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Perspectives from Nicole M. Furfaro, MSN, ARNP



In your experience, how has the addition of the NP/PA enhanced the practice of rheumatology?
When I started working in rheumatology as an RN, there were

very few advanced practice nurses and physician assistants in the specialty. Now, almost 13 years later, NPs and PAs are commonplace in general practice and in specialty fields, as well.

Initially, patients did not understand the role of nonphysician providers, but today it is unusual to find someone who has not experienced care by an NP or PA. Many patients now embrace the opportunity to be cared for primarily by an NP/PA or in conjunction with a physician.

NPs and PAs contribute to the quality of patient care in many ways. We typically have more time to spend with patients and family members, which creates a unique emotional connection. Through that special connection, we are able to focus on education and provide comprehensive care that includes not only the physical aspects of disease, but psychological aspects, exercise issues, nutrition counseling, referrals to physical and occupational therapy, etc. A specific strength of NP/PAs lies in our ability to tailor complex pathophysiology, medication information, and health promotion concepts to the level of the individual. Overall, we offer a unique viewpoint in patient care that includes diagnosing, managing chronic problems, and coordinating other services. This allows physicians to focus on the more complex rheumatic patients and do what they do best—diagnose and develop care plans for complex situations. We also cannot forget the ever-growing evidence that NP/PA utilization is cost-effective and helpful financially to rheumatology practices. It is no
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Biologic Therapy: Incorporating Evidence and Safety Into Clinical Practice of Rheumatoid Arthritis

Martin J. Bergman, MD, Senior Editor

Treatment of rheumatoid arthritis (RA) has changed significantly in recent years. Prior to the late 1980s, initial therapy was aimed at amelioration of pain and stiffness through the use of nonsteroidal anti-inflammatory drugs (NSAIDs). Lifestyle changes such as rest and pacing of activities were mainstream recommendations. The use of disease-modifying antirheumatic drugs (DMARDs) was reserved for patients who did not respond to initial therapy or who had advanced disease, usually patients with evidence of erosion on x-ray. This approach resulted in limited success.

A better understanding of RA immunopathogenesis has resulted in the development of biologically-specific therapies that block the production or activity of various inflammatory mediators implicated in RA. Different classes of biologics include:

- Tumor necrosis factor-alpha (TNF- α)-blocking agents (infliximab, etanercept, and adalimumab)
- Anti-CD20 agents (rituximab)
- Cytotoxic T-lymphocyte-associated antigen-4 immunoglobulin agent (CTLA-4 Ig) (abatacept)
- Anti-interleukin (IL)-6 receptor (tocilizumab), anti-CD22, and anti-lymphostat B in development

Because biologic agents block different pathways of the immune system, they provide alternative ways of controlling inflammation, the hallmark symptom of RA.

The efficacy and side effects of approved biologic agents for the treatment of RA and the impact on current clinical practice are discussed in this newsletter.

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Clinical Commentary: Nicole M. Furfaro, MSN, ARNP

What is the current rationale regarding the use of biologics for RA?

The advent of biologics has dramatically changed the way we treat RA. The paradigm shift in treatment arose from increasing knowledge of the natural destructive course of RA, as well as the recognition that by slowing disease activity, we may significantly help patients physically and emotionally. By using biologics earlier in aggressive disease, not only is the progress of disease (at physical and radiographic levels) slowed, but the impact of

RA over a patient's lifetime is lessened by decreasing the need for joint replacement surgery, decreasing disability, and moderating other physiologic problems resulting from chronic inflammation.

TNF- α Inhibitors Represent a Major Advance in the Treatment of RA

Early diagnosis and initiation of DMARD (including biologics) therapy is critical to prevent structural joint damage and disability associated with RA. Moreover, the availability of new therapies that block production of various inflammatory mediators

implicated in RA provides the potential for disease remission. TNF- α plays a central role in the pathology of RA.

Efficacy of TNF- α Inhibition Long-Standing RA

Clinical trials with all 3 TNF- α inhibitors have demonstrated efficacy in RA patients with established disease who had failed traditional DMARD therapy.

