

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

**How has the role of
the PA expanded in
the practice of
rheumatology?**



During the past 20 years, the practice of rheumatology has expanded 4-fold due to the increase in the number and specificity of treatments for common rheumatologic disorders such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), inflammatory spondyloarthropathies (SpAs), and crystal disease. In 1988, Wednesdays were known as "Gold Day" at the Arthritis Center, and I personally reviewed all patients with RA who received injectable solganol. Because toxicities were not uncommon, I was vigilant regarding all toxicities, particularly proteinuria and gold-induced skin eruptions. Methotrexate rapidly was becoming a mainstay of treatment, and with its use came a different set of toxicities. Today, the newer biologic response modifiers and B-cell targeted therapies halt radiographic disease progression and reduce the fatigue associated with inflammatory arthritis, while at the same time presenting a host of different issues. There now exist a multitude of extra-articular manifestations of inflammatory arthritis, such as

(continued on page 5)

Ankylosing Spondylitis and Crohn's Disease: Biologic Treatment Advances and Guideline Interpretation

Martin J. Bergman, MD, Senior Editor

Ankylosing spondylitis (AS) and Crohn's disease (CD) are characterized by chronic inflammation in the joints and gastrointestinal tract (GI), respectively. There is considerable overlap between these 2 diseases, as a substantial proportion of patients with AS have asymptomatic gut inflammation on biopsy or clinically evidenced CD. In addition, AS and inflammatory peripheral arthropathies can be extraintestinal complications of CD. Although the pathogenesis and etiology of both diseases are poorly defined, certain common underlying factors exist that may suggest pathways to optimal disease management.

This issue of PCE Updates in Rheumatology features information on AS, CD, and the link between the 2 diseases. Rick Pope, MPAS, PA-C, presents a case study of a patient with AS and CD.

The Link Between Ankylosing Spondylitis and Crohn's Disease

The inclusion of CD as a spondyloarthropathy (SpA) and the frequent presence of AS in individuals with CD suggest mutual underlying pathogenic and pathophysiologic mechanisms.¹⁻³ Both of these chronic diseases are inflammatory in nature, and it has been suggested that bacteria and the immune response to bacteria play a

predominant pathogenic role.² Reverse transcriptase polymerase chain reaction techniques in patients with SpAs have demonstrated the presence of bacterial DNA and RNA in synovial fluid. A T-cell-mediated immune response to gut bacteria may promote circulation of the bacterial antigens and degradation products to joints. As many as 60% of patients with SpAs have gut alterations,

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Fast Facts: Understanding Ankylosing Spondylitis

- A chronic inflammatory disease, prototypical of a group of disorders referred to as the SpAs
 - SpAs are characterized by overlapping aspects of inflammation of the entheses, the site of insertion of cartilage and ligament capsules into bone; sacroiliitis; and extra-axial manifestations
 - Rheumatoid factor is absent, as are subcutaneous nodules and the other extra-articular features typically seen in patients with rheumatoid arthritis (RA)¹
 - Initially, AS is manifested by sacroiliitis, although peripheral joints and extra-articular structures may be affected
 - Over time, irreversible damage occurs, notably fusion of the vertebrae. In advanced disease, this fusion ascends the spine, forming a long bony column—the so-called bamboo spine
 - An association with human leukocyte antigen B27 (HLA-B27) and a positive family history are also distinguishing features of SpAs
- The prevalence of AS parallels that of HLA-B27 seropositivity, generally affecting 197 per 100,000 individuals in the United States ≥ 20 years of age
- Following adjustment for age and sex, the incidence of AS in the United States remains steady at 7.3 per 100,000 patient-years
- First-degree family history of AS is a strong risk factor for the disease. Disease onset occurs at 15 to 40 years of age (mean, 28.3 years). Approximately only 6% of cases are diagnosed in persons >40 years of age
- Affects men 2- to 3-fold more than women. The disease is likely to be severe and affect the spine and pelvis, with lesser involvement of the chest wall, hips, shoulders, and feet. In contrast, women more often experience symptoms in the knees, wrists, ankles, hips, and pelvis, and less in the spine
- Similar to IBD, enteric bacteria appear to play a role in SpA, and bacterial infection may be the triggering episode, with the subsequent autoimmune response leading to AS. Immune reaction to gut bacteria may be important as evidenced by the association between frequent GI infections and AS

Rudwaleit M et al.³; Sieper J et al.⁵; van der Hiejde D et al for the ATLAS Study Group. Efficacy and safety of adalimumab in patients with ankylosing spondylitis. *Arthritis Rheum.* 2006;54:2136-2146; van der Linden S et al.¹

including asymptomatic chronic intestinal inflammation.

Genetics also may be involved in the pathogenesis of both diseases. HLA-B27 is strongly associated with AS, but a relationship with CD is less evident. Up to 20% of patients with irritable bowel disease (IBD) and sacroiliitis are positive for HLA-B27, a proportion similar to that in the general population.⁴ Conversely, CARD15 polymorphisms have been associated with both diseases.^{2,3} CARD15 is present in nearly 4 of 10 patients with AS complicated by subclinical gut inflammation and in 7 to 8 of every 10 patients with IBD complicated by sacroiliitis.⁴ CARD15 mutations have been shown to increase the risk for CD, as well as sacroiliitis in patients with IBD.

The immune response in both diseases share commonalities, specifically production of high levels of the proinflammatory cytokine TNF- α .^{2,3} Restoring the immune balance in both the gut

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Target Audience

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

Goal

To elucidate pathogenic commonalities between ankylosing spondylitis (AS) and Crohn's disease (CD) and review the use of biologic treatment for both diseases in accordance with published guidelines.

Learning Objectives

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

- Describe possible pathogenic factors involved in AS and CD.
- Define the role of tumor necrosis factor alpha (TNF- α) in AS and CD.
- Identify patient characteristics that correlate with guideline recommendations for the use of anti-TNF- α therapy for AS and CD.
- Discuss practice implications of findings from studies assessing the efficacy of anti-TNF- α in patients with AS, CD, or both conditions.

