

*Perspectives From
Rick Pope, MPAS, PA-C*

**What inspired you to
practice in the field
of rheumatology?**

When I started practicing in rheumatology in 1988 as a physician assistant (PA), I regarded my position as a *job*. Since then, the *job* has become a *career*. My physician supervisor, Dr Brian Peck, a rheumatologist in private practice, encouraged me to learn the specialty by attending as many American College of Rheumatology (ACR) and CME rheumatology conferences as possible. Additionally, participation in FDA phase 2 and 3 pharmaceutical-sponsored clinical trials put me in contact with national rheumatologists. This exposure inspired the founding of the Society of Physician Assistants in Rheumatology (SPAR), which we founded in 2002. The mission of SPAR is to ensure the best possible care for patients with rheumatoid arthritis (RA) by advancing the MD/PA team. I currently serve as president of the society.

The most grounding experience of my training was my exposure to patients with RA. When I started in practice, I saw every patient at the Arthritis Center of Connecticut with Dr Peck. This helped me develop my clinical skills as a PA in rheumatology and increased my ability to develop a rapport with patients. This patient/PA rapport is particularly important because the nature of RA mandates a long-term relationship between clinician and patient. I use this experience as the model for training new PAs who enter



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Rheumatoid Arthritis: Biologic Treatment Advances and Guideline Interpretation

Martin J. Bergman, MD, Senior Editor

The practical management of patients with rheumatoid arthritis (RA), including the use of tumor necrosis factor-alpha (TNF- α) inhibitor therapy, is the focus of this issue of PCE Updates in Rheumatology. Early diagnosis is an important factor in selecting and implementing the most effective treatment. Clinical guidelines that identify early symptoms of RA are necessary tools for rheumatologists, nurse practitioners (NPs), and physician assistants (PAs) who select the course of action for patients with RA. Early diagnosis is of critical importance because early and effective treatment optimizes the likelihood of positive outcomes. In addition, to ensure the most comprehensive patient care, the physical and educational needs of patients with RA must be addressed.

This issue of PCE Updates in Rheumatology provides a brief overview of RA management that includes a case study and clinical commentary by Rick Pope, MPAS, PA-C, (see page 8).

Clinical Presentation of RA

The clinical presentation of RA varies among patients. RA has an insidious onset with slowly progressing, symmetric, peripheral polyarthritis in 55% to 65% of patients that evolves over weeks or months. The initial symptoms may be systemic in some patients, with complaints that are more pronounced in the intermediate type onset. In 8% to 15% of patients, RA manifests as a rapid-onset process, where severe symmetric polyarthritis can develop in a few days. Intermediate type onset with symptoms

developing over days or weeks occurs in 15% to 20% of patients. Commonly, metacarpophalangeal (MCP) joints, proximal interphalangeal (PIP) joints, metatarsophalangeal (MTP) joints, and wrists initially are involved. Larger joints usually become symptomatic after small joints.¹

Importance of Early, Aggressive Treatment

Revolutionary changes in treatment strategies of RA have occurred during the past 15 years due to a better

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understanding of its pathology and the introduction of biologic response modifying agents that interfere with the inflammatory cytokine biology of this disease. In moderate to

severe or refractory disease, biologic agents alone or in combination with methotrexate (MTX) are the mainstay of therapy. In addition, the potential of biologic agents to

reduce or prevent RA disease progression has also led to their use in early aggressive RA.

An understanding of the basic mechanisms associated with the development of RA and its perpetuation within joints combined with an awareness that loss of function and destruction of joints begin early after the onset of synovitis in patients with established disease resulted in an aggressive approach to early management.² Treatment approaches in early RA aim for earlier identification and intervention with disease-modifying antirheumatic drugs (DMARDs), aggressive dosing of existing medications, combination DMARD therapy, and the use of anticytokine therapies such as TNF- α inhibitors.

A review of published studies assessing the development of radiographic damage indicated that erosive changes were apparent in 70% to 79% of patients with early disease. Almost all patients who developed erosive changes did so within the first 2 years of disease onset.³ Joint erosions also may develop

Understanding RA

- RA is a chronic, multisystemic, progressive, autoimmune disorder characterized by inflammation of multiple, symmetric, peripheral joint linings that causes pain, stiffness, swelling, and limitation of movement of the affected joints
 - Inflammation may extend to other articular tissues, causing bone and cartilage erosion and joint deformities
 - Extra-articular manifestations also can affect connective tissue and blood vessels, triggering inflammation in a variety of organs, including the lungs and heart
- The exact cause is unknown, but genetic, environmental, and biologic components are implicated in the development of RA
- Evidence from family studies has indicated a genetic predisposition for RA
 - In monozygotic twins, the concordance rate is 30% to 50% when 1 twin is affected compared to 1% in the general population
 - The risk of RA for a fraternal twin of a patient with RA is about 2% to 5%. However, this is not greater than the rate for other first-degree relatives. Few monozygotic twins are predisposed to RA, implying that factors other than genetics also have a role in the etiology of the disease
 - Multiple genes have been implicated in the etiology of RA, but the class II major histocompatibility complex (MHC) gene product HLA-DR4, often referred to as the “shared epitope,” plays a role in the recognition of foreign substances by the immune system and is believed to be a major genetic factor. Up to 70% of patients with RA express HLA-DR4 compared with only 30% of controls
 - Infectious agents such as bacteria, mycobacteria, mycoplasma, and their components, as well as viruses such as Epstein-Barr, parvovirus, and rubella have been implicated as causal agents of RA, but there is a lack of direct evidence

Harris E et al¹; Harris E et al. *Kelley's Textbook of Rheumatology*. 7th ed. Philadelphia, Pa: WB Saunders; 2004:chap 66; Symmons DP et al. *Arthritis Rheum*. 1997;40:1955-1961.

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Target Audience

Nurse practitioners (NPs), physician assistants (PAs), and physicians in the practice of rheumatology

Goal

To provide practical information regarding the use of biologic therapy in the management of rheumatoid diseases.

