

New Treatments for Chronic Inflammatory Disease

Arthur Kavanaugh, MD

A continuing medical education activity sponsored by NAMCP

Summary

Rheumatoid arthritis is an excellent model for discussing chronic inflammatory disease pathology and new treatments. A progressive disease, rheumatoid arthritis can cause significant disability that increases the costs related to the disease. New treatments such as tumor necrosis factor inhibitors, and T-cell modulators are proving to be valuable not only in symptomatic improvements but also in reducing progression of disease and preserving functional ability for many patients.

Key Points

- Rheumatoid arthritis is a progressive, disabling disease.
- Unlike older medications, new treatments are changing the treatment paradigm by being true disease modifiers.
- Although these agents are not yet a cure, with each new agent comes improved targeting of the underlying pathologic process.

RHEUMATOID ARTHRITIS (RA), which is the most common of the autoimmune diseases, can be used as a model when discussing chronic inflammatory diseases. Much of the information about the treatment of RA is applicable to other chronic inflammatory diseases, specifically Crohn's disease, psoriatic arthritis, and a number of others that are less common. Not only is the underlying pathophysiology similar, but also, and more importantly, the rationale for and development of new therapies is similar.

Three factors have been driving new pharmaceutical developments in the area of chronic inflammatory diseases. One is a better understanding of the underlying immunopathophysiology of these diseases. The second is an unmet clinical need; older treatments did not significantly alter the course of the diseases. The third factor is developments in biotechnology, primarily the ability to produce molecules that target the specific pathologic abnormalities.

Overview of Rheumatoid Arthritis

RA is relatively common, occurring in about 1 percent of the population. Women have RA more often than men, with the peak age of onset between 40 and 60 years of age.

The patient with RA has inflammation of synovial or diarthrodial joints. This usually presents in the small joints of the hands and feet. Untreated, joint inflammation can rapidly progress to joint destruction. One of the fundamental changes in RA treatment that has happened over the past couple of decades is a better understanding of what happens in the joint with this disease. Exhibit 1 illustrates what happens within a joint affected by RA in the early and late stages of the disease.¹

The natural history of rheumatoid arthritis is progression of damage (see Exhibit 2).² Joint pain, destruction, and dysfunction can lead to significant disability. As disability increases in the patient with RA, medical costs rise (see Exhibit 3).³

Although RA is a progressive disease, not every patient progresses at the same rate. Some patients have more severe disease and progress rapidly. There are surrogate markers that can help predict which patients should be treated more aggressively because of the possibility of rapid progression. These markers include such things as level of functional impairment, degree of joint damage at the time of diagnosis, and extra-articular disease (systemic manifestations). RA, like other chronic inflammatory diseases, is a systemic disease affecting more than just joints.