Anti-TNF- α agents are effective as monotherapy,¹⁻³ but when used in combination with methotrexate (MTX), demonstrate superior efficacy in terms of clinical and radiographic benefit.³⁻⁶

Early RA

The combination of anti-TNF- α agents with MTX has also shown efficacy in the early stages of RA.⁷⁻⁹ ACR 70 responses were attained in

19% to 21% of patients receiving MTX monotherapy in trials of early RA and in 33% to 40% of those receiving adalimumab combined with MTX.⁸ This is an improvement over the results in established RA, where ACR 70 responses occurred in approximately 25% of those patients receiving TNF- α inhibitors combined with MTX, demonstrating the benefit of early aggressive treatment.⁸ In early RA, remission rates also are higher when anti-TNF agents are combined with MTX, compared to MTX monotherapy. In this same study, after 2 years about 50% of patients with early RA attained disease remission (defined as disease activity score [DAS] 28 <2.6) when treated with adalimumab plus MTX combination therapy compared to 25% with MTX or adalimumab alone.⁸

Radiographic Improvement of Joint Damage

In 3 trials using etanercept (TEMPO), infliximab (ASPIRE), or adalimumab, (PREMIER), patients with RA were randomized

The Basics: TNF- α ...

Is a proinflammatory cytokine found in elevated levels in the synovium of RA patients

- Induces other inflammatory cytokines to amplify the inflammatory signal
- Promotes inflammation by stimulating fibroblasts to express adhesion molecules
 - Adhesion molecules interact with their respective ligands on the surface of leukocytes, resulting in increased transport of leukocytes into inflammatory sites
- Is a potent stimulator, as is IL-1, of synovial fibroblasts, osteoclasts, and chondrocytes, which release tissue-destroying matrix metalloproteinases (MMPs)
 - TNF- α and IL-1 inhibit the production of tissue inhibitors of MMPs by synovial fibroblasts. These dual actions are thought to lead to joint damage in RA
 - There are 3 TNF- α blockers approved for the treatment of RA:
 - Infliximab (Remicade), a chimeric (human-murine) IgG1 anti-TNF- α antibody administered intravenously (IV)
 - Etanercept (Enbrel), a fully human recombinant soluble p75 TNF- α receptor:Fc fusion protein administered subcutaneously
 - Adalimumab (Humira), a recombinant humanized monoclonal anti-TNF- α antibody administered subcutaneously
- All 3 agents neutralize and eliminate excess TNF- α from the circulation and at sites of inflammation

Choy EH et al.⁴⁶; Scott DL et al. *N Engl J Med.* 2006;355:704-712.

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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, the participant should be better able to:


- Restate the importance of TNF- α inhibition in modifying the disease process associated with rheumatoid arthritis (RA).
- Explain the benefits and risks associated with TNF- α inhibition.
- Identify educational techniques to assist patients in the long-term management of RA.

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.

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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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to receive combination TNF- α inhibitor and MTX or MTX monotherapy. The combination typically produced an ~2-fold greater improvement in ACR 50 response compared with MTX therapy alone (Figure 1).¹⁰ The author reviewed the radiographic outcomes of these studies, which used the modified Sharp/van der Heijde score (SHS) as the measure of joint damage, and demonstrated superior benefits with the

TNF- α and MTX combination compared with MTX monotherapy.¹⁰ There was at least a 4-fold increase in benefit with combination therapy compared with MTX alone (Figure 2). Although the clinical significance of the magnitude of radiographic improvement versus improvement in signs and symptoms is unknown, the decreasing progression to near zero change in SHS is noteworthy.¹⁰

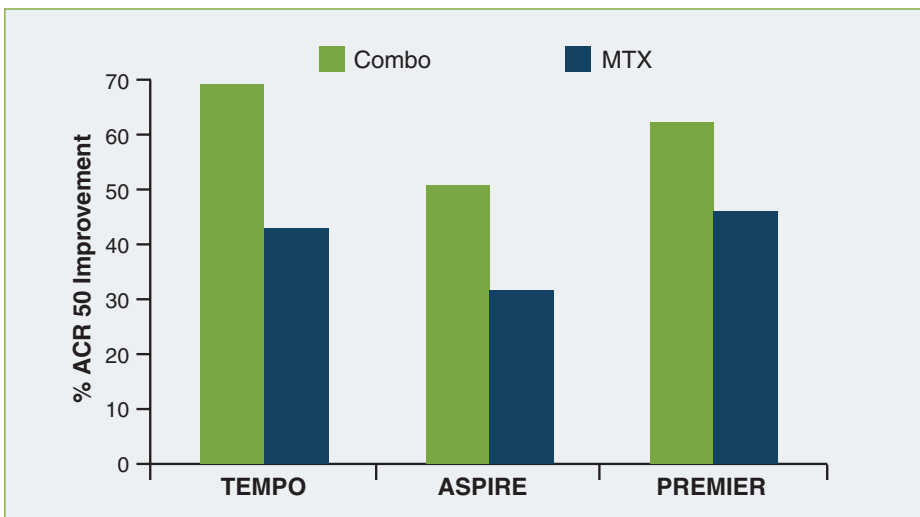


Figure 1. Greater improvement in ACR 50 with TNF- α agents plus MTX compared to MTX alone in 3 similarly designed clinical trials: TEMPO,⁴ ASPIRE,⁵ and PREMIER.⁸ Adapted from Weisman MH.¹⁰

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/rheumissue1. 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: September 15, 2007

Expiration: Required materials must be submitted before September 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 the Continuing Education Alliance at inquiries@cealliance.org for questions regarding this activity.