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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and joint may alter the progression of both diseases. This concept has been proven by the effectiveness of anti-TNF- α therapy in patients with AS, as well as patients with CD. The concurrence of both diseases in a substantial proportion of patients leads to the question of whether anti-TNF- α therapy would serve as an optimum treatment in these patients.

Diagnosing Ankylosing Spondylitis

The diagnosis of AS typically occurs long after onset of symptoms and frequently after irreversible damage has occurred.^{1,3} Radiologic evidence often is visible only late in the course of the disease, making diagnosis challenging. Physical examination and a thorough patient history may provide important diagnostic information, specifically a positive family history of the disease and the presence of back pain (Table 1).^{1,5} Low back pain that improves with exercise

or movement in a person <40 years of age is particularly important. New onset of AS in a patient >40 years of age is rare. Patients may experience arthritis in the hips and shoulders early in the disease⁵; neck pain and stiffness are more likely to be present in advanced disease. When the thoracic spine is involved, the patient may report chest pain that is exacerbated by coughing or sneezing, and chest expansion may be mildly or moderately reduced in early stages of AS.¹ Acute anterior uveitis is the most

common extra-articular manifestation of AS, although photophobia and increased lachrymation may develop.⁵ As many as 60% of patients with AS have asymptomatic IBD. Fulminant IBD does develop in some of these patients.

Diagnostic Tools

Laboratory tests are not diagnostic for AS.^{1,5} There are minimal data to support a relationship between clinical signs of the disease and elevated levels of C-reactive protein and erythrocyte sedimentation

Table 1. Diagnostic Characteristics of Ankylosing Spondylitis

- | | |
|---|---|
| <ul style="list-style-type: none"> • Inflammatory spinal pain • Onset <40 years of age • Insidious onset • Persistence of ≥ 3 months • Morning stiffness • Improvement with exercise • Chest pain • Alternate buttock pain | <ul style="list-style-type: none"> • Acute anterior uveitis • Synovitis (primarily of lower limbs, asymmetric) • Enthesitis (heel, plantar) • Radiographic sacroiliitis • Positive family history for AS, IBD, psoriasis |
|---|---|

From van der Linden S et al.¹

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rate, although both often are present in patients with AS.⁵ In patients with thoracic involvement, vital capacity typically is decreased and functional residual capacity increased, but ventilator function remains normal. The majority of white patients with AS (90%-95%) are positive for HLA-B27.

The Modified New York Criteria for AS include the clinical criteria of low back pain and stiffness of 3 months' duration that improves with exercise but is unrelieved by rest; limitation of motion of the lumbar spine in the sagittal and frontal planes; and limitation of chest expansion, as well as radiologic criterion of sacroiliitis (grade \geq II-IV bilaterally or grade III-IV unilaterally).⁶ A diagnosis of AS is definitive when the radiologic criterion is accompanied by at least 1 clinical criterion. The frequent lack of radiologic demonstration of the disease early in its course contributes to the difficulty in following these guidelines. The advancement of imaging technology, mainly magnetic resonance imaging (MRI), has facilitated the diagnosis of AS.⁷⁻⁹

Imaging Modalities

The earliest inflammatory lesions in AS are manifested within the subchondral bone and synovium of the sacroiliac joint.⁷ Because plain films and computed tomography detect only structural, not inflammatory abnormalities, the diagnosis of AS may be delayed for a prolonged period of time while the disease progresses. Magnetic resonance imaging, however, can detect the presence of subchondral bone marrow edema,

a prominent feature of AS. In addition, MRI may uncover synovitis, subchondral marrow inflammation, and capsular inflammation that occur early in the course of the disease. Magnetic resonance imaging may reveal inflammation in the spine that corresponds to the histopathologically confirmed Romanus lesion of AS.⁷ In addition, MRI is useful for assessing patient response to therapy, as T1-weight images are optimum for visualizing chronic changes associated with AS.

Attempts have been made to develop a scoring system to differentiate conditions associated with changes in disease activity and those secondary to treatment.⁸ Ongoing validation and refinement are needed before a sensitive and specific scoring system, as well as the optimum use of MRI in AS, are defined. Current proposals for the use of MRI are for diagnosing AS in patients with clinical features of inflammatory back pain in whom plain radiographs are normal and the diagnosis is uncertain, and for use in patients with established disease who continue to experience symptoms despite the use of standard therapies.⁷

Results of a recent study suggest the value of combination conventional radiography and MRI.⁹ Using MRI in patients in whom conventional radiography is negative might permit early diagnosis of AS, while assessing structural changes and inflammation by using both modalities might provide comprehensive information on the degree of sacroiliitis in patients with the disease.⁹

Role of TNF- α Inhibition in Managing Ankylosing Spondylitis

Treatment for AS has been limited by the lack of effective therapies to improve mobility, impact symptoms of axial AS, and affect the long-term course of the disease.¹⁰ Sulfasalazine has been shown to have some effect on the peripheral joint manifestations of AS, but its value in treating axial skeletal disease has not been clearly demonstrated. Elevated levels of TNF- α in serum and synovial tissues from patients with AS provided a rationale for targeting this proinflammatory cytokine.¹¹⁻¹⁵ Anti-TNF- α is effective therapy for other inflammatory diseases, such as RA, and the articular symptoms associated with CD and IBD.¹⁶⁻¹⁸ Three commercially available anti-TNF- α drugs—infliximab (Remicade[®]), etanercept (Enbrel[®]), and adalimumab (Humira[®])—are approved for the treatment of AS. Due to their effects on the inflammatory process in AS, these medications have the potential to provide symptom relief and alter the disease course.¹⁹