Exhibit 1: Rheumatoid Arthritis—Early and Late Progressive Changes¹

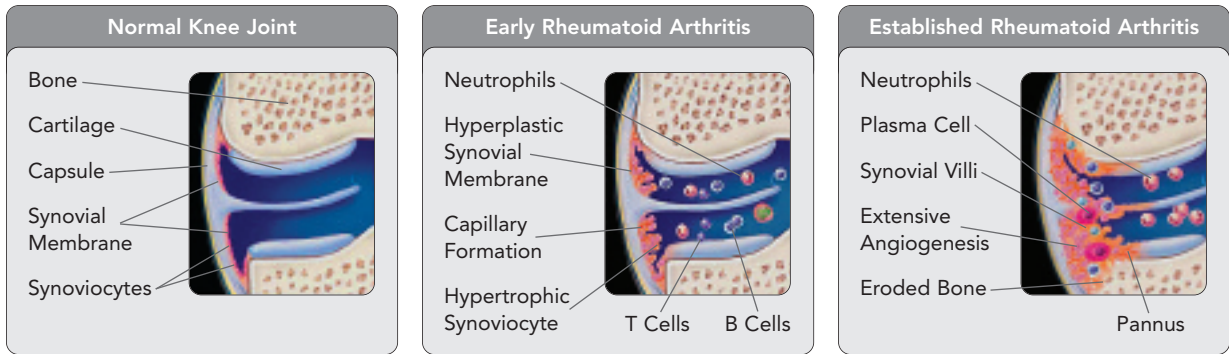


Exhibit 2: RA Is a Progressive Disease²

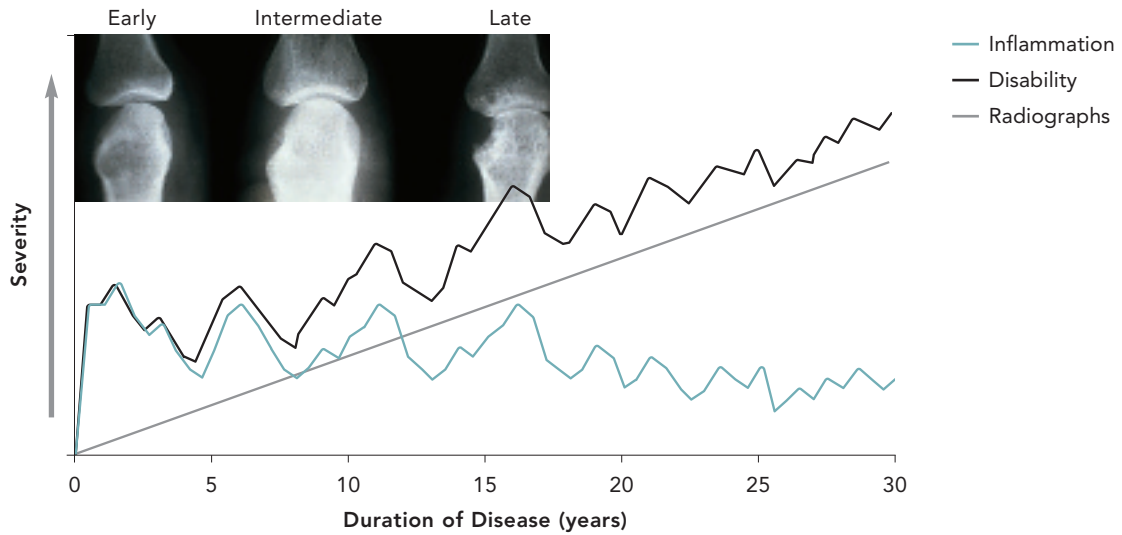
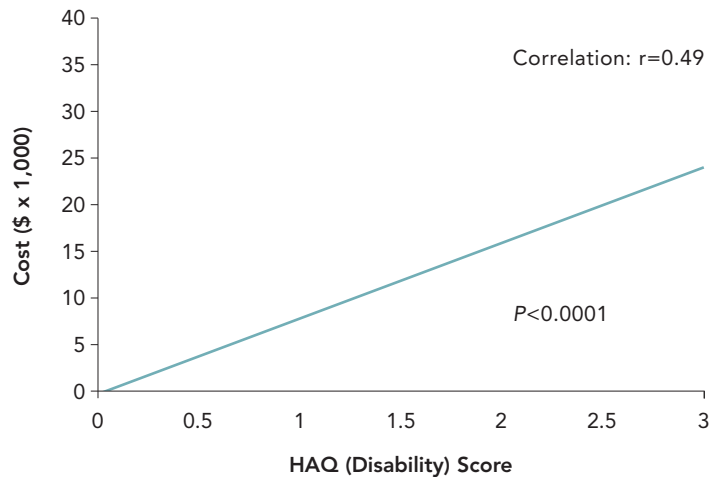


Photo: Copyright © American College of Rheumatology

Exhibit 3: Costs Rise with Increasing Disability³



Treatment

The goals of therapy in RA are:

- Prevent joint destruction, loss of joint function, deformity, disability, and early death
- Preserve quality of life
- Relieve symptoms, including fatigue, pain, swelling, and stiffness
- Achieve clinical remission.