Perspectives from Nicole M. Furfaro, MSN, ARNP

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wonder that some of the most popular talks at rheumatology meetings involve the question of how to bring an NP or PA into a rheumatology practice.

What is the impact of the NP/PA on the management of patients with RA?

NPs and PAs tend to focus on really getting to know the patient over time. Again, since we spend a lot of time in education, there is a special bond that develops between practitioner and patient. Studies in chronic illnesses, such as diabetes and heart disease, demonstrate that adherence to treatment plans is greater in patients who understand why a particular therapy is essential and when their concerns have been adequately addressed. In rheumatology, this is so critical because we understand the importance of early and effective treatment to optimize positive outcomes for our patients. So many NP and PAs I have spoken with really grasp the importance of managing the whole patient, not just their RA. That may include actual treatment of an issue such as high blood pressure, lipid management, depression, infections, etc, or referring to primary care or other specialty providers, if needed. In any event, patient care is enhanced by close attention to all needs both physical and emotional.

How will the role of the NP/PA in the management of patients continue to evolve?

Our roles in management of patients are constantly changing and evolving as we grow in knowledge and numbers. Studies have shown good outcomes in patient care and high levels of patient satisfaction with treatment by nonphysician providers. Our focus on treating the whole individual will contribute greatly to positive long-term outcomes for our RA patients. We all recognize the importance of controlling RA symptoms and disease progression. With a relative shortage of physicians to care for rheumatologic patients, our roles in management will continue to grow significantly. In recent years, we have seen an explosion in effective treatment options and an expansion in our knowledge of the pathophysiology of RA and the immune system. As long-term outcome measures demonstrate better outcomes in our tightly controlled RA patients, NPs and PAs will play a significant role in managing this chronic disease.

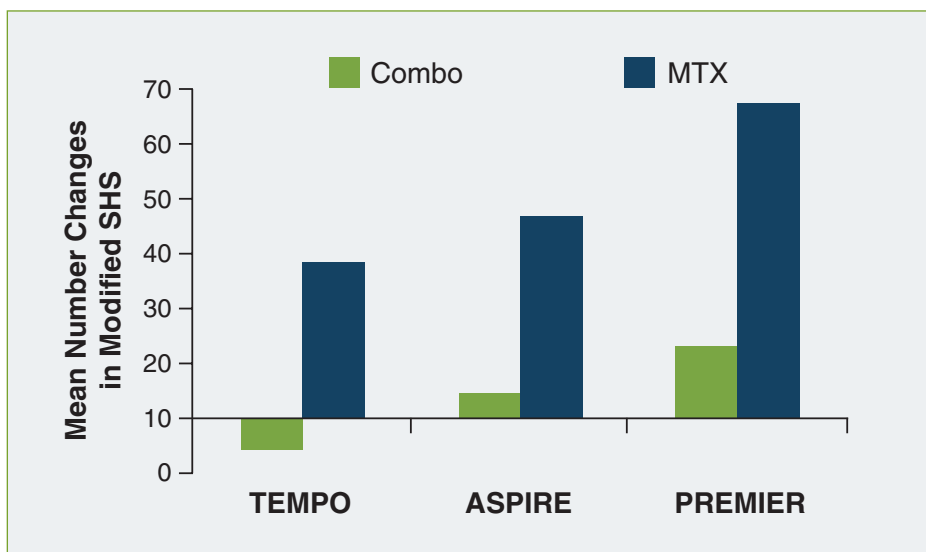


Figure 2. Greater radiographic improvement with TNF- α agents plus MTX compared to MTX alone in 3 similarly designed clinical trials: TEMPO,⁴ ASPIRE,⁵ and PREMIER.⁸ Mean numeric changes in the modified SHS are shown. Adapted from Weisman MH.¹⁰