Learning Objectives

After completing this activity, participants should be better able to:

- Differentiate the clinical efficacy and safety of biologic agents.
- Initiate biologic therapy for patients who have not achieved optimal benefit from DMARD therapy for chronic RA (DMARD refractory).
- Identify measures to educate patients on the possible side effects of biologic therapy and the need for long-term management of the disease.

Accreditation Information



This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of Continuing Education Alliance and the University of Nebraska Medical Center, Center for Continuing Education.

The University of Nebraska Medical Center, Center for Continuing Education is accredited by the ACCME to provide continuing medical education for physicians.

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This activity is provided for 1.0 contact hour under ANCC criteria.

Provided for 1.2 contact hours under Iowa Provider #78. Provider approved by the California Board of Registered Nursing, Provider #13699 for 1.2 contact hours.

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before arthritis is clinically apparent. This was shown in an 'early RA' clinic where at least 25% of patients referred to the clinic within 30 days of disease onset presented with erosions at the first visit.⁴ Even patients receiving treatment for persistent, aggressive synovitis had severe erosive disease. Despite treatment, up to 90% of these patients have evidence of bone erosions within 2 years of diagnosis.⁵

Functional health status declines early in the course RA. Mild functional loss can occur as soon as 1 year after disease onset, moderate to severe functional losses can occur by year 6,⁶ and ~90% of patients with RA have some form of disability within 2 decades of onset.⁷

RA Puts Patients at Risk

RA patients are at increased risk of:

- Increased morbidity and mortality rates predicted by and proportional to clinical status as measured by the Health Assessment Questionnaire (HAQ). Poorer outcome is associated with more severe and active disease⁸

- Comorbidities such as chronic pulmonary disease, congestive heart failure (CHF), and dementia compared with age- and gender-matched healthy individuals⁹
- Cardiovascular events, such as myocardial infarction or stroke¹⁰
- Infection and lymphoma, which could be related to ongoing inflammation in these patients¹¹

A study that followed RA patients over a 40-year period reported a significantly higher risk of death in patients with RA with a standardized mortality ratio (SMR) of 1.27 compared with age- and sex-matched individuals from the general population.¹²

Early diagnosis and initiation of DMARD (including biologic) therapy are critical to prevent structural damage, disability, morbidity, and mortality in patients with RA. Several studies have shown that early treatment of RA is likely to provide a successful outcome as measured by clinical signs and symptoms and maintained function.¹³⁻¹⁶ Data from these studies indicate an interval of time may exist in which

the introduction of DMARD therapy can result in a change in the natural course of the disease. This "window of opportunity" appears to be within the first 2 years of the onset of RA, but may occur as early as 2 weeks from disease onset.^{16,17} DMARD therapy should be initiated early in the disease process before there is significant joint damage and functional decline.¹⁷

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this field. My inspiration is the learning environment provided by Dr Peck, and that experience has influenced my relationships with patients, PAs, nurse practitioners (NPs), and physicians that I hope will last for the next 20 years.

What are your specific patient responsibilities in your practice?

My responsibilities have increased as my exposure to the art and science of rheumatology have increased. Due to my accessibility and availability, many physicians use me as a source to help patients understand confusing clinical pictures or to manage clear rheumatologic disorders.

Routine tasks for a PA include obtaining prior authorization, particularly for biologic medications; answering patients' questions about side effects; providing reassurance about patient management; filling out disability forms; and particularly in this last year, giving advice about Medicare Part D. I clear patients medically prior to TNF infusions and manage acute reactions if they occur. More recently, I developed a protocol to screen patients for IV bisphosphonate infusions. Twice yearly, I give a talk on a rheumatologic disorder to our medical staff, which includes 2 rheumatologists and 3 PAs, that is a valuable educational experience that keeps everyone current on a given disease state.

How to Receive Credit

Participants wishing to earn CME/CE credit must:

1. Read the newsletter.
2. Relate the content material to the learning objectives.
3. Complete the self-assessment questions and evaluation form online at www.practicingclinicians.com/rheumupdates. Enter code CPCE42407-2. Successful completion of the self-assessment is required to earn CME/CE credit. Successful completion is defined as a cumulative score of at least 70%.

The estimated time to complete this activity is 1 hour.

Release date: November 15, 2007

Expiration: Required materials must be submitted before November 15, 2008.

Disclaimer

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Disclosures

Dr Bergman: *consultant:* Amgen, Centocor Inc., Genentech, Inc., Wyeth; *consultant/research:* Bristol-Myers Squibb Company; *speakers bureau/consultant/research:* Abbott Laboratories.

Ms Furfaro: *honorarium:* Roche; *consultant/speakers bureau:* Biogen Idec, Genentech, Inc; *faculty/consultant/speakers bureau:* Abbott Laboratories.

Mr Pope: *consultant:* Abbott Laboratories, Alliance for Better Bone Health, Amgen, Wyeth; *speakers bureau:* Novartis, Procter & Gamble.

The Planning Committee for this activity included Catherine A. Bevil, RN, EdD, and Lisa Anzai, RN, MA, of the University of Nebraska Medical Center College of Nursing Continuing Nursing Education; Lois Colburn and Brenda Ram of the University of Nebraska Medical Center, Center for Continuing Education; and Ruth Cohen of Continuing Education Alliance. The members of the Planning Committee have no significant relationships to disclose.

Please contact Continuing Education Alliance at inquiries@cealliance.org for questions regarding this activity.

Tools for Diagnosis of Early RA

The diagnosis of early RA is based on clinical signs and symptoms, serologic testing, and imaging modalities.

Clinical Guidelines

The American College of Rheumatology (ACR) has established guidelines for the initial evaluation of RA (Table 1).¹⁸ The ACR criteria for the diagnosis of RA are based on established disease.