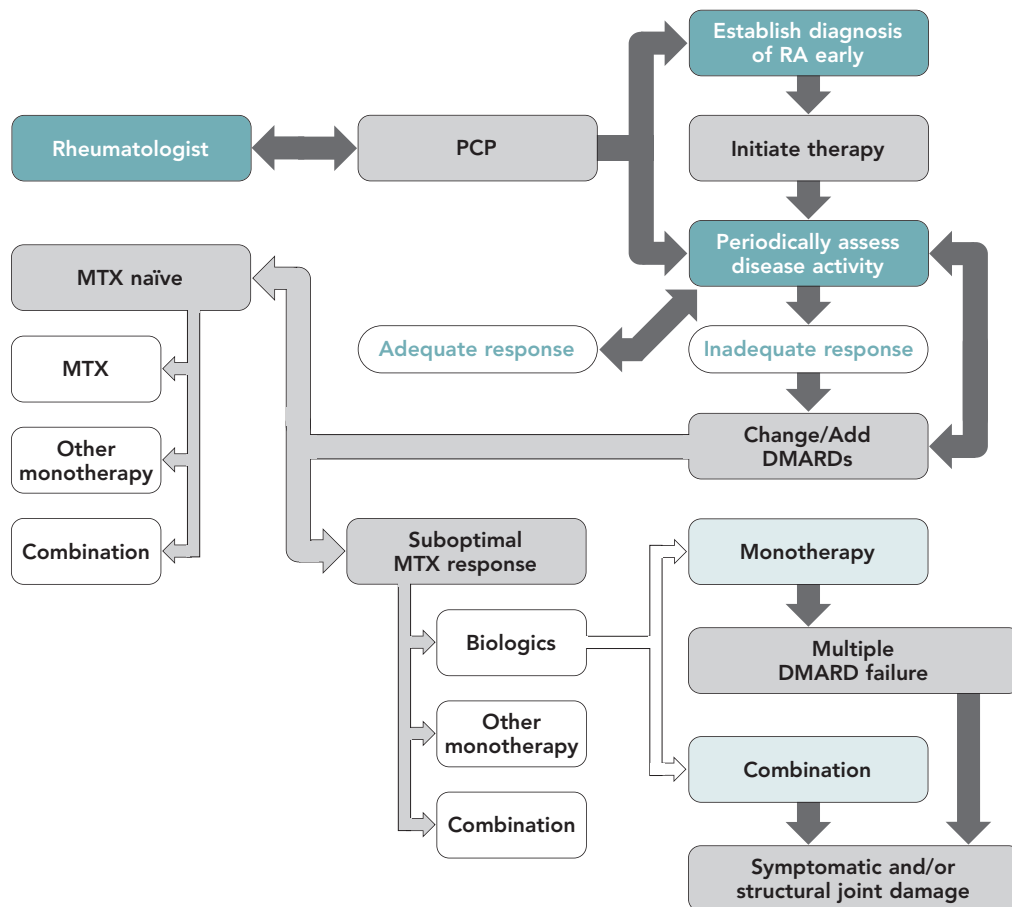
Traditionally, RA has been treated with many different classes of medications. Adjunctive therapy to manage pain includes nonsteroidal anti-inflammatory agents and corticosteroids but these agents do not change the course of the underlying disease. A mainstay of treatment for years has been disease-modifying anti-rheumatic drugs (DMARDs). Methotrexate, leflunomide, sulfasalazine, and hydroxychloroquine are the most commonly used agents. Gold, azathioprine, minocycline, and cyclosporine are less frequently used. Although named disease-modifying agents, these medications do not directly target the immune abnormalities of RA or other chronic inflammatory diseases. They appear to have either anti-inflammatory

activity, nonspecific immune suppressant activity, or a combination of both. These agents can help improve disease symptoms and some can modestly impact progression of joint damage but very seldom put people into remission.

The treatment paradigm of RA changed with the introduction of biologic agents that are specially targeted to the immune system alterations. Three types of biologics are currently available: tumor necrosis factor (TNF) inhibitors (etanercept, infliximab, adalimumab); interleukin-1 (IL-1) inhibitors (anakinra); and T-cell modulators (abatacept). The available IL-1 inhibitor is not as effective as the TNF inhibitors, so it is not discussed here.

Treatment guidelines from the American College of Rheumatology (ACR) are given in Exhibit 4.⁴ Methotrexate is still considered a mainstay of RA therapy. This agent is usually the initial disease modifying therapy started, but biologics are beginning to be used earlier in the treatment scheme. Early, aggressive treatment to get the disease under control appears to be the most important issue in preventing

