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GUIDELINES IN RHEUMATOLOGY: THE DIAGNOSIS AND MANAGEMENT OF ANKYLOSING SPONDYLITIS

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Statement of Need

Ankylosing Spondylitis (AS) is a painful, chronic, and progressive inflammatory disease affecting the spine and the joints and ligaments that normally allow a person's back to move and flex. Over time new bone can develop and replace the elastic tissue of ligaments or tendons. Eventually a person's vertebrae can fuse together, causing complete loss of motion and a stooped-over posture. This disease affects approximately 350,000 people in the United States; however, according to the Spondylitis Association of America (SAA), this disease is widely underdiagnosed. A recent international meeting held in Berlin, Germany, January 2003 among thought leaders in rheumatology produced a new set of guidelines for the management of AS. The new guidelines, published in the September 2003 issue of the *Annals of Rheumatic Diseases*, specifically review treatment with TNF inhibitors and the points at which this therapy should be initiated. An addendum to the guidelines has been developed for physicians in the United States and is available on the SAA website, www.spondylitis.org/Medicalresearch/spartanguideline.aspx. It is of utmost importance that this new information be disseminated to rheumatologists who treat this patient population to enable them to enhance patient treatment and outcomes. *Guidelines in Rheumatology: The Diagnosis and Management of Ankylosing Spondylitis* was developed with this in mind.

Learning Objectives

At the conclusion of this activity, you will be able to:

1. Improve assessment and increase early diagnosis of Ankylosing Spondylitis (AS)
2. Identify treatment regimens, including the use of TNF inhibitors, as well as strategies to improve patient outcomes
3. Effectively manage patients with AS through practical application of clinical data and expert treatment recommendation

Target Audience

A nationwide audience of rheumatologists.

Course Director

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Faculty Disclosure

The Faculty Disclosure Policy of the Albert Einstein College of Medicine requires that faculty participating in a CME activity disclose to the audience any relationship with a pharmaceutical or equipment company which might pose a potential, apparent, or real conflict of interest with regard to their contribution to the activity. It is required by the ACCME that each speaker disclose to the audience any discussion of unlabeled use of a commercial product or device not yet approved in the United States.

Chaim Putterman, MD

Dr Putterman has received research support and honoraria from Biogen Idec.

Muhammad Asim Khan, MD, MACP, FRCP

Dr Khan has served as a consultant/advisory board member to Amgen Inc., Wyeth, and Centocor. He has received honoraria from Amgen Inc., Wyeth, Centocor, Schering Plough, and Pfizer.

John C. Davis, Jr, MD, MPH, MS, FACP, FACR

Dr Davis has received grants/research support from Abbott and Amgen, Inc. He has received honoraria from Amgen, Inc., and Wyeth.

John D. Reveille, MD

Dr Reveille reports no conflict of interest.

Dr Reveille reports that his presentation will include a discussion of infliximab, an investigational product in the management of ankylosing spondylitis.

Accreditation

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 joint sponsorship of Albert Einstein College of Medicine and the Spondylitis Association of America. Albert Einstein College of Medicine is accredited by the ACCME to provide continuing medical education for physicians.

Albert Einstein College of Medicine designates this educational activity for a maximum of 2 Category 1 Credits toward the AMA Physician's Recognition Award. Each physician should only claim that credit that he/she actually spent in the activity.

This CME activity was planned and produced in accordance with ACCME Essentials.

Estimated time to complete activity: 2 hours

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Chaim Putterman, MD, received his medical degree from Technion-Israel Institute of Technology, Faculty of Medicine, Haifa, Israel. He completed his residency in internal medicine at the Hadassah University Hospital in Jerusalem in 1993, and a fellowship in rheumatology at the Albert Einstein College of Medicine in 1996. Since 1998, Dr Putterman has been Assistant Professor of Medicine (Rheumatology) and Microbiology and Immunology at the Albert Einstein College of Medicine. In 2003, he was promoted to Associate Professor in the Division of Rheumatology at the Albert Einstein College of Medicine. Dr Putterman was certified in internal medicine by the American Board of Internal Medicine (ABIM) in 1996 and in rheumatology by the ABIM in 1997. Since 1998, Dr Putterman has been the Director of the Arthritis Clinic at Montefiore Medical Center-University Hospital for the Albert Einstein College of Medicine.