Improved Function and Quality of Life

Particularly important to individual patients is improvement in quality of life (QOL). Clinical trials of patients with RA who consistently used anti-TNF agents demonstrate improved function and improvement in QOL measures. When the Health Assessment Questionnaire (HAQ) and/or the Medical Outcomes Study 36-item Short-Form General Health Survey (SF-36) were used, an even greater improvement was noted with the anti-TNF plus MTX combination.^{3,6,8,9} Furthermore, a qualitative study that assessed patients' perspectives regarding treatment with TNF- α inhibitors reported that the majority of patients surveyed reported that not only were the agents effective and safe, but these patients were pleased with the results. Patients' experience with anti-TNF- α therapy was particularly favorable in the areas of physical function and well-being¹¹ and work stability.^{11a}

Clinical Commentary: Nicole M. Furfaro, MSN, ARNP

What are the identification criteria for patients who will benefit from treatment with biologics?

As clinicians, we all have experience with the patient who has a clear need for biologic treatment from those who have aggressive early-onset disease, significant disease burden from high swollen and tender joint counts to those who have failed to respond to MTX or other nonbiologic DMARDs. Additional criteria used in decision making involve objective measures of disease activity such as progression of radiographic damage, elevated inflammatory markers such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), and relying on validated measures for assessing when a patient is experiencing response to therapy such as through DAS 28 scores, HAQ, etc. Using validated measures of disease activity in clinical practice will help standardize the identification of patients who require treatment with biologics and ultimately should be adopted by all clinicians treating patients with RA.

TNF- α Inhibition and Adverse Events: A Brief Review of the Literature

Minor Adverse Events

In general, TNF- α inhibitors have been well tolerated by patients in clinical trials. Common minor adverse events include injection site reactions with etanercept and adalimumab and infusion reactions with infliximab.¹² Injection site reactions tend to be mild to moderate in severity and diminish in frequency after the first month of treatment. Erythema, pruritus, pain, and swelling are the most common injection site reactions. Infusion reactions such as fever, chills, pruritus, urticaria, chest pain, hypotension, hypertension, and shortness of breath occur in 16% of infliximab-treated patients as opposed to 6% of placebo-treated patients.

Longer term follow-up and pharmacovigilance data have highlighted some important safety issues regarding the use of anti-TNF- α agents. While TNF- α works in RA by impacting key inflammatory components of the immune system, it also helps maintain normal immune function. Therefore, inhibition may predispose treated patients to certain adverse events (AEs) (Table 1).¹³ Important safety considerations with the use of TNF- α antagonists include:

- Serious infection
- Opportunistic infection (including tuberculosis [TB])
- Malignancy
- Congestive heart failure (CHF)
- Hepatotoxicity

Comorbid medical conditions, concomitant use of other immunosuppressive medications, and disease variables may increase the patient's risk for certain AEs (Table 2).¹³

Risk of Infections

Blockade of TNF- α may place patients at greater risk of infection because TNF- α plays an important role in the body's defense against bacterial and viral invasion.¹⁴ Despite this theoretical concern, rates of serious infection seen during clinical trials of etanercept, infliximab, and adalimumab in RA (3-4 serious infections/100 patient-years) were not significantly increased compared with those in the placebo arms (2-4 serious infections/100 patient-years).^{2,3,5,6,8,9,15,16} In contrast to controlled trials, there are conflicting data from postmarketing observations, pharmacovigilance programs, RA databases and registries, and safety trials regarding the rates of infection among patients treated with TNF- α inhibitors.¹³ A British registry study reported an increase in serious infections with all 3 TNF- α antagonists (n = 525) compared to DMARDs (n = 56).¹⁷ When these results were analyzed for confounding variables, the overall risk of serious infections was not increased with all 3 anti-TNF- α antagonists.¹⁷ The excess risk attributable to treatment is hard to define because of the higher baseline prevalence of infection in patients with RA, particularly those with severe disease.¹⁸ This is supported by data from a German biologics registry, RABBIT. In this registry, patients taking etanercept and infliximab had a higher risk of infection than those taking conventional DMARDs. After adjusting for disease activity, this risk was reduced from an odds ratio (OR) of ~6 to ~2.¹⁹ However, a recent study looking at Pennsylvania Medicare/Medicaid patients showed no increase in the rates of serious infections.²⁰

