement with metal and plastic components; profound improvements in procedures and prostheses over the past 20 years now produce excellent outcomes.

## CONCLUSION

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RA is a systemic, autoimmune disease that, without aggressive, early treatment, will lead to a life-shortening, functionally limiting, joint-damaging illness. RA results from the interaction of both genetic and environmental factors, which contribute to its occurrence and expression. A virus may be the cause; smoking is a trigger. Due to an impressive combination of expanded scientific knowledge and understanding of the destructive potential of this disease, new, effective, relatively safe medications have been developed that have profoundly improved the outcome in RA patients. Rheumatologists have borrowed important therapeutic concepts from their oncology and endocrinology colleagues: combina-

tion therapy, goal setting for no evidence of disease, a global disease approach, and tight control of treatment. The addition of these tools to therapeutic decision-making has made all the difference.

As we move toward the future, our challenges are clearer than ever. The etiology of RA must be more precisely defined. Is smoking the actual trigger, and if so, what is it about cigarettes that sparks the disease? Are other pollutants also capable of activating RA? In terms of treatment, will more aggressive therapy decrease the amount of osteoporosis, atherosclerosis, lymphoma, and infections? Will our newer drugs provide symptom relief over greater periods of time? Long-term studies will provide answers. What other biologics can be developed? Will new drugs work better in combination with some of the drugs we presently use? As in cancer therapy, will we be able to find a small molecule that can accurately target the cells in RA that we want to hit? Will such drugs be oral rather than parenteral? Will these new drugs be affordable so that all patients who need them can obtain them?

Finding answers to these questions should be our goal. We are now arguably at the best vantage point for understanding RA, refining what we know as we go along.

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