Dr Putterman has been the recipient of several honors and awards since 1993, more recently the Arthritis Foundation Hulda Irene Duggan Arthritis Investigator Award (2000-2004) and a Lupus Research Institute (SLE Foundation) Novel Research Project in Lupus Award (2001-2004). Presently, he is the Chairman of the Medical Advisory Board for the Bronx Chapter of the Lupus Foundation of America, the Vice Chairman of the Medical and Scientific Committee for the New York Chapter of the Arthritis Foundation, and a member of the CME Advisory Committee since 2001.

Dr Putterman has written or cowritten more than 90 peer-reviewed publications, case reports, reviews, and book chapters. He is on the editorial board of *Clinical and Developmental Immunology* and lectures frequently in the United States and internationally. His research is focused on antigenic triggers and the mechanisms of renal pathogenicity of anti-double stranded DNA antibodies in systemic lupus erythematosus.

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Dr. Khan is a Professor of Medicine (tenured) at Case Western Reserve University (CWRU) in Cleveland, Ohio. He received his medical degree from King Edward Medical College, Punjab University, in Lahore, Pakistan in 1965. After serving in the Pakistan Army Medical Corps he began his postgraduate medical training in the United Kingdom in 1967 and later continued that in the United States. He joined the faculty of CWRU in 1973 after completing his Fellowship in Rheumatology.

He has been the recipient of many academic awards including: Mastership of the American College of Physicians (MACP) in 2003, Distinguished Rheumatologist Award of the American College of Rheumatology in 2000, A Lifetime of Dedication and Devotion to People with Spondylitis Award in 1998 from the Spondylitis Association of America (SAA), and the Distinguished Alumnus Award of Academic Excellence from his Medical College alumni in 1998. He is a Fellow (FRCP) of the Royal College of Physicians (London). He serves on the Advisory Board of the SAA, and the Assessment in Ankylosing Spondylitis International Working Group, and has served on the National Institute of Health's National Advisory Board for Arthritis and Musculoskeletal and Skin Diseases.

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Since 1990, Dr Davis has been the recipient of several honors and awards, most recently the Ira M. Goldstein Award for Outstanding Teaching in Rheumatology, Division of Rheumatology, University of California, San Francisco in 2001, and ACR Delegate 2003 ACR/EULAR International Academic Exchange Program. He was elected Fellow of the American College of Physicians in 2002. Dr Davis has been involved with several committees and currently serves as a member of the Medical and Scientific Advisory Board of the Spondylitis Association of America, a member of the Steering Committee of ASAS—ASessment in Ankylosing Spondylitis Working Group.

Dr Davis has written or cowritten over 80 peer-reviewed publications, review articles, book chapters, and meeting abstracts, and frequently lectures on numerous subjects including ankylosing spondylitis and systemic lupus erythematosus. He is involved in development/conduct of translational research in systemic lupus, Wegener's granulomatosis, Sjogren's syndrome, and ankylosing spondylitis.

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John D. Reveille, MD, received his bachelor's degree from the University of Florida, Gainesville, and his medical degree from The Johns Hopkins University School of Medicine, Baltimore, Maryland in 1977. He completed his residency in the Department of Medicine at the University of Miami School of Medicine in Florida. He subsequently completed his post doctoral fellowship in the Division of Rheumatology at The Johns Hopkins University School of Medicine. In 1980, he was named Diplomat of the American Board of Internal Medicine, and in 1982, Diplomat of the American Board of Internal Medicine, Subspecialty of Rheumatology. Since 1997, Dr Reveille has been Professor of Medicine, Division of Rheumatology and Clinical Immunogenetics at the University of Texas Medical School at Houston, and in 2002 was named Director, Division of Rheumatology and Clinical Immunogenetics at the University of Texas-Houston Health Science Center.

Dr Reveille has been the recipient of several honors and awards since 1981, including the Dean's Teaching Excellence Award, 1990-1995 and the Alfred and Anna Brohn Memorial Award for Service to the Lupus Foundation of America in 1997. In 1998, he was elected to Alpha Omega Alpha Honor Medical Society, Delta Chapter. Presently, Dr Reveille is on the medical advisory board for the Spondylitis Association of America and the Houston Center for Clinical Research.