The concept of RA patients having a higher baseline risk for infections is

Table 1. Adverse Events Associated With Biologic Agents for Treatment of RA

Biologic Agent	Adverse Event
TNF-α antagonists Adalimumab, etanercept, infliximab	<ul style="list-style-type: none"> • Infections/serious infections (URI/sepsis/pneumonia) • TB/opportunistic infections • Malignancies (lymphoma) • Demyelination • Autoantibodies/drug-induced lupus • CHF • Hepatotoxicity/HBV reactivation • Hematologic abnormalities • Administration reactions • Immunogenicity
IL-1 receptor antagonist Anakinra	<ul style="list-style-type: none"> • Infections • Administration reactions • Immunogenicity
Anti-CD20 Ig Rituximab	<ul style="list-style-type: none"> • Infusion reaction • Cardiac arrhythmias/hypertension • Infection/opportunistic infection • Hepatitis B reactivation • Cytopenias • Tumor lysis syndrome • Hypersensitivity reaction
CTLA-4 Ig Abatacept	<ul style="list-style-type: none"> • Infusion reaction • Infection • Hypersensitivity reaction • COPD exacerbation

HBV = hepatitis B virus; COPD = chronic obstructive pulmonary disorder; URI = upper respiratory tract infection.

established. In addition, advanced age as well as certain comorbid conditions such as diabetes and chronic lung and kidney disease may account for the increased risk of infection in RA patients.^{16,21}

Nonetheless, the impact of medication on increasing risk of infection cannot be overlooked, eg, increased risk of infection has been noted with higher doses of infliximab. Infliximab at 10 mg/kg has been associated with a significantly higher risk of infection than infliximab at 3 mg/kg (relative risk of 1.003 vs 3.1, $P = .013$).²¹ The risk of infection also increased significantly

when biologic agents are combined. A higher rate of serious infection was noted in RA patients when etanercept was combined with anakinra²² or with abatacept²³ without an increase in efficacy. Thus, combination biologic therapy currently is contraindicated in patients with RA.

Surveillance data have also shown higher incidences of atypical infection including TB, atypical mycobacteria, histoplasmosis, aspergillosis, and other opportunistic pathogens.¹³ In the case of TB, more than 50% of the cases were extrapulmonary infections. Most of these infections

Table 2. Factors Contributing to Increased Risk of Adverse Events With Biologic Agents

Patient demographics	<ul style="list-style-type: none"> • Older age • Lower education
Comorbidities	<ul style="list-style-type: none"> • Chronic lung disease • Diabetes • Alcoholism • Chronic renal failure • Organic brain disease • Current smoker • Leukopenia • CHF
Disease variables	<ul style="list-style-type: none"> • Extra-articular manifestations • Presence of rheumatoid factor • Elevated inflammatory markers • Poor functional capacity • Longer disease duration
Medications	<ul style="list-style-type: none"> • Prior exposure to cyclophosphamide • Current use of corticosteroids • Higher dosages of DMARDs or biologics

Doran MF et al.¹⁸

occurred in patients with a known history of TB, suggesting reactivated latent infection. Although the increased susceptibility to TB has been seen with all 3 TNF- α inhibitors, mechanistic and pharmacokinetic/pharmacodynamic differences among the agents, variability in avidity, and different susceptibility of the populations treated may be associated with the differences in risk among agents.²⁴ Because reactivation of TB remains a major concern with all TNF- α inhibitors, it is strongly recommended that all patients be screened for latent TB prior to initiating any anti-TNF therapy.

Risk for Malignancy

The risk of malignancy is an important safety concern with the use of TNF- α inhibitors, however, the overall risk of malignancies associated with these agents is controversial.

A systematic review of randomized, controlled trials reported a dose-related increased risk of cancer with infliximab and adalimumab (etanercept was excluded from this analysis).²⁵ In contrast, national RA registries have not yet found an increased risk of solid cancers in RA patients treated with TNF- α inhibitors (Table 3).^{26,27}

An increase in lymphoma has been reported with all TNF- α inhibitors compared to “healthy controls,” however, because there is a pre-existing association of lymphoma with severe RA and systemic inflammation, the exact contribution of anti-TNF- α therapy is difficult to discern.^{25,28-31}

Risk for Hepatic Dysfunction

Mild-to-moderate liver function test (LFT) elevation (generally <3 times the upper limit of normal)

has been observed with TNF- α inhibitors in clinical trials and spontaneous reporting.^{6,8,21,32} Many of these cases were confounded by comorbid conditions and concomitant use of medications (eg, NSAIDs, MTX, leflunomide). Given the potential for liver failure, periodic laboratory monitoring of patients receiving biologics should be considered.