Serologic Tests

Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) level, and rheumatoid factor (RF) may also be helpful in the diagnosis of early RA.¹⁹ Recently, the presence of antibodies to cyclic citrullinated peptide (CCP) has proven to be a highly specific diagnostic tool (98% specificity for RA) and facilitates identification of patients who are more likely to have aggressive and progressive disease with worse clinical and functional outcomes.²⁰ Anti-CCP antibodies can also predict the development of RA in individuals with undifferentiated arthritis and healthy individuals.²¹ Since testing for anti-CCP and RF in concert provides strong serologic evidence of RA, this combination may be especially useful in the diagnosis of very early RA.²² However, as ESR and CRP can be normal in 40% of patients being diagnosed with RA, and RF and anti-CCP may be normal in as many as 25% of patients with RA, serologic testing should be considered an adjunctive tool to sound clinical judgment.

Imaging Modalities

Radiographs, magnetic resonance imaging (MRI), and ultrasound can facilitate the diagnosis of early RA and predict outcome.

Table 1. Baseline Evaluation of Disease Activity and Damage in Patients With Rheumatoid Arthritis

Subjective	
• Degree of joint pain	• Duration of fatigue
• Duration of morning stiffness	• Limitation of function
Physical Examination	
• Actively inflamed joints (tender and swollen joint counts)	
• Mechanical joint problems: loss of motion, crepitus, instability, malalignment, and/or deformity	
• Extraarticular manifestations	
Laboratory	
• Erythrocyte sedimentation rate/C-reactive protein level	
• Rheumatoid factor*	
• Complete blood cell count†	
• Electrolyte levels‡	
• Creatine level‡	
• Hepatic enzyme levels (AST, ALT, and albumin)†	
• Urinalysis‡	
• Synovial fluid analysis‡	
• Stool guaiac‡	
Other	
• Functional status or quality-of-life assessments using standardized questionnaires	
• Physician's global assessment of disease activity	
• Patient's global assessment of disease activity	
Radiography	
• Radiographs of selected involved joints§	

*Performed only at baseline to establish the diagnosis. If initially negative, may be repeated 6-12 months after disease onset. †Performed at baseline, before starting medications, to assess organ dysfunction due to comorbid diseases. ‡Performed at baseline, if necessary, to rule out other diseases. May be repeated during disease flares to rule out septic arthritis. §Helps to establish a baseline for monitoring disease progression and response to treatment. AST = aspartate aminotransferase; ALT = alanine aminotransferase.

Adapted from the ACR Subcommittee on Rheumatoid Arthritis Guidelines.¹⁸

Radiographs can demonstrate erosions that are indicative of destruction of cartilage and bone. However, erosions are not evident in some patients for 6 months, and in 30% of patients for 1 year with this modality. MRI can demonstrate inflammatory changes, including synovitis, tendonitis, bone edema, and bone erosion as early as 4 months after onset of symptoms. The severity of these early changes has been predictive of radiographic

damage and clinical parameters that occurred 6 years later.²³ Bone erosions and/or edema on extremity MRI have been predictive of joint damage on radiographs 1 year later.²⁴

Patient questionnaires are the best predictors of clinical outcomes such as disability, joint replacement surgery, and death.²⁵ These tools are simple to incorporate into clinical practice and can be used to monitor functional levels and direct patient care.

Effect of TNF- α Inhibitors in Patients With RA

There are 3 TNF- α blockers approved for the treatment of RA—etanercept (Enbrel®), infliximab (Remicade®), and adalimumab (Humira®). These biologic agents are indicated in patients with moderate to severe active RA.²⁶⁻²⁸ In this patient population, all 3 agents used as monotherapy have significantly reduced the signs and symptoms of RA, inhibited the progression of structural damage, and improved physical function compared with placebo.²⁹⁻³¹ When used concomitantly with MTX, all 3 agents (infliximab, etanercept, and adalimumab) have shown greater efficacy compared with monotherapy with MTX or a TNF- α inhibitor.³¹⁻³⁴ Moreover, the combination of anti-TNF- α and MTX has been shown to have even greater efficacy in the early stages of RA than in established disease.³⁵⁻³⁷ In patients with early RA, greater remission rates also have been achieved with TNF- α plus MTX combination therapy versus MTX monotherapy.

Safety data from clinical trials have indicated that TNF- α inhibitors are well tolerated. (See *PCE Updates in Rheumatology, Issue 1* for a detailed review of safety data on TNF- α inhibitors.)

Combination Treatment for RA: Real-World Experience

According to the ACR Guidelines, the initiation of DMARD therapy, which includes TNF- α inhibitors, should not be delayed beyond 3 months in patients with an established diagnosis of RA and an inadequate response to NSAIDs.¹⁸ Treatment often includes combination therapy with

NSAIDs, DMARDs including biologics and glucocorticosteroids.¹⁸

In 3 trials using etanercept (TEMPO), infliximab (ASPIRE), and adalimumab (PREMIER), patients were randomized to receive combination TNF- α inhibitor and MTX or MTX monotherapy. Both the ASPIRE (N = 1049) and PREMIER (N = 799) trials included subjects with early RA and the TEMPO subjects (N = 682) had a diagnosis of RA for a mean duration of 7 years. Combination therapy typically produced a >50% clinical improvement and an ~2-fold greater improvement in ACR 50 response compared with MTX monotherapy.

The results from TEMPO and ASPIRE are known to the RA community of healthcare professionals, because both of these studies were reported in the literature in 2004,

and etanercept and infliximab have been available for the treatment of RA since 1994 and 2000, respectively (Table 2). Adalimumab is the latest anti-TNF- α agent to be approved by the FDA; therefore, its clinical trial data may be less well known and NPs and PAs may have less clinical experience using this agent. For these reasons, the PREMIER trial is presented in more depth. The REACT trial is also reported in this newsletter to address the paucity of data on the use of anti-TNF- α agents with a variety of clinically available DMARDs, which was investigated in that trial. (See *PCE Updates in Rheumatology, Issue 1* for an in-depth review of TNF- α inhibitors.)