Infliximab, Etanercept, and Adalimumab in Treating Ankylosing Spondylitis

Infliximab. The effectiveness of infliximab was assessed in 34 patients with active AS during a 12-week period.²⁰ As evaluated by the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), the primary outcome of the placebo-controlled study was at

least a 50% regression of disease activity. There were more men in both the study and control groups (68% and 63%, respectively). No significant differences were observed in any other baseline characteristics, such as age, duration of disease, HLA-B27 seropositivity, and disease activity. Infliximab (5 mL/kg) was infused over 2 hours at weeks 0, 2, and 6. At week 12, 53% of the patients receiving infliximab achieved a 50% reduction in BASDAI score compared with only 9% in the placebo group.²⁰ Notably, 41% of patients in the infliximab group experienced a 50% improvement in disease activity by week 2. Peripheral arthritis and enthesitis were present in 44% of the infliximab patients at baseline. At week 12, peripheral arthritis remained in 17% of these patients and enthesitis in 27%. None of the patients receiving placebo experienced improvement in these extra-axial manifestations of AS.²⁰ The serious adverse events included systemic tuberculosis in the lymph node and spleen; high fever, enlarged lymph nodes, and pulmonary lesions diagnosed as bronchiocentric allergic granulomatosis of the lungs; and transient leukopenia. The most commonly occurring adverse effect was upper respiratory infection, which developed in 51% of placebo patients and 35% of infliximab patients. Generally, treatment was well tolerated.²⁰

Etanercept. In a placebo-controlled, double-blind, randomized trial, investigators assessed the effectiveness of etanercept in patients with AS.²¹ Baseline characteristics

and disease history were similar between the etanercept subjects (n = 138) and placebo subjects (n = 139).²¹ Similar to the study reported for infliximab, the majority of subjects (76% in both groups) were men. Patients received etanercept 25 mg subcutaneously twice a week for 24 weeks. The primary outcome was the proportion of patients attaining the Assessments in Ankylosing Spondylitis 20% response (ASAS20)²² at 12 weeks. If there was a difference between the study drug and placebo groups at that time, the proportion of patients with ASAS20 at 24 weeks was to be compared. The ASAS20 indicates an overall improvement of 20% and a positive change of at least 10 units on a 100-mm visual analogue scale (VAS) in 3 or more of the ASAS domains concomitantly without any deterioration.²¹

Patients receiving etanercept responded early, with a significant improvement observed at week 2 compared with placebo subjects. A significantly higher percentage of patients who received etanercept achieved ASAS20 at both 12 weeks and 24 weeks compared with placebo. Patients treated with etanercept showed improvement in all individual components of the ASAS domains, as well as the BASDAI at weeks 12 and 24. Compared with placebo subjects, etanercept subjects experienced significant improvements in spinal mobility at week 12 ($P < .04$) and week 24 ($P < .01$).²¹

Generally, side effects were similar between the 2 study groups

Perspectives From Rick Pope, MPAS, PA-C

(continued from page 1)

cardiopulmonary conditions and vascular risk factors.

The American College of Rheumatology (ACR) and Allied Rheumatology Health Professionals (ARHP) offer CME programs throughout the year that culminate in an annual meeting that includes basic science and clinical tracts on developments in RA. This increase in knowledge has resulted in an expanded role of the PA and NP in the recognition, diagnosis, and management of rheumatologic diseases.

According to the ACR and ARHP, the combination of national PA programs requiring a master's degree and a shortage of rheumatologists, resulting from a drop-off in fellowship trainees and an aging physician population, have resulted in a 3-fold increase in PAs entering this subspecialty during the past 5 years. Our traditional clinical role, as well as that of NPs, is expanding to include involvement in investigational studies for new drug applications (NDAs), information gathering from genetic studies, increasing evaluation and management of the patient with inflammatory disease, teaching primary care physicians about our subspecialty, providing accredited schools didactic exposure to rheumatology, offering feedback to the National Certification Commission of Physician Assistants, and contributing to professional journals.

As the number of rheumatologists decreases, the responsibilities of PAs and NPs will increase. Our role will continue to expand as research presents ever-increasing targets for rheumatologic disorders.

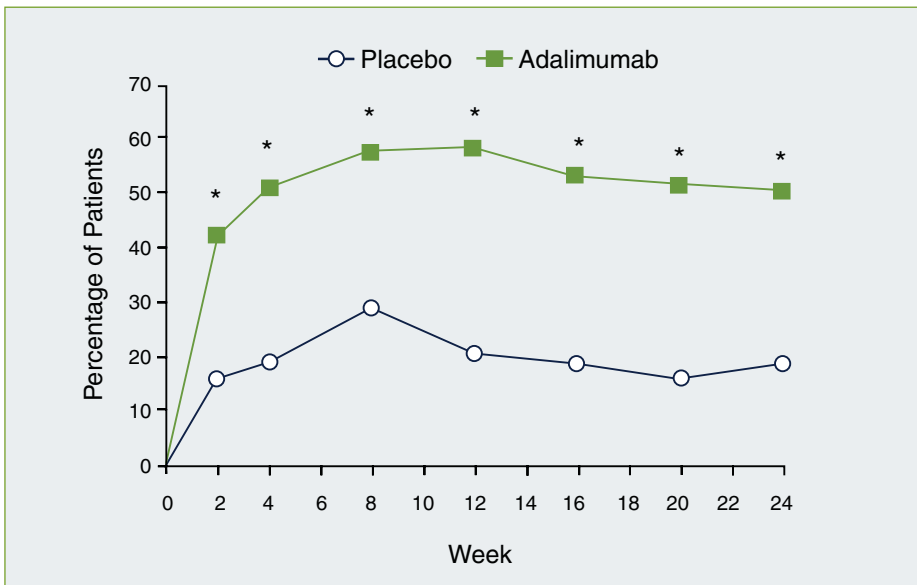


Figure 1. Subjects with AS receiving adalimumab therapy experience significant improvement compared with placebo. There was a significantly greater proportion of subjects in the adalimumab group who achieved a 20% response to treatment compared with the placebo group ($*P < .001$). At week 12, the percentage of subjects achieving an Assessments in Ankylosing Spondylitis 20% (ESAS20) response was more than 2-fold that in placebo subjects. The study findings demonstrate the durability of patient response to adalimumab therapy. Van der Heijde D et al.¹⁰

and of mild or moderate intensity. Injection-site reactions, upper respiratory infection, and accidental injury occurred more often in etanercept subjects than in placebo subjects ($P < .05$).²¹ Three patients who received etanercept had non-neutralizing anti-etanercept antibodies in their serum at week 24. The investigators summarized that etanercept was effective and safe for the treatment of AS over 24 weeks.²¹