TNF- α has also been implicated in the pathogenesis of chronic viral hepatitis. TNF- α levels are elevated in patients with chronic hepatitis B virus (HBV) and hepatitis C virus (HCV).³³ Possible reactivation of hepatitis virus following immunosuppression is a concern with the use of TNF- α inhibitors. There has been 1 reported case of a patient with RA and chronic hepatitis B who developed hepatitis B reactivation while on combination therapy with infliximab and MTX for 18 months.³⁴

Despite this rare incidence, safety concerns have been raised regarding the use of TNF- α inhibitors in the treatment of RA patients with concurrent viral hepatitis. This has led to a recommendation for serologic testing for chronic HBV and HCV prior to TNF- α inhibitor treatment (or MTX). Prophylaxis with lamivudine or other effective antiviral agents should be considered in patients who are hepatitis B surface antigen-positive and require TNF- α inhibitor therapy. It should be noted that there are data to suggest that TNF- α inhibitors may play a role in the treatment of hepatitis C infections.³⁵ Regardless of these findings, in patients with viral hepatitis, treatment with TNF- α inhibitors should be approached with caution, close supervision, and the involvement of other specialists, such as a gastroenterologist/hepatologist.

Risk for Congestive Heart Failure

Progression of CHF associated with TNF- α inhibitors may seem counterintuitive as serum levels of TNF- α are elevated in patients with CHF and correlate with degree of severity.³⁶ This finding led to the rationale for using TNF- α inhibitors in the treatment of CHF. Unfortunately, initial clinical trials assessing this hypothesis failed to show any benefit and resulted in increased morbidity and mortality.^{37,38} Moreover, cases of worsening and new-onset CHF have been reported in RA patients treated with anti-TNF- α agents, therefore, TNF- α inhibition is strongly discouraged in patients with moderate-to-severe CHF (NYHA Class III-IV).³⁹⁻⁴¹

Care should be taken when interpreting the evidence for new-onset CHF in patients with RA who receive anti-TNF- α therapy, as cardiovascular disease (CVD) is the leading cause of death among patients with RA, with increased standardized mortality ratios compared with the general population.⁴² In addition, there is evidence that the excess risk of CVD and heart failure in RA patients may be ameliorated by anti-TNF- α therapies. Patients with RA treated with TNF- α inhibitors have been shown to have a lower prevalence and incidence of CHF and CVD and lower mortality than RA patients not treated with TNF- α inhibitors.⁴³⁻⁴⁵

Clinical Commentary: Nicole M. Furfaro, MSN, ARNP

What screening procedures are required prior to biologic therapy?

In clinical practice, the decision to use a biologic therapy is based upon risk versus benefit. Broad screening and individual risk factors should be

Table 3. Risk of Malignancies With Anti-TNF- α Agents

Study	All Cancers	Solid Tumors	Lymphoma
Meta-analysis of clinical trials of infliximab and adalimumab ²⁵	Patients: 0.9% Controls: 0.2% NNH: 154		
National Registry: United Kingdom ²⁶	Patients receiving all agents: 0.86/100 PY Controls: 1.42/100 PY		
National Registry: Sweden ^{27,30}		Patients receiving all agents: 0.9 SIR Controls: 1.1 SIR	Patients receiving all agents: 2.9 SIR Controls: 2.0 SIR
US National Databank ²⁸			Patients receiving all agents: 2.9 SIR Controls: 1.9 SIR

NNH = number needed to harm; PY = patient-years; SIR = standardized incidence ratio.

taken into account. Screening procedures prior to biologic therapy always include history and physical examination, which focus on current health as well as history of infections, comorbid conditions such as CHF, possible hepatitis exposure, TB exposure, etc. Laboratory screening often includes baseline blood counts, liver enzymes, and purified protein derivative (PPD) screening with chest radiographs if positive. Consideration should be given to patients at risk for hepatitis and appropriate lab work ordered.

Risk reduction includes screening prior to initiating biologic therapy and educating patients about the potential for increased risk of infection and the need for prompt medical evaluation in the event of an infection. I recommend that all adults have updated immunizations according to the Centers for Disease Control (CDC) guidelines, particularly annual influenza vaccine, updated diphtheria booster, and pneumococcal vaccine when applicable. Recently, the availability of the

shingles vaccine has added a new consideration in prebiologic counseling because it is a live virus and therefore should be given prior to initiation with an anti-TNF agent, but cannot be given to any patient on another immunosuppressive agent, such as MTX.

Educating patients with comorbid conditions, such as diabetes and chronic infections, about the increased risk of infection and AEs associated with biologic therapy may help them recognize when it is appropriate to seek medical intervention for an infection. Issues other than safety include establishing disease activity and prognosis through laboratory markers (rheumatoid factor, ESR, CRP, anticyclic citrullinated peptide [CCP], etc) and baseline radiographs, if indicated.