Dr Reveille has written or cowritten over 350 peer-reviewed publications, abstracts, invited articles, and book chapters on rheumatic diseases including systemic lupus erythematosus, ankylosing spondylitis, and rheumatoid arthritis. He serves on the editorial board of *Rheumatology Index and Reviews* and *Revista de la Asociacion Peruana de Rheumatologia* and lectures frequently in the United States and internationally. Dr Reveille is currently working on several research supported projects on systemic lupus erythematosus, scleroderma, ankylosing spondylitis, and genetic susceptibility to anterior uveitis.

CME Self-Assessment Pretest Questions

Before proceeding with this activity Albert Einstein College of Medicine, the sponsoring institution, requires your completion of the following Pretest questions. This is only a measurement tool and in no way will have an effect on your eligibility to receive credit. Circle the one best answer for each question. Return this page with your completed Application for Credit and Evaluation Form (back of booklet) to Albert Einstein College of Medicine, Bronx, NY.

1. According to current clinical trends, what is the male/female ratio for the prevalence of AS?
a. 1:1 b. 1:3.5 c. 1:5 d. 2.5:1 e. 4:1
2. What is the average delay between the time of disease onset and diagnosis of AS?
a. 6 months b. 2.7 years c. 5.9 years d. 7.2 years e. 8.9 years
3. A survey of patients with AS revealed that all of the following are common quality-of-life concerns except:
a. Pain b. Fatigue c. Headaches d. Stiffness e. Sleep problems
4. All of the following are functions of tumor necrosis factor (TNF) except:
a. Induces inflammatory cytokine production
b. Inhibits release of collagenases by synovial cells
c. Stimulates fibroblast proliferation
d. Inhibits synthesis of proteoglycans in cartilage
e. Recruits white blood cells in inflamed synovium
5. Which patients qualify for initiation of anti-TNF therapy according to US modifications of ASAS Guidelines?
a. Patients with axial symptoms and a lack of response to 3 NSAIDs for 3 months, and a BASDAI score of 4 or more.
b. Patients with a BASDAI score of 2.
c. Patients with peripheral arthritis symptoms and intolerance to 2 NSAIDs for 2 months.
d. Patients with a Physician Global Assessment of 1.
6. Anti-TNF therapy is contraindicated in patients with the following conditions except:
a. Tuberculosis b. Multiple sclerosis c. Diabetes d. Lupus e. Malignancy
7. Following 6 to 8 weeks of anti-TNF treatment, what defines a response to therapy?
a. Reduction of 1 or more units on the BASDAI and improvement of more than 1 on the Physician Global Assessment.
b. Increase of 1 or more units on the BASDAI and improvement of more than 1 on the Physician Global Assessment.
c. Reduction of 2 or more units on the BASDAI and improvement of more than 1 on the Physician Global Assessment.
d. Increase of 2 or more units on the BASDAI and improvement of more than 1 on the Physician Global Assessment.
8. Which is not an FDA-approved treatment indication for etanercept?
a. Psoriatic arthritis
b. Ankylosing spondylitis
c. Rheumatoid arthritis
d. Crohn's disease
e. Juvenile rheumatoid arthritis
9. According to the AS treatment algorithm, how long is an adequate trial of NSAIDs?
a. 2 weeks b. 3 months c. 6 months d. 1 year
10. Levels of TNF are elevated in ankylosing spondylitis.
a. True b. False

GUIDELINES IN RHEUMATOLOGY: THE DIAGNOSIS AND MANAGEMENT OF ANKYLOSING SPONDYLITIS

Introduction: Prevalence and Burden of Illness

Muhammad Asim Khan, MD, MACP, FRCP

Ankylosing spondylitis (AS) is a common, complex, and systemic inflammatory disease with the potential to cause severe debilitation.¹⁻³ Although etiology remains unknown and pathogenesis is not fully understood, a strong association between AS and HLA-B27 (an allele of the major histocompatibility complex) suggests a genetic predisposition. Prevalence of this allele and expression of the disease vary. For example, 8% of western European whites are positive for HLA-B27, and it is detected in over 90% of white patients with primary AS; but 2% of African Americans are positive for HLA-B27, and it is present in only 48% of African Americans with AS.⁴⁻⁶ A sample of recent prevalence studies among various ethnic groups and regions is listed in Table I. Gender differences also exist: AS is two to three times more common in males than in females.⁴

Table I: Prevalence of AS Among Different Ethnic Groups and Regions

Ethnic Group or Region	Frequency of HLA-B27 in Population	Prevalence of Ankylosing Spondylitis in Adults	
		General Population	HLA-B27-Positive Persons
		←————— % ———→	
Eskimos (Alaska)	40	0.4	
Eskimos (Alaska and Siberia) and Chukchi	25-40		1.6
Sami	24	1.8	6.8
Northern Norway	10-16	1.4	
Mordovia	16	0.5	
Western Europe	8	0.2	2.0
Germany (Berlin)	9	0.9	6.4

Khan MA. *Ann Intern Med.* 2002;136:896-907.