The efficacy and safety of adalimumab as combination therapy with MTX in early RA (PREMIER),³⁶ as monotherapy in patients with established RA

Table 2. Review of TEMPO and ASPIRE

TEMPO (etanercept)³²

- Randomized double-blind, multicenter controlled trial
- Duration of study: 52 weeks
- Subjects had an inadequate response to 1 DMARD; were anti-TNF- α naïve
- Combination therapy with etanercept and MTX was significantly better than MTX or etanercept alone for
 - Reduction in disease activity
 - Improvement in functional ability
 - Inhibition of radiographic progression
 - Treatment was well tolerated
 - Rates of infections and AEs were similar in all treatment groups

ASPIRE (infliximab)³³

- Randomized multicenter trial
- Duration of study: 54 weeks
- Subjects were MTX or biologic naïve
- All patients received MTX and either placebo or infliximab
- Combination therapy with infliximab and MTX vs MTX monotherapy for patients with active early RA provides greater benefits
 - Clinically
 - Radiographically *and*
 - In functionality
- Infliximab therapy was associated with a significantly higher incidence of serious infections, especially pneumonia

(monotherapy trial),³⁰ and as monotherapy or as combination therapy with standard DMARDs in a clinical practice setting (ReACT)³⁸ have been established.

PREMIER: Efficacy of Adalimumab in MTX-Naïve Patients With Early RA

PREMIER was a 2-year, multicenter, randomized, double-blind study that evaluated the safety and efficacy of adalimumab as monotherapy or in combination with MTX in subjects (N = 799) with moderate to severe early RA (<3 years disease duration) who were MTX naïve.³⁶ Patients were also randomized to monotherapy with MTX. Baseline demographic and clinical characteristics of the study population reflected a population with early RA and were comparable among the 3 treatment groups.³⁶

ACR Response

After 1 year of treatment, an ACR 50 response was achieved in 62%, 41%, and 46% of patients who had combination therapy, adalimumab

monotherapy, and MTX monotherapy, respectively ($P < .001$ for both comparison treatments vs combination therapy). At year 2, ACR 50 responses were sustained in the combination group and were statistically superior to responses in both monotherapy groups ($P < .001$). Similar statistically significant patterns were observed for ACR 20, ACR 70, and ACR 90 responses. At 2 years, patients in the combination arm had 5 times greater inhibition of radiographic progression than patients in the MTX arm. Although ACR responses were comparable in the 2 monotherapy arms, there was significantly less progression in the adalimumab arm compared with the MTX monotherapy arm at all time points ($P < .001$ for all comparisons).³⁶

Radiographic Progression

Significantly less radiographic disease progression at 6 months, 1 year, and 2 years was apparent among patients who had received combination therapy compared with those in either monotherapy arm (Figure 1).

Approximately twice as many patients in the combination arm showed no radiographic progression (change in TSS ≤ 0.5 from baseline) at 1 and 2 years (64% and 61%) compared with those in the MTX arm (37% and 34%) ($P < .01$). A significantly greater number of patients in the adalimumab monotherapy arm (51% and 45% at years 1 and 2, respectively) also had no radiographic progression.³⁶

Clinical Remission

At 2 years, 50% of patients on combination therapy attained clinical remission in this study, approximately twice the number of either monotherapy arm. After 1 and 2 years of treatment, 43% and 49% of patients receiving combination therapy achieved clinical remission compared with 23% and 25% of patients receiving monotherapy, and 21% and 25% of patients receiving MTX monotherapy (both $P < .001$), respectively. Moreover, after 2 years of treatment, approximately twice the number of patients on combination therapy (49%) exhibited a major clinical response, defined as maintaining a 70% ACR response for 6 consecutive months compared to either monotherapy arm (25% on adalimumab and 27% on MTX) ($P < .001$). Based on the Health Assessment Questionnaire Disability Index (HAQ-DI), combination therapy significantly improved physical function of patients compared with MTX monotherapy after 1 and 2 years of treatment.³⁶

The rate of adverse events (AEs), infectious AEs, tuberculosis (TB), malignancies, and lymphomas did not differ significantly among the 3 treatment groups. The rate of serious infections in the adalimumab arm was significantly lower than in the

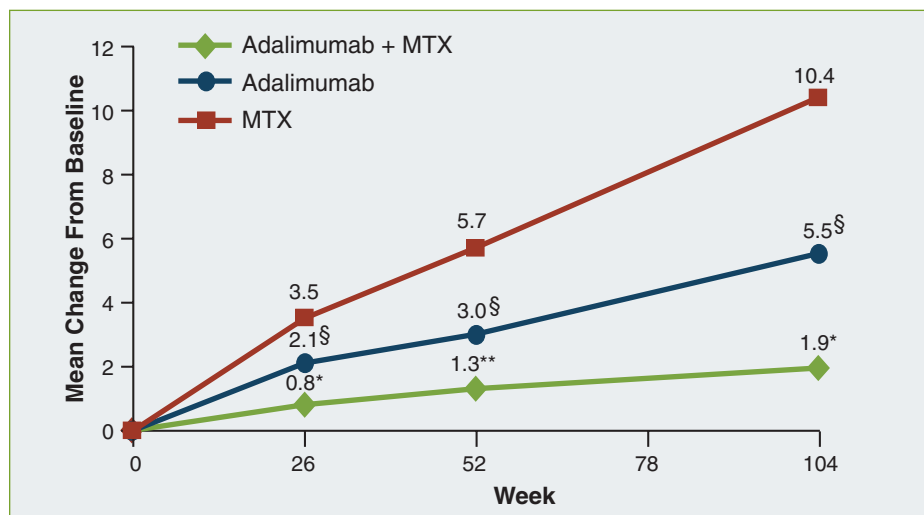


Figure 1. The impact of adalimumab (ADA) treatment on radiographic progression in the PREMIER trial. Mean change from baseline in total Sharp scores over time by treatment group are shown.

* $P < .001$ vs ADA alone and vs MTX alone; § $P < .001$ vs MTX alone; ** $P = .002$ vs ADA alone and $P < .001$ vs MTX alone. Breedveld FC, et al.³⁶

combination arm, but not significantly different from the MTX arm.

The PREMIER study demonstrates the response that can be achieved in treating an early, MTX-naïve RA population with aggressive combination therapy. These efficacy results support the concept of treating early RA aggressively to achieve better long-term outcomes.