Other Biologic Agents for Treatment of RA

In addition to TNF- α inhibitors, other biologic agents have been approved that target various inflammatory mediators in RA.

Anakinra

Anakinra is a recombinant, humanized IL-1 antagonist that binds to IL-1 type 1 receptors and down-regulates the inflammatory effects of IL-1. Interleukin-1 is among the proinflammatory cytokines found in the synovium of RA patients and is believed to play a role in the pathogenesis of RA.⁴⁶ The efficacy of anakinra has been demonstrated when used as monotherapy or in combination with MTX. In patients with active disease despite treatment with MTX, significant improvements in ACR 20 response, ESR and CRP levels, and HAQ scores have been obtained within 4 weeks of initiation of anakinra therapy compared to placebo.⁴⁷ Anakinra administered as monotherapy for 48 weeks has also been shown to slow radiographic progression of joint damage in RA.⁴⁸

Injection site reactions are the most common AE reported with anakinra. They usually are dose related, affecting up to 70% of patients, but in some patients, seem to lessen in severity with continued use.⁴⁸⁻⁵⁰ Rates of serious infection and malignancies associated with anakinra therapy are comparable to those with placebo (2% vs 1%).^{47,50} However, the combination of TNF- α inhibitors and anakinra has resulted in a higher incidence of serious infections without added clinical benefits.²² Thus, biologic combination therapy with anakinra is discouraged.

Rituximab

Rituximab is a chimeric monoclonal antibody directed against the CD20 antigen present on mature B cell surface. Rituximab binds to CD20 and causes apoptosis of these cells

without targeting stem cells or existing plasma cells.⁵¹ Within 24 to 48 hours of infusion, rituximab markedly depletes peripheral B cells. Despite its actions on B cells, the overall levels of serum immunoglobulins generally remain stable during treatment.⁵²

Rituximab in combination with MTX recently has been approved for the treatment of (moderately to severely active) RA in patients who had an inadequate response to TNF- α inhibitors.⁵² The efficacy of rituximab in improving the clinical signs and symptoms of RA, as well as in reducing or preventing radiographic disease progression has been shown in 3 large trials.⁵³⁻⁵⁵ Improvement has also been demonstrated in patient-related outcomes such as HAQ-DI, patient global visual analog scale (VAS), fatigue, disability, and QOL.

Given the rapid and complete depletion of peripheral B cells observed in response to rituximab, the possibility of subsequent infection risk is a concern. However, in all 3 large trials of rituximab, the rate of serious infections was similar (3% vs 2.5%⁵⁴ and 2% vs 1%⁵⁶) or slightly elevated (5.7 vs 3.7 per 100 patient-years⁵⁵) compared with placebo. While the risk of infection with rituximab is low, serious reactivation of chronic viral infections after rituximab therapy is a possibility.

[Editor's Note: There are conflicting data in RA regarding the ability of patients to respond adequately to influenza vaccination after treatment with rituximab. Based on the data, it is still advisable to administer influenza vaccine in these patients, but they may not benefit from complete protection. Live vaccinations, ie, rubella,

zoster, or yellow fever should not be administered to patients on rituximab or other immunosuppressive agents, including MTX, leflunomide, anti-TNF agents, and abatacept. **M. Bergman, MD]**

In all trials of rituximab, infusion reactions (pruritus, urticaria/rash, headache, transient hypotension, cough, bronchospasm, fever, chills and rigours) were the most commonly reported AEs. The frequency of these reactions was higher with the first infusion (~35%) and reduced with the second infusion (~10%).²⁵ Premedication with IV corticosteroids substantially reduced the incidence and severity of the infusion reactions by about 30% without affecting efficacy.

A recent study reported an increase in the number of patients who when re-treated experienced a drop in their IgM levels below the normal range. To date, no increase in infections or serious infections has occurred in these patients.⁵⁷

Abatacept

Abatacept (CTLA-4 Ig) is a soluble chimeric human protein consisting of the extracellular domain of CTLA-4 (CD152) and the Fc portion of human IgG.²³ Abatacept, administered IV, is approved as monotherapy or in conjunction with background DMARDs (other than TNF- α inhibitors) for treatment of active RA in patients who had an inadequate response to 1 or more DMARDs, such as MTX, or TNF- α antagonists.