Exhibit 4: ACR Treatment Algorithm⁴



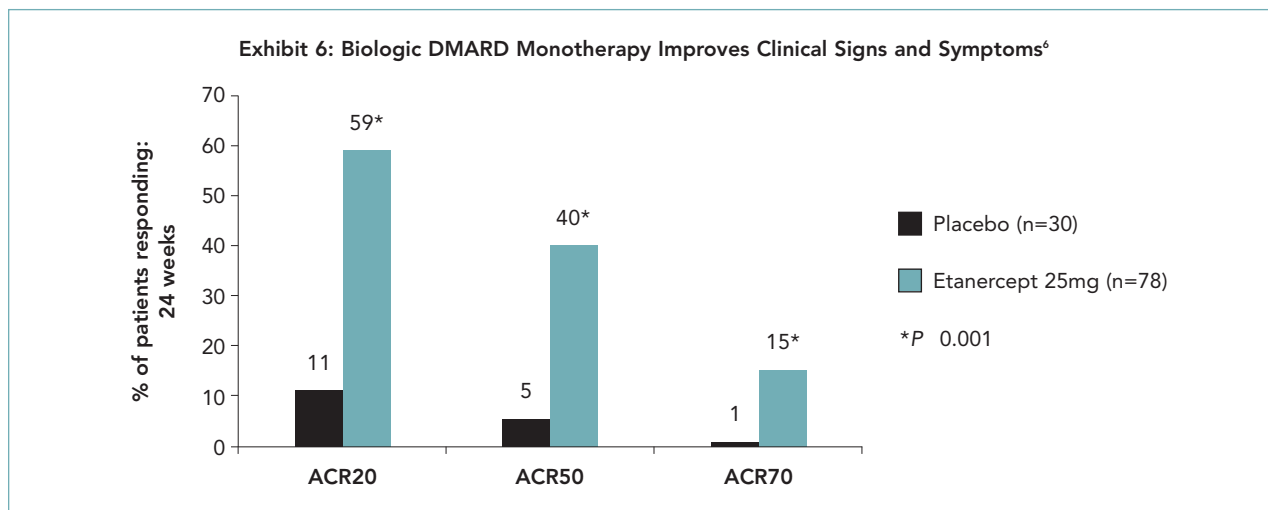
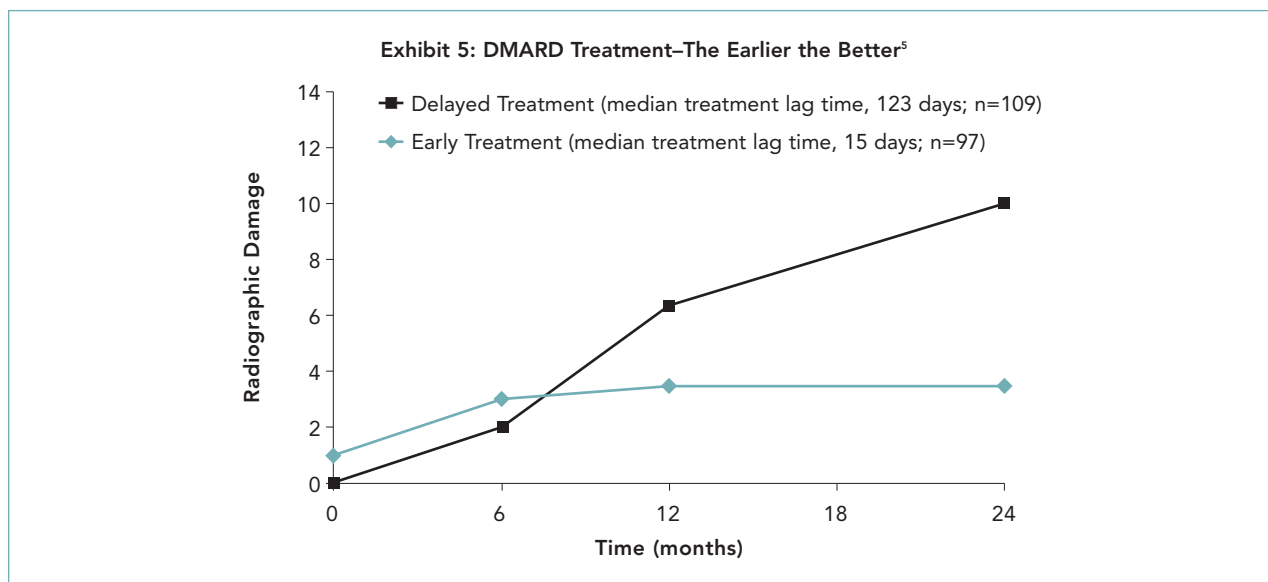
joint damage rather than which medication is used first (see Exhibit 5).⁵ The majority of the joint damage that occurs with RA happens in the first few years.