Adalimumab. A multicenter, randomized, placebo-controlled study, the Adalimumab Trial Evaluating Long-term Efficacy and Safety for Ankylosing Spondylitis (ATLAS) was conducted to assess the efficacy and safety of adalimumab.¹⁰ Baseline demographic and clinical characteristics were similar between the adalimumab and placebo subjects. Patients in the drug study group ($n = 208$) received adalimumab 40 mg subcutaneously every other week for 24 weeks; patients in the comparative group ($n = 107$) received placebo during the study period. The primary outcome was the proportion of patients achieving ASAS20 at week 12. Other measures of disease activity, mobility, and function, as well as ASAS20 at week 24 served as secondary outcomes.¹⁰

Intent-to-treat analysis showed that the percentage of adalimumab subjects who achieved ASAS20 was significantly higher than the percentage in the placebo group.¹⁰ This difference was first observed at week 2 and continued throughout

Table 2. ASAS Core Set of Domains/ASAS20 Criteria and Recommendations for Initiating Anti-TNF- α Therapy

Domains	Domain Measure
Physical function	BASFI
Pain	Pain VAS
Patient global assessment	Global assessment
Inflammation	BASDAI* morning stiffness VAS

ASAS20 criteria = $\geq 20\%$ change and $\geq 10\%$ units in each of 3 domains and absence of worsening in the fourth domain.

*BASDAI: A 1-10 scale, 1 being no problem and 10 being the worst problem, used to answer 6 questions pertaining to symptoms of AS: fatigue, spinal pain, joint pain/swelling, areas of localized tenderness (enthesitis or inflammation of tendons and ligaments), morning stiffness duration, and morning stiffness severity.

ASAS Recommendations for Initiating Anti-TNF- α Therapy

- Diagnosis of definitive AS
- Active disease for at least 4 weeks (sustained BASFAI ≥ 4 on a 0- to 10-point scale)
- Expert opinion based on clinical findings
- Refractory disease, indicated by failure of at least 2 nonsteroidal anti-inflammatory drugs during a 3-month period, failure of intra-articular steroids if indicated, and failure of sulfasalazine in patients with predominantly peripheral arthritis
- Applications of usual precautions and contraindications for the use of biologic treatment

BASFI = Bath Ankylosing Spondylitis Functional Index.

From Braun J et al.²³

the 24-week study (Figure 1).¹⁰ At week 12, the proportion of patients in the adalimumab group who attained an ASAS20 response was more than twice that noted in placebo subjects (58.2% vs 20.6%; $P < .001$). The magnitude of response occurring at week 8 in adalimumab subjects continued through week 24. During the last 12 weeks of the study when patients on placebo could receive adalimumab, 59.5% of the 74 patients who previously received placebo achieved ASAS20 at week 16. Significant improvements in all 4 ASAS20 domains occurred at weeks 12 and 24 ($P < .001$). There was also improvement in BASCAI scores ($P < .001$) of the patients in the adalimumab group. Overall, the use of adalimumab resulted in significant improvement in all other signs and symptoms of AS. The overall incidence of adverse events and that of injection-site reactions were significantly higher in adalimumab subjects compared with placebo subjects ($P < .05$ for both).⁸ Generally, adalimumab was well tolerated and was not associated with an unexpected or medically unmanageable adverse event.¹⁰ Because of the significant reduction in signs and symptoms of AS in patients who received adalimumab and the sustained clinical response, the investigators urge additional study to establish the long-term safety and durability of response to adalimumab for the treatment of AS.¹⁰

Clinical Implications of TNF- α for Ankylosing Spondylitis; ASAS Consensus Statement

The ASAS Working Group proposed recommendations for clinical use of anti-TNF- α therapy in patients with AS in 2003 and published an update in 2006.²³ Update recommendations:

- Data support the effectiveness of anti-TNF- α therapy for up to 3 years; however, the optimal dosage has not been determined
- Ongoing trials may better define the use of anti-TNF- α agents for the treatment of AS
- Available information suggests younger patients and those with a shorter disease duration may respond better to anti-TNF- α therapy
- Therapy should be initiated in patients with a diagnosis of AS, usually based on the Modified New York Criteria, as well as other criteria (Table 2)²³
- Patients receiving therapy should be monitored with the

ASAS core set for clinical practice and the BASDAI

- An improvement of at least 50% or 2 units on the 0- to 10-point scale of the BASDAI defines response. Discontinuation of therapy is appropriate in those patients who fail to respond after 6 to 12 weeks of treatment²³

The best hope for improved outcomes in the management of patients with AS lies in early diagnosis, careful monitoring, and effective treatment. Anti-TNF- α therapy has been shown to offer patients with AS options to improve the signs and symptoms of AS and, to date, are the only therapies shown to reduce axial skeleton disease. Patients with AS often also have CD, which is the focus of the next section.

Diagnosing Crohn's Disease

Making a definitive diagnosis can be challenging because CD mimics other diseases of the GI tract and its onset is often insidious.²⁴ However, it is important to differentiate the

Table 3. Diagnostic Characteristics of Crohn's Disease

Frequent symptoms in patients with CD include:

- Pain
- Vomiting
- Diarrhea: chronic, but not bloody; nocturnal diarrhea is not uncommon
- Weight loss^{24,36}
- History of fever and rectal bleeding, that with other symptoms are characteristic of the inflammatory process²⁴
- Ileum and colon are most common foci of CD. Can be complicated by obstruction, inflammatory mass, or abscess
- Anal and perianal fistulas³⁶
- Abnormal perianal region (violaceous coloration of the anal margin, skin tags, fissures, abscess, or fistulas) occurs in >90% of patients