Several studies with abatacept alone or in combination with MTX in patients who had an inadequate response to DMARDs or TNF- α inhibitors have shown clinical efficacy without an increased rate of serious AEs such as malignancies and opportunistic infections.^{23,58}

However, a study assessing the safety of abatacept in combination with either nonbiologic or biologic DMARDs found a higher incidence of serious AEs at 1-year follow-up in patients treated with a combination of abatacept and a biologic agent (22.3% in abatacept and a biologic agent vs 11.7% in abatacept and a traditional DMARD vs 12.5% in the biologic agent-only group). Based on the findings of this study, combination therapy with abatacept and other biologic agents is not recommended. The addition of abatacept to traditional DMARDs appeared to be safe with a comparable incidence of AEs to DMARDs alone (11.7% vs 12.2%, respectively).²³

Clinical Commentary: **Nicole M. Furfaro, MSN, ARNP**

What is the role of patient education in the effective management of RA?

Patient education is important because patients who are well informed about the seriousness of RA and the need to aggressively control inflammation are more likely to feel like “partners” in their plan of care and adhere to recommendations for treatment. Some basic principles of patient education include the following:

- Use terminology that is appropriate to the level of patient understanding
- Slowly introduce concepts so the patient is not overwhelmed
- Tailor information to meet the patient’s current needs

A patient who is newly diagnosed with RA not only needs to understand how RA causes stiffness and swelling of the joints, but also how RA can affect QOL as patients may experience fatigue and difficulty with household chores and employment. They need to understand that while RA

cannot be cured, there are a number of effective and relatively safe treatments that limit the effects of inflammation and disease progression.

The ability to slow or stop joint damage using TNF blockers in combination with other DMARDs is strong and promising with regard to safety. Importantly, anti-TNF medications tend to work quickly, sometimes after 1 or 2 doses. Evidence is mounting that if one biologic does not work well, others may be tried with good response.

It is important to help patients who have severe or active disease burden understand the evolving knowledge of the role that inflammation plays in CVD, infection, and lymphoma risk. Patients who have RA for years still need ongoing up-to-date information on new treatments, the reality of risks versus benefits of DMARDs, including biologics, and how their disease is changing or hopefully not progressing.

Last, patients need guidance on where to find appropriate information on RA, whether from our files, the American College of Rheumatology/Association of Rheumatology Health Professionals, the Arthritis Foundation, or other institutions. It is important to guide patients toward reputable treatment resources and science-based evidence.

What are the effective measures to maintain patients on pharmacologic/biologic therapy and for long-term follow-up?

Fortunately, biologic therapy has improved the lives of many patients. Never has there been a time in RA treatment when patients have so many options for managing disease. In my clinical experience, patients who respond well may experience full remission in clinical signs and symptoms of RA and chronic inflammation, and others have varying levels of improvement. A patient’s

own response to therapy is often the biggest factor in keeping patients on such treatments, as well as fewer side effects of the biologics compared to traditional DMARDs. Newer therapies tend to require less frequent laboratory monitoring. Still, all medications carry risks and patients need to be reminded of the need for laboratory and radiographic follow-up to assess disease progression. We continue to regularly monitor blood counts and liver enzymes in our patients treated with MTX and that often suffices for patients treated with biologics (currently there is no consensus on how often to monitor labs in patients treated with biologics). With regard to long-term follow-up, there is more use of forms or measures that combine patient-reported disease activity with objective measures such as ESR/CRP, swollen joint count, etc. Examples of validated measures in RA include the DAS, HAQ, or the less time-intensive RAPID. By adopting a method of following disease activity, clinicians will be better able to objectively measure patient response to treatment, make changes in therapy if necessary, and communicate results of disease activity to patients and the rheumatology community at large.

Conclusion

The introduction of biologic therapies and early aggressive management has resulted in the ability to inhibit the progression of structural joint damage in some patients with moderate to severe RA. Significant disease activity reduction, retardation of radiographic progression, and improvement in functional disability have been demonstrated with the administration of TNF- α inhibitors in early and long-standing RA. These results provide hope that remission, the ultimate goal in RA treatment, might be attainable.

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About PCE Updates in Rheumatology...

Welcome to the first 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 of biologic therapy for the management of the natural progression of RA. Clinical commentary by Nicole M. Furfaro, MSN, ARNP, discusses how biologic agents have revolutionized the way RA currently is treated. Subsequent newsletters will provide up-to-date information on RA, psoriatic arthritis (PsA), and the association between ankylosing spondylitis (AS) and Crohn's disease. Rick Pope, MPAS, PA-C, current president of SPAR, and Nicole Furfaro present case studies and clinical commentary that will expand on the available options and management techniques they use in caring for patients with rheumatic diseases. Martin Bergman, MD, serves as Senior Editor for all 4 issues.

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