ReACT: Efficacy of Adalimumab Plus DMARDs in Clinical Practice

The efficacy and safety of TNF- α inhibitors in combination with MTX are well established. However, data on the efficacy and safety of TNF- α antagonist therapy in combination with the wide range of traditional DMARDs commonly used to treat RA patients in clinical practice is lacking.

ReAct was an open-label, multicenter study of adalimumab 40 mg every other week for 12 weeks, with an optional extension phase. Patients with a disease duration of ≥ 3 months, active RA (defined as DAS28 of ≥ 3.2), and failed treatment with at least 1 traditional DMARD or with a TNF- α inhibitor were included in this trial.³⁸ Patients were allowed to continue pre-existing traditional DMARDs (defined as MTX, leflunomide [LEF], SSZ, chloroquine or hydroxychloroquine [AMs], azathioprine [AZA], and parenteral or oral gold) or any combination of DMARDs, glucocorticoids (prednisone equivalent (10 mg/day), and NSAIDs. By protocol, cyclosporin A (CsA) was not to be used as a concomitant DMARD, however, as a general precaution against excessive immunosuppression, 25 patients received CsA concomitantly. Safety and efficacy of adalimumab were evaluated at weeks 2, 6, 12, and every 8 weeks thereafter.

ACR Response

At week 12, 69%, 40%, and 18% of patients achieved an ACR 20, ACR 50, and ACR 70 response, respectively, while 83% and 33% of patients achieved a moderate and a good European League Against Rheumatism (EULAR) response, respectively. The ACR 20 response rates were within the range reported in randomized, double-blind studies of adalimumab,^{30,34,36,39} demonstrating that adalimumab is effective when used in combination with a variety of DMARDs (Figure 2). The addition of ADA to AMs was comparably effective to the combination of ADA and MTX. Concomitant treatment with adalimumab and LEF was slightly less effective than concomitant adalimumab treatment with MTX, AM, or SSZ, but more effective than adalimumab alone after adjustment for differences in baseline characteristics between subgroups. In addition, at week 12, 25% of all patients had a HAQ DI < 0.5 , which is considered a low level of functional impairment.³⁸

Clinical Remission

Clinical remission, as defined by a Disease Activity Score (DAS28) < 2.6 , was achieved by 20% of all patients at week 12. Throughout the study, adalimumab was well tolerated. The number or type of concomitant DMARDs did not affect the safety profile of adalimumab, and the rate of AEs did not increase as the number and variety of concomitant DMARDs increased.

This open-label study conducted in a large cohort of patients in multiple countries and a variety of clinical practice sites provides reassurance about the efficacy and safety of adalimumab in clinical practice.

Goals of RA Management

In the absence of either a cure or prevention options for RA, optimal disease management requires early diagnosis and treatment to control the underlying inflammatory process, thereby

(continued on page 10)

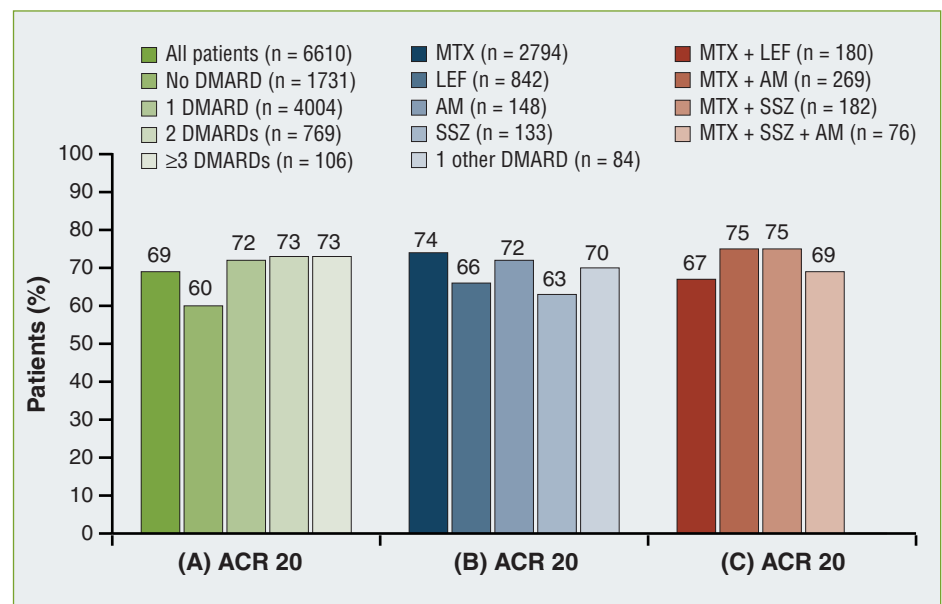


Figure 2. The efficacy of adalimumab in combination with a variety of DMARDs used in clinical practice. (A) ACR 20 responses by number of concomitant DMARDs; (B) ACR 20 responses by exclusive concomitant DMARD; (C) ACR 20 responses by combinations of concomitant DMARDs. Adapted from Burmester GR, et al.³⁸

Case Study in RA

Rick Pope, MPAS, PA-C

Present Illness

- 45-year-old woman diagnosed with RA 3 years prior
- Complains of moderate pain for 4 weeks, swelling in PIPs, MCPs, wrists
- Hands and feet stiffness in the morning for ~90 minutes and in the evenings; some difficulty using hands; decreased grip strength
- Last seen 2 months prior, doing well at that time with <20 minutes of morning stiffness; no arthralgias of PIPs, MCPs, and wrists bilaterally, with visible swelling over PIPs, wrists
- No history of sick contacts, fevers, chills, sweats
- Review of systems: otherwise negative

Current Medications

- MTX 20 mg PO QW
- Naproxen 500 mg PO BID
- Omeprazole 20 mg QD

RA History

- Diagnosed 3 years prior; presented with pain, swelling and morning stiffness in MCPs, ankles, MTPs
- Initial treatment: prednisone 10 mg PO QD; hydroxychloroquine 200 mg PO BID
- MTX was added due to incomplete response and increased to 20 mg PO QW. Optimal response noted, prednisone gradually discontinued

- Radiographs of hands and wrists prior to MTX initiation were normal, except for some periarticular osteopenia in MCPs and PIPs bilaterally