Fast Facts: Understanding Crohn's Disease

- A complex, heterogeneous disease characterized by focal, asymmetric, transmural, and on occasion, granulomatous inflammation in the GI tract
- May be associated with systemic and extra-intestinal complications, including AS and sacroiliitis, peripheral arthritis, cutaneous conditions, ocular inflammation, primary sclerosing cholangitis, and hypercoagulability, as well as malabsorption complications
 - Disease of long duration may be associated with adenocarcinoma of the GI tract, and less often, lymphoma
 - Onset occurs during adolescence and young adulthood, although persons of all ages can be affected. In the United States, the incidence approximates 5 per 100,000, while the prevalence is an estimated 50 per 100,000
 - Similar to AS, a role for bacteria in the development of the disease has been proposed
 - A complete understanding of the etiology and pathogenesis of CD remains elusive. Several associated components have been identified, but the precise mechanisms of each in the disease process continue to be investigated
- The prevalence of CD and ulcerative colitis has increased during the past century, leading to speculation that a single environmental insult or a combination of environmental insults is involved in CD. Smoking has been definitively linked to clinical, surgical, and endoscopic recurrence in CD

Fiocchi C. Inflammatory bowel disease: etiology and pathogenesis. *Gastroenterol.* 1998;114:182-205; Hanauer SB. Inflammatory bowel disease. *N Engl J Med.* 1996;334:841-848; Hanauer SB et al.²⁴

disease from other IBDs to maintain patients' quality of life and reduce the risk for adverse sequelae and complications. Endoscopic, radiographic, and pathologic findings often are needed to confirm the diagnosis (Table 3).

Imaging Modalities

Contrast radiography is useful for localizing the disease and identifying intestinal complications.²⁴ In addition, upper or lower GI endoscopy provides information on disease location, aids in diagnosis, and permits tissue sampling for pathologic evaluation. Biopsy also can distinguish between ulcerative colitis and CD.

Goals of Management for Crohn's Disease: American College of Gastroenterology Guidelines

An appreciation of the location of the disease, its severity, and presence of extraintestinal complications guides therapeutic decision making.²⁴ While clinical trials have used criteria to determine disease severity, such as the Crohn's Disease Activity Index, these tools are not applicable in clinical practice. Generally, the goals of treatment are to eliminate or reduce the severity of symptoms and maintain the patient's general well-being with as few side effects and long-term effects as possible.

The American College of Gastroenterology (ACOG) and its Practice Parameters Committee have proposed working definitions of disease activity to assist clinicians in managing CD (Table 4).²⁴ All therapy is individualized to meet the needs of the patient; the guidelines recommend surgery for obstructing stenoses, suppurative complications, and medically intractable disease.

Role of TNF- α Inhibition in Managing Crohn's Disease

Conventional medical therapy for CD includes the use of aminosalicylates, antibiotics, corticosteroids, and immunomodulators; however, these medications have been associated with limited efficacy, delayed onset of action, frequent dosing regimens, and treatment-limiting adverse events.^{24,25} Nonsteroidal anti-inflammatory drugs may provoke a flare of the disease and should be avoided. Anti-TNF- α therapy, infliximab and adalimumab, is indicated for patients who do not respond to conventional therapy. Etanercept is not indicated for the treatment of CD. The rationale for the use of anti-TNF- α treatment in patients with CD includes the presence of the cytokine in the serum, stool, and intestinal tissue of persons with IBD and TNF-expressing cells in the gut mucosa and lamina propria of those with CD.²⁵ Further study showed that secretion of TNF- α may be increased in CD, concurrent with inadequate release of soluble TNF receptors by mononuclear cells in the lamina propria.⁴

The effects of anti-TNF- α therapy are seen soon after initiation of treatment.²⁶ The use of these biologic agents may reduce fistula drainage, enhance mucosal healing, and allow gradual discontinuance of corticosteroids. Although not confirmed in a large-scale, randomized study, anti-TNF- α therapy may alleviate the fatigue patients with CD frequently experience.²⁷ Anti-TNF- α agents are beneficial for induction therapy and maintenance of remission compared with episodic treatment, as the latter may lead to the formation of antibodies against the agents.²⁷ Combining anti-TNF- α agents with immunomodulators also may reduce the emergence of antibodies against these medications.²⁸ Current data support the efficacy and safety of anti-TNF- α to manage CD, and additional study may define optimal dosages and long-term treatment pathways.

Infliximab and Adalimumab in Treating Crohn's Disease

Infliximab. In the multicenter, double-blind, randomized A Crohn's disease Clinical trial Evaluating infliximab in a New long-term Treatment regimen trial (ACCENT I), infliximab was infused at week 0 and at weeks 2 and 6 (5 mg/kg) and then every 8 weeks (5 or 10 mg/kg) thereafter in patients who responded to the initial infusion. Clinical response and clinical remission were highest in patients who received infliximab 10 mg/kg at the 8-week dosing intervals (vs infliximab 5 mg/kg or

Table 4. Definitions of Severity of Crohn's Disease

MILD-MODERATE DISEASE: Ambulatory patients able to tolerate oral alimentation without manifestations of dehydration, toxicity (high fevers, rigors, prostration), abdominal tenderness, painful mass, obstruction, or >10% weight loss

MODERATE-SEVERE DISEASE: Patients who have failed to respond to treatment for mild-moderate disease or those with more prominent symptoms of fever, significant weight loss, abdominal pain or tenderness, intermittent nausea or vomiting (without obstructive findings), or significant anemia

SEVERE-FULMINANT DISEASE: Patients with persisting symptoms despite introduction of corticosteroids as outpatients or individuals presenting with high fever, persistent vomiting, evidence of intestinal obstruction, rebound tenderness, cachexia, or evidence of an abscess

REMISSION: Patients who are asymptomatic or without inflammatory sequelae, including those who have responded to acute medical intervention or have undergone surgical resection without gross evidence of residual disease. Patients requiring corticosteroids to maintain well-being are considered "steroid-dependent" and usually are not considered in remission

From Hanauer SB et al.²⁴

placebo). The difference between the higher dose infliximab arm and placebo was significant at week 54 for clinical response and remission. At the end of the 54-week trial, the number of patients who discontinued corticosteroid therapy while in remission was 3-fold higher in the combined 2 infliximab groups compared with the placebo group.²⁹

Infliximab was shown to produce clinical remission for a median of 38 weeks in patients with CD of at least 3 months' duration and a score on the Crohn's Disease Activity Index (CDAI) between 220 and 400 (higher score on the CDAI indicates more severe disease).²⁹ Another benefit for the 335 patients who responded to induction therapy was tapering of corticosteroids.