RA, psoriasis, and inflammatory bowel disease are thought to be caused by an imbalance in cytokines. Cytokines are small proteins that have myriad actions in the body. In patients without disease, there is a balance between opposing cytokines. For example, there is a balance between inflammatory and anti-inflammatory factors. In patients with disease, there is excess activity of inflammatory cytokines that is not compensated by the body's naturally occurring down regulators. Biologics agents reestablish the balance.

TNF is thought to be a central cytokine, which directs the activity of other cytokines. Most patients respond to TNF inhibitors with a reduction in signs and symptoms and some achieve remission of their disease. Clinical efficacy with the TNF inhibitors requires continued therapy. These agents are not a

cure; when they are stopped, disease symptoms return because the imbalance returns.

Studies have shown that these agents have significant effects on slowing disease progression as evidenced by X-ray examination, improving quality of life, and preserving functional status. In an early study of etanercept versus placebo, 59 percent of the subjects achieved an ACR20 response, 40 percent an ACR50 response, and 15 percent an ACR70 response (see Exhibit 6).⁶ The efficacy of agents for RA is evaluated primarily using the American College of Rheumatology (ACR) core criteria for response (ACR20, ACR50, and ACR70), functional measures, and radiographic evidence of joint changes. The items measured in the ACR criteria include tender joint count (TJC), swollen joint count (SJC), patient's assessment of pain, patient's and physician's global assessment of disease activity, patient's assessment of physical function, and laboratory evaluation of one



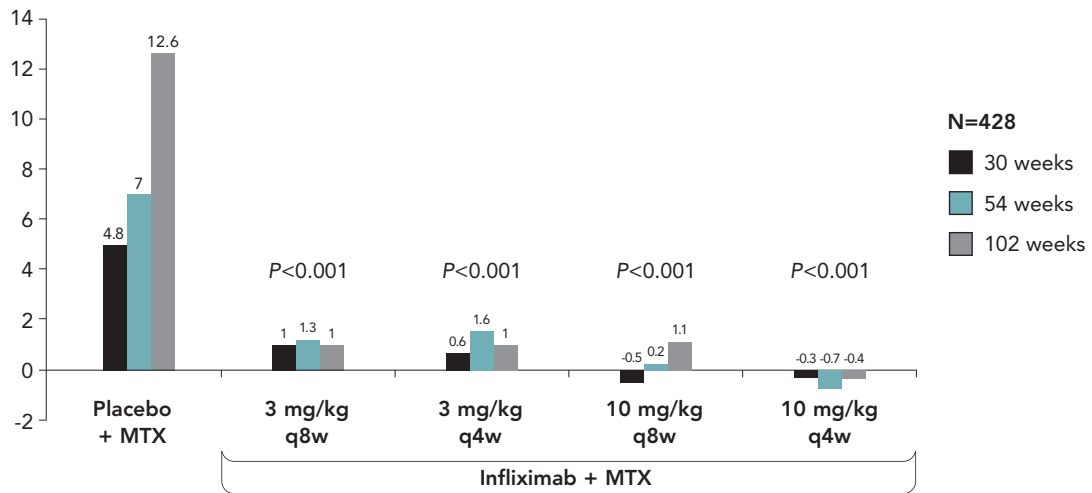
measure of inflammation (erythrocyte sedimentation rate [ESR] or C-reactive protein [CRP]). An ACR20 response is defined as a 20 percent improvement in TJC and SJC and 20 percent improvement in three of the five remaining ACR core set measures.⁷ The ACR50 and 70 responses are defined in the same manner as the ACR20, but with improvements in 50 percent and 70 percent, respectively.⁷ The goal of these measurements was to standardize outcome assessments in clinical trials. ATTRACT was the first study to demonstrate that a combination of a TNF inhibitor, infliximab, and methotrexate slowed radiographic progression of RA (see Exhibit 7).^{8,9} Patients on this combination had very little to no progression. Data

from a study of adalimumab in conjunction with methotrexate demonstrates the ability of TNF inhibitors to reduce disability (see Exhibit 8).¹⁰

A combination of a TNF-inhibitor with methotrexate is the current gold standard for RA treatment because this combination is synergistic. In cases where one TNF inhibitor is not effective, a growing body of data suggests switching from one to another is a reasonable strategy. TNF inhibitors also are effective in ankylosing spondylitis, psoriasis, psoriatic arthritis, and Crohn's disease. They are being tested for treatment of other chronic inflammatory diseases.