Physical Examination

- **Vital signs:** BP 120/80 mm Hg; pulse 72 bpm; respiration 12; temperature 98.7°C
- **Musculoskeletal:** good range of motion with no tenderness in cervical spine, shoulders, elbows
- **Wrists:** trace effusion and synovial thickening bilaterally; decreased flexion and extension with tenderness to palpation
- **Hands:** right 2nd PIP and left 4th PIP with soft spongy swelling and tenderness on palpation; soft spongy swelling and warmth over 2nd to 4th MCPs bilaterally, tender to palpation. No swelling or bony changes in distal interphalangeal joints (DIPs)
- **Back, hips, knees, ankles:** unremarkable
- **MTPs:** bilaterally tender on squeeze test
- **Remainder of examination:** normal

Radiographs of Hands

New erosions in the left 4th PIP and right 2nd IP, with periarticular osteopenia of MCPs

Clinical Commentary

Rick Pope, MPAS, PA-C

In this patient, RA is flaring despite MTX and hydroxychloroquine

- Add prednisone 40 mg PO QD

This option is not appropriate because corticosteroids (eg, prednisone 10-40 mg QD until flare subsided) are effective in suppressing synovial inflammation associated with RA, but their use is limited due to the long-term side effects. These agents should not be used instead of DMARDs or as monotherapy.

- Switch NSAID to another class of NSAID

NSAIDs could be switched to another class because individuals respond with a high degree of variability to these agents. This decision, however, will *not* modify the erosive component of RA. The expectation would be a 25% improvement in pain, stiffness, and range of motion. This approach usually is only partially helpful to patients.

- Discontinue hydroxychloroquine, continue MTX 20 mg PO QW, and initiate a TNF- α inhibitor

TNF- α inhibitors offer significant hope to patients with inflammatory arthritis. A few screening procedures should be performed prior to the administration of these drugs.

How would you treat this patient?

- This patient could be treated with corticosteroids with a dose not to exceed 10 mg QD and tapered, while waiting for approval from the insurance carrier to administer a TNF- α inhibitor, a process that can take up to 1 month
- A history of TB is important to note because TNF- α inhibitors have been shown to reactivate latent disease. All candidates for these agents should be skin-tested for TB, and the response documented in the chart. If the skin test is positive, a chest x-ray is indicated. If the results are suspicious for active disease,

a CT scan should be ordered and a pulmonology consult considered. If the chest x-ray is normal, the patient should be treated with isoniazid (INH) for 9 months. As the patient is also on MTX, close monitoring of the liver function tests (LFTs) are necessary.

What techniques would you use to educate the patient about her disease process and why she requires a biologic?

- There are 2 goals in managing RA: the patient wants the symptoms to subside, and the clinician wants to modify the disease. The clinician has to communicate the importance of the prevention of erosions that clearly correlate to increasing disability. Joint erosion is a slow process that occurs over years. Because it often will go unnoticed by patients, they don't have a sense of urgency to treat it. Many patients express reluctance to change their management course and incur increased out-of-pocket expense for biologic agents. The presentation of the situation the patient and the practitioner face is critical to successful management of RA and the overall clinical outcome. I tell patients that TNF- α inhibitors have are effective in preventing further erosive disease and improving pain, function, and overall well-being, including lessening fatigue.

What changes or improvement did this patient report at follow-up?

- In this case, the patient's morning stiffness lasts <5 minutes, there were no signs of swelling, and there was an improvement in her level of energy.
- After initiation of a biologic, I schedule a follow-up visit in 2 to 4 weeks, depending on the patient's schedule, the severity of RA, and other factors. Counseling patients on degrees and time to response is critical to adherence. Therefore, I try to temper their expectations. Some patients experience an almost steroid-like improvement quickly, but others need encouragement to stay on therapy for 3 to 6 months until improvement is apparent.

For patients who are reluctant to take biologics, how do you educate them on the possibility of remission, reducing joint disability, and improving function and quality of life?

- Reluctance to change is common among patients with RA. If symptoms of RA interfere with work, relationships, routine activities, and sleep, then patients often are more willing to accept a change in their regimen. When discussing biologics, I review the 3 available agents and let patients choose the appropriate agent for their lifestyle. I impress on patients that there has been continued

response with these agents for more than 5 years and educate them about side effects and the importance of adherence. Once I explain the nature of the disease process and its progression, patients are more willing to comply. This process may take several follow-up visits to complete, depending on the patient's perception of the disease and general uneasiness with the initiation of a new medication.

How do you convince patients to call you if they get bronchitis, sinusitis, or other infections?

- Constant reminders about infections are critical when counseling patients on biologics. Specific examples of types and locations of prior infections are helpful reminders to encourage the patient to call. Most patients need frequent reminders at follow-up office visits.

When you recommend a biologic that requires self-administration, how do you ease patients' concerns about injections?

- Self-injection of medication can be an issue for many patients. First, using a small pad, I demonstrate how to inject, and then I observe the patient's technique. The simplicity of the procedure in combination with the small needle size makes this process practically painless and much more acceptable. The most reluctant patient sometimes requires another patient's reassurance that the injection is simple to do and relatively painless.

How do you manage injection site reactions?

- In my experience, injection site reactions, which occur in approximately one third or fewer patients, are infrequent and abate over the first month of administration. Infusion reactions are not uncommon with infliximab, which is administered IV and requires a 2-hour infusion.²⁷ These are most often mild and require halting the infusion for approximately 20 minutes and reinfusing at a slower rate. For more severe reactions, I discontinue the drug, provide supportive measures, and switch to a different biologic at a later date.

How long do you wait to make sure there is an adequate response to the biologic?