Infliximab antibody titers were similar between the placebo group and the 2 infliximab groups, although test results for antibodies to infliximab were inconclusive in 46% of patients.²⁹ Immunomodulator therapy and corticosteroids plus immunomodulator therapy given with infliximab appeared to confer a protective effect against antibody formation. The most commonly occurring adverse effects of infliximab therapy were headache, abdominal pain, and upper respiratory infection. The study results show the efficacy of infliximab maintenance therapy in patients who respond to an initial infusion.²⁹ These patients are more likely to taper corticosteroid use and maintain remission for a longer duration when infliximab is

Case Study in AS and CD

Rick Pope, MPAS, PA-C

Present Illness

- 23-year-old woman presents with low back pain radiating to the right buttock and down the right leg
- Complaints of low back pain for at least 5 years

Medical History

- Diagnosed at age 13 with Crohn's disease
- Developed shingles when treated with steroids during a flare of Crohn's disease

Physical Examination

- Wrists and hands: unremarkable
- Back: straight with no discernable kyphosis or scoliosis. No SI tenderness is noted at the time of the examination; straight leg raising was negative
- DTRs: symmetrical
- Hips, knees, ankles, feet: normal
- Laboratory tests, radiographs of the pelvis, EMG/NCT, and PT ordered

Current Medications

- Diclofenac 75 mg BID with food

DECISION POINT/CLINICAL COMMENTARY

There was no definite evidence this patient had anything other than mechanical back pain. Ankylosing spondylitis was suspected because approximately 5% to 15% of persons with Crohn's disease develop AS. Note: because NSAIDs can cause severe activation of bowel disease requiring hospitalization, many gastroenterologists and rheumatologists believe they are contraindicated in patients with inflammatory bowel disease.

The association between inflammatory spondylitis and Crohn's disease is clear. Because this patient had back pain for several years, the practitioner needs to identify whether the pain is mechanical or inflammatory. Before taking additional action, I waited for the clinical response and accumulating test data.

FOLLOW-UP VISIT

Lab results

WBC	11.3	H	(4.5-10.5)
RBC	3.64	L	(4.2-6.2)
Hgb	12.4	WNL	
Hct	36.8	WNL	(<0.8)
ESR	23 MM/h	H	(0-20)
CRP	.45	WNL	
RF	NEG		
ANA	NEG		
LYME	NEG		
B-12	356	WNL	(250-1000)
Folate	2.6	WNL	(2.0-19.7)

Radiographs

Standing pelvis: evidence for bilateral sacroiliitis, right greater than left

FIRST FOLLOW-UP VISIT

What is the next step in management of this patient?

- The patient did not respond to diclofenac. She did experience loose stool and nausea with this intervention. The CD remained stable.
- There was radiologic evidence of bilateral sacroiliitis. While the ESR of 23 may suggest inflammation, patients with AS

infused every 8 weeks. Generally, long-term infliximab therapy is well tolerated and safe.

In A Crohn's Disease Clinical Trial Evaluating Infliximab in a New Long-Term Treatment Regimen in Patients With Fistulizing Crohn's Disease Trial (ACCENT II), infliximab 5 mg/kg was infused at weeks 0, 2, and 6 in 306 patients with CD and at least

1 draining abdominal or perianal fistula of at least 3 months' duration.³⁰ The objective of this placebo-controlled, double-blind, randomized study was to determine if infliximab provides effective maintenance therapy in patients with CD with fistulas, which often present treatment challenges. Response to infliximab infusions was defined as a reduction

in the number of draining fistulas of at least 50% from baseline. Patients who responded to therapy at both weeks 10 and 14 were randomized to placebo maintenance or infliximab maintenance (5 or 10 mg/kg at week 14 and every 8 weeks thereafter).³⁰

A total of 195 patients experienced a response to treatment at week 14; 95 of these patients

Case Study in AS and CD

are more likely than patients with RA to have a normal ESR or CRP (can be >40% of the time in RA). Although a biologic is a consideration, we start with counseling on exercise, maintenance of weight, and smoking cessation (this disease could ascend the spinal column and cause restrictive airway disease), and a discussion of the disease process. We explain the autoimmunity notion and list the potential target organs that are primarily ligamentous and tendonous. Some of these patients will develop peripheral articular disease, but the spine and SI joints are the main targets.

What are the appropriate screening tests before starting a biologic?

- If we decide a biologic is required, we do a skin test for TB. If the test is positive, a chest x-ray and/or chest CT are ordered to be sure there is no evidence of disease.

Discuss your experience treating AS with biologics.

- The use of biologics for the treatment of AS definitively helps our patients. The stiffness and pain often dissipate quickly, in most cases within the first 6 weeks. Patients with AS report significant fatigue, but this symptom also improves. Many patients report feeling better than they have for years.

How does the patient react to initiation of treatment with biologics?

- Once the diagnosis is explained and the patient understands there is clear evidence for hope with the use of biologics, the acceptance of the treatment is not difficult. Although the cost of biologics is significant, all pharmaceutical companies that manufacture biologics offer patient assistance programs.

Although the process is difficult for some patients, most patients will receive medication within 30 days.

SECOND FOLLOW-UP VISIT

How does the patient respond to treatment?

- Patients judge the treatment course by the number of severe flares of pain and stiffness. For this patient, the flares of pain and stiffness, which settled in the right SI joint, almost disappeared. As a result, she was more energetic.

Does she achieve remission of the CD?

- Crohn's disease was not active when this treatment began. However, AS was diagnosed, and the AS symptoms completely abated with treatment with a biologic. She has responded well during the 3 years of treatment. If the illness stopped responding to this biologic, evidence in the RA literature indicates that switching to a different TNF- α inhibitor to improve outcome is an option.

If symptoms did not subside with the initial biologic, do you switch to another agent in this class and consult a gastroenterologist before the switch?