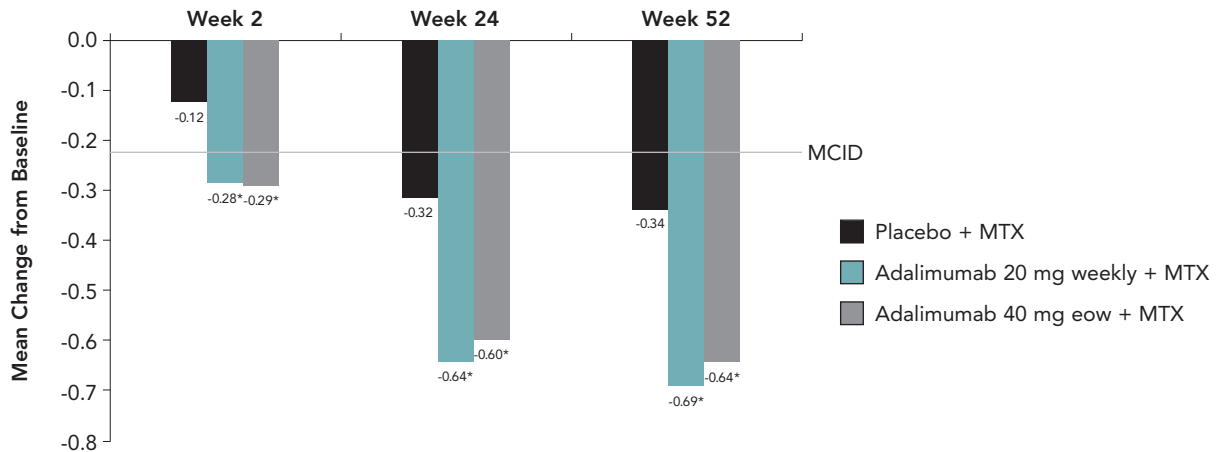
Studies have found TNF inhibitors ineffective in

Exhibit 7: Biologic DMARD + MTX Combination Slows Radiographic Progression^{8,9}



P values are versus placebo + MTX. ATTRACT = Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy

Exhibit 8: Biologic DMARD + MTX Combination Reduces Disability¹⁰



*P 0.001 versus placebo + MTX; eow = every other week; MCID = minimal clinically important difference

heart failure, Wegener's granulomatosis, polymyalgia rheumatica, and temporal arteritis.

TNF inhibitors do have some significant adverse effects. Some agent-related effects are injection site or infusion reactions. The majority of serious adverse effects are related to blocking TNF. TNF, being important in inflammation, has some beneficial aspects. One of these is protecting the body from invading organisms. Opportunistic infections (e.g., tuberculosis) are of particular concern. The patients selected for treatment with biologic agents tend to have the most severe disease and have a higher risk of infection irrespective of the treatment chosen. Data suggests that this prior risk is increased by treatment with TNF inhibitors.¹¹ Patients treated with biologics need to be closely monitored for infection development.

Additionally, demyelinating conditions, hematologic abnormalities, congestive heart failure, possible increased risk of lymphomas, and autoantibodies can all result from blocking TNF. Autoantibodies are antibodies against the patient's DNA. Although greater than 40 percent of patients treated with TNF inhibitors will develop some type of autoantibodies, these do not seem to be relevant clinically. A few people do get lupus-like syndromes, but this is rare.

Obstacles to Curing RA

Despite the availability of new, highly effective, targeted therapies that provide unprecedented opportunities to treat rheumatoid arthritis, major obstacles still stand in the way of a cure. These include 1) a lack of knowledge of the etiology of the disease, 2) a lack of means to intervene in the most relevant disease processes, 3) the inability to make an early diagnosis, and 4) limited ability to recognize those at risk for significant disability. Although data have long hinted that bacteria, viruses, nonspecific inflammation, and autoantibodies might be pathogenic factors in at least some cases of RA, the basic mechanisms that initiate and sustain this disease remain elusive. Even the most advanced therapies currently available appear to suppress relatively peripheral pathways of inflammation and not central abnormalities of cell function that underlie the disease. The considerable clinical, pathological, and immunological heterogeneity of RA may also influence the capacity to induce remission. By the time physicians are able to spot clinical signs of the disease, it is probably too late to bring tissues back to normal. One of the most important obstacles is an inability to detect the earliest events that lead to the development of persistent, destructive synovitis.