- For most biologics, 3 months is a fair treatment trial, although some would recommend 4 and even 6 months. By that point, many patients will report they feel more energetic and the stiffness in their wrists and pain in their hands have improved. We try to keep patients on low doses of MTX because most clinical trial data suggest that this combination is more effective in preventing erosions than a biologic or MTX alone.

reducing the probability of irreversible joint damage. The ultimate goals of treatment, according to the ACR Guidelines, are to reduce pain and stiffness, improve joint movement, minimize loss of function, and prevent deformities.¹⁸ The key considerations for management of RA include regular evaluation of disease activity, patient education/rehabilitation interventions, use of DMARDs (including biologics), use of local or low-dose oral glucocorticosteroids, decreasing the impact of RA on the patient's functionality, ongoing assessment of adequate treatment, and general health maintenance.¹⁸

Rheumatoid arthritis is associated with economic considerations for patients as well as providers of care. Persons with RA have

3 times the direct medical costs, 2 times the hospitalization rate, and 10 times the work disability rate of an age-and sex-matched population.¹⁸ In today's cost constrained environment, if efficacy and toxicity of available treatments are equivalent, the lower-cost agent will likely be used. However, healthcare professionals are facing challenges whereby treatments are no longer equivalent or there is only a partial response to treatment. Patients may have comorbid conditions that contraindicate the use of more traditional therapies or high-risk or severe disease that requires the use of newer agents. Providers with longitudinal experience in treating RA are the best qualified to balance cost with the frequently progressive natural course of the disease.¹⁸

Conclusion

An increased understanding of the RA disease process has led to the development of biologic agents that block key cytokines implicated in the inflammatory process associated with RA. TNF- α inhibitors are one such class of agents. Large controlled studies of TNF- α inhibitors such as infliximab, etanercept, and adalimumab have shown significant clinical and radiographic benefits when used in conjunction with MTX or as monotherapy when indicated. Current evidence also indicates that effective aggressive DMARD therapy (including TNF- α inhibitors) initiated early in the disease process provides greater benefit than when initiated after RA is established. Moreover, arresting RA early in the disease process provides a chance for remission, which was not attainable with traditional therapy.

References

- Harris ED Jr, Budd RC, Firestein GS, et al. *Kelley's Textbook of Rheumatology*. 7th ed. Philadelphia, Pa: WB Saunders; 2004:chap 65.
- Harris ED Jr, Budd RC, Firestein GS, et al. *Kelley's Textbook of Rheumatology*. 7th ed. Philadelphia, Pa: WB Saunders; 2004:chap 67.
- van der Heijde DMFM. Joint erosions and patients with early rheumatoid arthritis. *Br J Rheumatol*. 1995;34(suppl 2):74-78.
- van der Horst-Bruinsma IE, Speyer I, Visser H, et al. Diagnosis and course of early-onset arthritis: results of a special early arthritis clinic compared to routine patient care. *Br J Rheumatol*. 1998;37:1084-1088.
- Sharp JT, Wolfe F, Mitchell DM, Bloch DA. The progression of erosion and joint space narrowing scores in rheumatoid arthritis during the first twenty-five years of disease. *Arthritis Rheum*. 1991;34:660-668.
- Wolfe F, Cathey MA. The assessment and prediction of functional disability in rheumatoid arthritis. *J Rheumatol*. 1999;18:1298-1306.
- Emery P, Breedveld FC, Dougados M, et al. Early referral recommendation for newly diagnosed rheumatoid arthritis: evidence based development of a clinical guide. *Ann Rheum Dis*. 2002;61:290-297.
- Pincus T, Callahan LF, Sale WG, et al. Severe functional declines, work disability, and increased mortality in seventy-five rheumatoid arthritis patients studied over nine years. *Arthritis Rheum*. 1984;27:864-872.
- Gabriel SE, Crowson CS, O'Fallon WM. Comorbidity in arthritis. *J Rheumatol*. 1999;26:2475-2479.
- Solomon DH, Goodson NJ, Katz JN, et al. Patterns of cardiovascular risk in rheumatoid arthritis. *Ann Rheum Dis*. 2006;65:1608-1612.
- Scott DL, Kingsley GH. Tumor necrosis factor inhibitors for rheumatoid arthritis. *N Engl J Med*. 2006;355:704-712.
- Gabriel SE, Crowson CS, Kremers HM, et al. Survival in rheumatoid arthritis: a population-based analysis of trends over 40 years. *Arthritis Rheum*. 2003;48:54-58.
- A randomized trial of hydroxychloroquine in early rheumatoid arthritis: the HERA Study. *Am J Med*. 1995;98:156-168.
- Tsakonas E, Fitzgerald AA, Fitzcharles MA, et al. Consequences of delayed therapy with second-line agents in rheumatoid arthritis: a 3 year follow-up on the hydroxychloroquine in early rheumatoid arthritis (HERA) study. *J Rheumatol*. 2000;27:623-629.
- Boers M, Verhoeven AC, Markusse HM, et al. Randomised comparison of combined step-down prednisolone, methotrexate and sulphasalazine with sulphasalazine alone in early rheumatoid arthritis. *Lancet*. 1997;350:309-318.
- Landewe RB, Boers M, Verhoeven AC, et al. COBRA combination therapy in patients with early rheumatoid arthritis: long-term structural benefits of a brief intervention. *Arthritis Rheum*. 2002;46:347-356.
- O'Dell JR. Treating rheumatoid arthritis early: a window of opportunity? *Arthritis Rheum*. 2002;46:283-285.