- If the patient did not respond to the initial biologic and had gastrointestinal complaints, a gastroenterologist would be consulted. Most rheumatologists would consider switching to a different anti-TNF- α agent. However, supporting data are lacking.

received infliximab maintenance therapy (5 mg/kg, n = 68; 10 mg/kg, n = 28).³⁰ Of the 99 patients randomized to placebo maintenance, 50 crossed over to 5-mg/kg infliximab maintenance therapy. Data for these patients were analyzed and showed a significantly ($P < .001$) prolonged period before loss of response compared with placebo patients. The median time

to loss of response among these patients was 40 weeks. Recrudescence of fistulas occurred in 16% of patients in the infliximab maintenance group compared with 22% in the placebo maintenance group. Nearly one half (46%) of patients receiving infliximab maintenance therapy continued to have a response at week 54 ($P = .001$); 36% demonstrated a complete

response ($P = .009$). Of note, 36% of patients with a baseline CDAI score >220 continued to have a response at week 54. Of the patients with no response at week 14, but who subsequently received infliximab therapy, 21% had a response compared with 16% of those who received placebo. It is of interest that 45% of patients randomized to

infliximab maintenance therapy were current smokers.³⁰

A similar proportion of patients in both groups demonstrated antibodies to infliximab; however, concomitant baseline administration of corticosteroids and immunomodulators appeared to confer protection against antibody formation.³⁰ A similar percentage of patients in the placebo and study drug groups experienced an adverse event (92% and 89%, respectively). While 8% of patients taking placebo discontinued the study due to the emergence of an adverse event, only 4% of those receiving infliximab discontinued. The study results show that anti-TNF- α therapy is effective in patients with CD and fistulas. Patients who respond to infliximab induction therapy may continue to experience response during maintenance therapy.³⁰

Adalimumab. The Clinical assessment of Adalimumab Safety and efficacy Studied as Induction therapy in Crohn's Disease (CLASSIC-I) trial was conducted to assess the efficacy of adalimumab as induction therapy in patients with moderate-to-severe CD who were anti-TNF- α therapy-naive.³¹ The study also evaluated the effects of various adalimumab doses. Patients were randomized to placebo (n = 74) or 1 of 3 treatment groups: subcutaneous adalimumab administration at weeks 0 and 2 at doses of 40 mg and 20 mg (n = 74), 80 mg and 40 mg (n = 75), or 160 mg and 80 mg (n = 76), respectively. The primary outcome was difference in

remission rates among the groups for which remission was defined as a CDAI score of ≤ 150 points.³¹

Intent-to-treat analysis showed adalimumab induced remission in a significantly ($P = .004$) higher percentage of patients with moderate-to-severe CD compared with placebo.³¹ At week 4 following administration of the 2 doses, 24% of patients receiving adalimumab 80 mg and 40 mg at weeks 0 and 2, respectively, achieved remission; remission was documented in the adalimumab 160-mg/80-mg group. The remission rate in patients taking placebo was 12%, and in patients receiving the lowest dose of adalimumab, 16%. Response occurred as early as week 1 in patients receiving adalimumab 80 mg and 40 mg at weeks 0 and 2. In both the adalimumab 40-mg/20-mg group and 80-mg/40-mg group, 1 patient discontinued therapy due to an adverse event.³¹

No patients in the highest adalimumab dose group experienced an adverse event that resulted in cessation of treatment, while 2 patients in the placebo group left the trial due to an adverse event.³¹ Adverse events, the most common of which was injection-site reactions, occurred with similar rates across the 4 study groups. Antibodies against adalimumab were detected in 1 patient in the highest-dose adalimumab group. The antibody assay was positive at week 2, but a subsequent test at week 4 was negative.³¹

The findings confirmed the efficacy of adalimumab for induction therapy in CD patients, with

the 2 higher doses being most effective.³¹ Treatment generally was well tolerated over the course of the 4-week study.

The subsequent CLASSIC II study evaluated the long-term efficacy and safety of adalimumab for maintenance of remission in patients who participated in CLASSIC-I.³² Those patients who achieved remission after 4 weeks in CLASSIC-I and then maintained remission for another 4 weeks were randomized to receive placebo (n = 18), 40-mg adalimumab weekly (n = 18), or 40-mg adalimumab every week (n = 19) for 52 weeks. Patients who did not achieve and maintain remission in CLASSIC-I were given the option of switching to open-label adalimumab (40 mg every other week) with the option of increasing the dosage to 40 mg weekly with nonresponse or disease flare-up (n = 204). Remission was defined as a CDAI score of ≤ 150 points, and a reduction of at least 70 points indicated response. Patients maintained all other medications, with the exception of corticosteroids. The dose of corticosteroids was tapered beginning at week 8, after which the daily dose of prednisone was reduced by at least 5 mg weekly in patients receiving 10 mg/day. Tapering of the steroid dosage continued until patients were receiving 10 mg/day, at which time the dosage was lowered by 2.5 mg/week until discontinuance. The dosage of budesonide was tapered similarly by 3 mg every week to discontinuance.

At week 56, 83% of patients receiving 40-mg adalimumab

weekly were in remission compared with 79% of patients in the 40-mg adalimumab every other week group and 44% of patients taking placebo ($P < .05$ for each study drug group vs placebo) (Figure 2).³² The mean reduction in CDAI score in the adalimumab weekly group was 197.7, and that for the every-other-week group was 150.8. In contrast, a mean decline in CDAI of 119.6 in the placebo group (last observation carried forward, $P < .05$) for each study drug group versus placebo was reported. Response was evident as early as week 12 in patients receiving adalimumab. Among patients in the weekly adalimumab group, 88% discontinued corticosteroid therapy; the percentage in the every-other-week adalimumab group was slightly lower at 67%, and 57% of placebo patients stopped taking steroids. Among open-label patients, the remission rate was 46%, and the response rate was 72%. The mean reduction in CDAI score in these patients was 158.4.³²