The Newest Agent

One promising agent that reached the market in 2006 for RA is abatacept (Orencia). This agent selectively modulates antigen-specific autoimmune T-cell activation. Existing autoimmune T-cells are induced by this agent to quit working. A decrease in autoimmune T-cell activation reduces amounts of inflammatory cytokines, such as TNF and IL-1. Abatacept appears to interrupt the autoimmune response underlying RA, both at initiation and at the established stage. This agent has been shown to slow progression of structural damage and to significantly improve symptoms and quality of life even in patients who did not respond to TNF inhibitors.¹²

Conclusion

RA, along with other chronic inflammatory diseases, has a significant impact on patients' lives. New treatments currently available are revolutionizing the treatment of chronic inflammatory diseases by better targeting the underlying pathologic processes. **JMCM**

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Faculty

Arthur Kavanaugh, MD, is director of the Center for Innovative Therapy and a professor of medicine in the Department of Rheumatology, Allergy, and Immunology at the University of California-San Diego.

Disclosure

Dr. Kavanaugh has no real or perceived financial relationships that present a conflict of interest.

Accreditation

The National Association of Managed Care Physicians (NAMCP) is accredited by the Accreditation Council for Continuing Medical Education to sponsor continuing medical education for physicians. NAMCP designates this activity for a maximum of 1 AMA PRA Category I credits™. Each physician should claim credit commensurate with the extent of their participation in the activity.

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This activity has been approved by the American Board of Managed Care Nursing for 1.2 contact hours toward CMCN recertification requirements.

This activity was held live at the NAMCP Spring Managed Care Forum. This activity is valid from Sept. 1 to Dec. 31, 2006.

POST TEST

INSTRUCTIONS

Read the article, answer the post test questions, complete the evaluation form, and submit to Ann Patrick either by fax 804-747-5316 or mail: 4435 Waterfront Drive, Suite 101, Glen Allen, VA 23060.

1. The factors driving new developments in chronic inflammatory disease are:

- a. Understanding the immunopathophysiology of these diseases
- b. Ability to produce molecules that target specific abnormalities
- c. Requests from patients
- d. Unmet needs by older treatments
- e. A, B, D
- f. A, C, D

2. In the natural progression of RA, joint pain, destruction, and dysfunction can lead to significant disability.

- a. True
- b. False

3. Surrogate markers can help clinicians predict which patients to treat more aggressively.

- a. True
- b. False

4. Therapy goals for RA include:

- a. Prevention of joint destruction
- b. Achieve clinical remission
- c. Preserve quality of life
- d. Relieve symptoms
- e. All of the above

5. DMARDs impact the progression of joint damage, improve symptoms, and some can place patients in remission.

- a. True
- b. False

6. An imbalance of cytokines is the cause of RA, psoriasis and inflammatory bowel disease.

- a. True
- b. False

7. Through continued therapy of TNF inhibitors most patients have a decrease in symptoms and achieve remission.

- a. True
- b. False

8. Combination therapy of an TNF inhibitor and methotrexate demonstrates a reduction in disability and is considered the gold standard for RA.

- a. True
- b. False

9. Obstacles to a cure for RA include:

- a. Inability to recognize patients at risk for RA
- b. No means to intervene in the relevant disease processes
- c. Inability to make early diagnosis
- d. Lack of knowledge of the etiology of RA
- e. All of the above

CID ANSWER SHEET

There is only one correct answer per question.
Circle your answers clearly.

1. a b c d e f

2. a b

3. a b

4. a b c d e

5. a b

6. a b

7. a b

8. a b

9. a b c d e

ACTIVITY EVALUATION

1. Please evaluate this activity based on the following scale:

4 Excellent 3 Good 2 Fair 1 Poor

Activity met my expectations

4 3 2 1

Activity was free of bias

4 3 2 1

Activity content was understandable

4 3 2 1

Presenters were free of bias

4 3 2 1

Method of learning was beneficial

4 3 2 1

I will change my practice patterns by (please specify):

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