18. American College of Rheumatology Subcommittee on Rheumatoid Arthritis Guidelines. Guidelines for the management of rheumatoid arthritis. *Arthritis Rheum.* 2002;46:328-346.
19. van der Heijde DM, van Riel PL, van Leeuwen MA, et al. Prognostic factors for radiographic damage and physical disability in early rheumatoid arthritis: a prospective follow-up study of 147 patients. *Br J Rheumatol.* 1992;31:519-525.
20. van Gaalen FA, Linn-Rasker SP, van Venrooij WJ, et al. Autoantibodies to cyclic citrullinated peptides predict progression to rheumatoid arthritis in patients with undifferentiated arthritis: a prospective cohort study. *Arthritis Rheum.* 2004;50:709-715.
21. Avouac J, Gossec L, Dougados M. Diagnostic and predictive value of anticyclic citrullinated protein antibodies in rheumatoid arthritis: a systematic literature review. *Ann Rheum Dis.* 2006; 65:845-851.
22. Matsui T, Shimada K, Ozawa N, et al. Diagnostic utility of anticyclic citrullinated peptide antibodies for very early rheumatoid arthritis. *J Rheumatol.* 2006; 33:2390-2397.
23. McQueen FM, Benton N, Perry D, et al. Bone edema scored on magnetic resonance imaging scans of the dominant carpus at presentation predicts radiographic joint damage of the hands and feet six years later in patients with rheumatoid arthritis. *Arthritis Rheum.* 2003;48:1814-1827.
24. Lindegaard HM, Vallo J, Horslev-Petersen K, et al. Low-cost, low-field dedicated extremity magnetic resonance imaging in early rheumatoid arthritis: a 1-year follow-up study. *Ann Rheum Dis.* 2006; 65:1208-1212.
25. Pincus T. A multidimensional health assessment questionnaire (MDHAQ) for all patients with rheumatic diseases to complete at all visits in standard clinical care. *Bull NYU Hosp Jt Dis.* 2007;65:150-160.
26. Enbrel® (etanercept) Prescribing Information. Thousand Oaks, Calif: Immunex Corp; 2007.
27. Remicade® (infliximab) Prescribing Information. Malvern, Pa: Centocor, Inc; 2007.
28. Humira® (adalimumab) Prescribing Information. Chicago, Ill: Abbott Laboratories; 2007.
29. Moreland LW, Schiff MH, Baumgartner SW, et al. Etanercept therapy in rheumatoid arthritis: a randomized, controlled trial. *Ann Intern Med.* 1999;130:478-486.
30. van de Putte LB, Atkins C, Malaise M, et al. Efficacy and safety of adalimumab as monotherapy in patients with rheumatoid arthritis for whom previous disease modifying antirheumatic drug treatment has failed. *Ann Rheum Dis.* 2004;63:508-516.
31. van der Heijde D, Klareskog L, Rodriguez-Valverde V, et al. Comparison of etanercept and methotrexate, alone and combined, in the treatment of rheumatoid arthritis: two year clinical and radiographic results from the TEMPO study, a double-blind, randomized trial. *Arthritis Rheum.* 2006;54:1063-1074.
32. Klareskog L, van der Heijde D, de Jager JP, et al. Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomized controlled trial. *Lancet.* 2004;363:675-681.
33. Lipsky PE, van der Heijde DM, St Clair EW, et al. Infliximab and methotrexate in the treatment of rheumatoid arthritis. Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. *N Engl J Med.* 2000;343:1594-1602.
34. Keystone EC, Kavanaugh AF, Sharp JT, et al. Radiographic, clinical, and functional outcomes of treatment with adalimumab (a human anti-tumor necrosis factor monoclonal antibody) in patients with active rheumatoid arthritis receiving concomitant methotrexate therapy: a randomized, placebo-controlled, 52-week trial. *Arthritis Rheum.* 2004;50:1400-1411.
35. Breedveld FC, Emery P, Keystone E, et al. Infliximab in active early rheumatoid arthritis. *Ann Rheum Dis.* 2004;63:149-155.
36. Breedveld FC, Weisman MH, Kavanaugh AF, et al. The PREMIER Study: a multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who have not had previous methotrexate treatment. *Arthritis Rheum.* 2006;54:26-37.
37. St. Clair EW, van der Heijde DM, Smolen JS, et al. Combination of infliximab and methotrexate therapy for early rheumatoid arthritis: a randomized, controlled trial. *Arthritis Rheum.* 2004;50:3432-3443.
38. Burmester GR, Mariette X, Montecucco C, et al. Adalimumab alone and in combination with disease-modifying antirheumatic drugs for the treatment of rheumatoid arthritis in clinical practice: the Research in Active Rheumatoid Arthritis (ReAct) trial. *Ann Rheum Dis.* 2007;66:732-739.
39. Weinblatt ME, Keystone EC, Furst DE, et al. Adalimumab, a fully human anti-tumor necrosis factor monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: the ARMADA trial. *Arthritis Rheum.* 2003;48:35-45.

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About PCE Updates in Rheumatology...

Welcome to the second of 4 issues of *PCE Updates in Rheumatology*, developed for those NPs and PAs who serve patients in rheumatology practices throughout the country. "The demands for rheumatologic services are increasing exponentially with the aging population, while the number of physicians entering the rheumatology specialty is shrinking," according to the Society of Physician Assistants in Rheumatology (SPAR). Rheumatologists treating patients with rheumatoid diseases increasingly rely on specialist NPs and PAs to take an active management role in the frequent clinical contacts these patients require.

As healthcare professionals, NPs and PAs collectively provide a vital and increasing role in the diagnosis and management of acute and chronic illness. As clinicians, you spend more time with patients than most physicians, with your emphasis being patient disease state counseling and preventive care. Most importantly, NPs and PAs report that their roles have evolved from assisting physicians to treating and following their own patients. This increased role includes writing prescriptions, monitoring patient progress, and seeing patients in your own examination rooms. As NPs and PAs, you are rapidly emerging as key providers of patient care. You practice with greater autonomy and prescribe more medication than ever before.

Approximately 286 NPs and 188 PAs see patients in rheumatology practices that provide ongoing care for patients with rheumatoid diseases. Therefore, you need to be thoroughly familiar with innovative and complex biologic therapies: how and why such agents are useful, how to identify patients who are likely to benefit from biologic therapy, how to administer biologic treatments to ensure the greatest clinical advantage, and which clinical markers to monitor in balancing benefit versus risk. As prescribers, some NPs and PAs require information regarding the clinical features and drug properties of the specific biologics approved for similar indications.

This issue of *PCE Updates in Rheumatology* focuses on the advances in the management of the natural progression of RA. Clinical commentary by Rick Pope, MPAS, PA-C, current president of SPAR, discusses a case study of a patient with RA. Subsequent newsletters will provide up-to-date information on the association between ankylosing spondylitis (AS) and Crohn's disease, and psoriatic arthritis (PsA), respectively. Martin J. Bergman, MD, serves as Senior Editor for all 4 issues.

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