The patients tolerated adalimumab well. The incidence of adverse events and serious and severe adverse events resulting in discontinuance was higher in patients taking placebo than in those receiving adalimumab.³² The most commonly occurring adverse events in subjects receiving adalimumab were nasopharyngitis, aggravated Crohn's disease, and sinusitis. Overall, antibodies formed in few patients (2.6%); however, the statistical power of the study was inadequate for

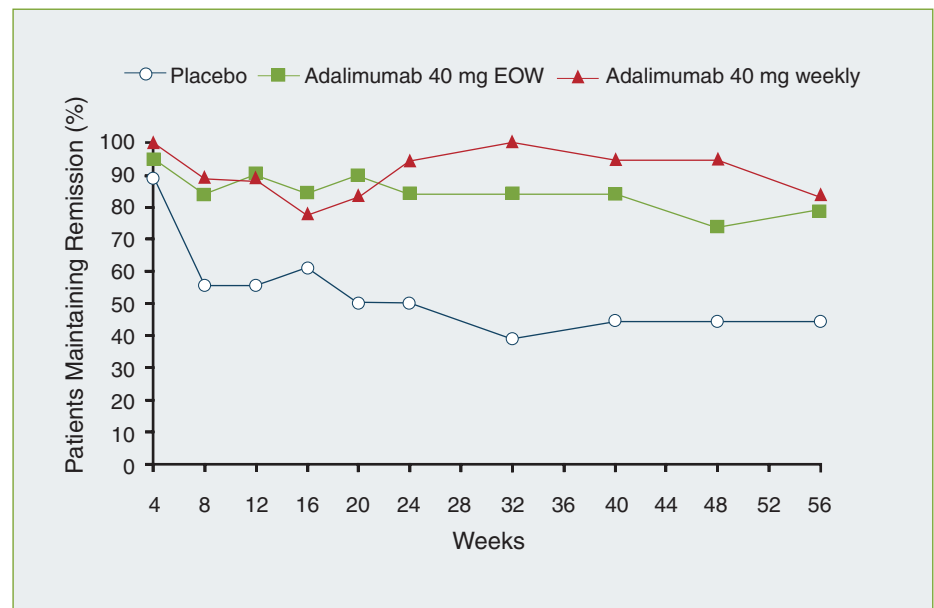


Figure 2. Maintaining remission in subjects with CD. Remission was maintained in more than 3 of every 4 subjects who received adalimumab—either 40 mg weekly or 40 mg EOW contrast to fewer than half the subjects in the placebo group. Efficacy of maintenance therapy was observed up to week 56. EOW = every other week. Sandborn WJ et al.³²

estimating the frequency of antibody formation compared with placebo and assessing any influence immunomodulators and corticosteroids might have on antibody development.³²

The results of this study show that long-term maintenance therapy with adalimumab is effective and safe in patients with severe-to-moderate disease who have responded to adalimumab induction therapy.³² As in other studies, anti-TNF- α therapy generally was well tolerated. The corticosteroid-sparing effect of adalimumab therapy is of particular interest.

The Gauging Adalimumab Efficacy in Infliximab Nonresponders (GAIN) trial was a 4-week, placebo-controlled trial that included patients with moderate-to-severe CD who had discontinued infliximab therapy because of failure to respond, emergence of

adverse events, or inability to take the medicine.³³ The goal of GAIN was to determine if patients who fail to respond to an anti-TNF- α agent can be switched successfully to another anti-TNF- α therapy.³³ A total of 325 adults with moderate-to-severe CD of at least 4 months' duration who had received infliximab therapy were randomized to placebo or adalimumab 160 mg at week 0 and 80 mg at week 2. The primary outcome was proportion of patients with remission (reduction of at least 150 points in the CDAI score) at week 4.³³

A total of 301 patients completed the study—156 in the placebo group and 155 in the intervention group.³³ Compared with placebo, adalimumab was significantly more efficacious as reflected by the 21% of patients receiving adalimumab who achieved remission versus the 7% in the placebo

group ($P < .001$). The mean decrease in CDAI score in the study drug group was 87 points compared with a mean decrease of 49 points in the placebo group. Among patients receiving corticosteroids at baseline, the percentage achieving remission was 33% in contrast to the 15% of patients who reached the same outcome but were not taking steroids. The percentage of patients who experienced any adverse event was lower in the adalimumab group (57%) compared with the placebo group (73%). The most commonly reported adverse events occurring in at least 5% of the intervention group was injection-site reaction (11%) and infection (15%). No serious infection developed in patients who received adalimumab. Only 1 patient in the study drug group discontinued therapy. No patients receiving adalimumab developed antibodies to the drug; however, the presence of measurable drug may limit interpretation of this finding. Nonetheless, the findings suggest that patients with CD have options to switch from one anti-TNF- α agent to another if efforts with the initial agent fail to induce and maintain remission.³³

Summary

There are several similarities between AS and CD, which are chronic diseases characterized by inflammation. Bacteria, genetics, and an immune imbalance wherein elevated TNF- α is prominent contribute to the development and continuance of signs and symptoms in both diseases. There is

considerable overlap between the 2 diseases, with both presenting in a substantial proportion of patients. Treatment for either AS or CD is inadequate in many patients owing to risk for toxicity, inadequate effects on symptoms, and lack of effect on the course of the disease. The presence of high levels of TNF- α in both diseases led investigators to assess the effects of blockage of this proinflammatory cytokine on symptoms and disease progression. Several placebo-controlled studies have demonstrated the effectiveness of the anti-TNF- α agents infliximab, etanercept, and adalimumab for the management of AS and infliximab and adalimumab for induction and maintenance therapy in patients with CD. A steroid-sparing effect was observed in 1 trial in patients with CD who received adalimumab. Guidelines provide criteria for the use of anti-TNF- α agents in patients with AS and CD. Patients with both diseases, a not uncommon occurrence, may derive particular benefit from TNF blockade.

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About *PCE Updates in Rheumatology*...

Welcome to the third of 4 issues of *PCE Updates in Rheumatology*, developed for those rheumatologists, 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 ankylosing spondylitis and Crohn's disease. The fourth newsletter will provide up-to-date information on psoriatic arthritis. Martin J. Bergman, MD, serves as Senior Editor for all 4 issues.

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