Generally underreported and underdiagnosed, the natural history of AS is highly variable. AS is characterized by periods of spontaneous remissions and exacerbations, particularly in the early stages of the disease. Severity ranges from a mild condition with limited sacroiliac joint and lumbar involvement to severe, debilitating disease.

The “pre-spondylitic” phase is an often-unrecognized period of progressive structural damage lasting 5 to 10 years. In many cases, it is not until easily recognizable physical findings and radiographic abnormalities accompany the back pain that a correct diagnosis is made.⁷ Relatively recent studies in Germany indicate that the average age of AS onset is 25.7 years, but the mean delay in diagnosis is 8.9 years.⁸ This delay in diagnosis, which ultimately means a delay in treatment, is disastrous in a disease in which 81% of patients lose their spinal mobility and 40% suffer severe spinal restriction within 10 years of its onset.⁹

Functionally and socioeconomically, the burden of illness is immense for patients with AS. Clinical patterns vary over the many years of disease activity, leaving numerous individuals to cope with a lifetime of progressive structural deterioration, pain, functional disability, and such potential complications as spinal fracture.^{2,7,10} The impact of AS on the patient’s quality of life is all-encompassing, with surveyed individuals regarding stiffness, pain, fatigue, and sleep problems as their most common concerns.¹¹ Functional disability is predictive of work loss and therefore a major determinant of medical expenses. AS costs an average \$6,720 annually, of which 75% is due to indirect medical costs as measured according to decreased productivity (ie, number of workdays missed or number of activity-limited days).¹²

The potential to hinder progression and avoid the complications associated with AS render it desirable to diagnose and treat the disease early; however, diagnostic and classification limitations often preclude successful realization of this goal.⁷ Assorted AS assessments have been proposed, but none are universally accepted. Nor are there established guidelines for use of assessment measures. Recently, though, the ASsessment in Ankylosing Spondylitis (ASAS) Working Group defined a core set of domains for AS evaluation during drug treatment. But the instruments most appropriate to assess the domains are still under discussion.⁷ The assessment methods that several experts prefer to employ to determine response to therapy will be presented in the subsequent section.

Revolutionary treatment breakthroughs are linked to advances in molecular biology and biotechnology that have enabled researchers to gain insight into the pathogenesis of AS. Until recently the mainstay of AS treatment was supportive therapy with nonsteroidal anti-inflammatory drugs (NSAIDs). Although they temporarily help relieve inflammatory back pain, gastrointestinal (GI) side effects and the risk of serious GI symptoms sometimes limit their long-term use. Selective cyclo-oxygenase-2 (COX-2) inhibitors lower the risk of serious GI adverse events, but their efficacy is similar to that of conventional, nonselective NSAIDs. Disease-modifying antirheumatic drugs (DMARDs) are considered second-line therapy though evidence supporting their efficacy is lacking. Therefore novel therapies that alter the natural course of AS through targeted influence on the newly identified pathophysiological processes are necessary.⁷

Anti-tumor necrosis factor (TNF) agents fulfill this targeted approach and show promise in the treatment of AS.⁷ The advent of these biologic treatment options compelled the ASAS Working Group to address the need for universal standards in disease classification and treatment outcomes to more accurately define the role of the new agents in disease management.¹³ The group also used an experts’ opinion approach and a Delphi technique to develop an international consensus statement that would ensure the appropriate use of the medications.¹⁴ In addition, the group recommended that the guidelines undergo modification to meet the specific realities of clinical practice in each country. The US-based modifications will be reviewed in this program.

Overview of Ankylosing Spondylitis

John C. Davis, Jr, MD, MPH, MS, FACP, FACR

What is the current understanding of the pathogenesis of AS?

The spondyloarthropathies are a multifactorial group of diseases with genetic, environmental, and immunologic components. Interaction between HLA-B27 and the T-cell response has been cited as a key factor in the pathogenesis of ankylosing spondylitis (AS)². The pathogenesis is not completely understood, but tumor necrosis factor TNF is thought to play a role in the inflammatory reactions observed with the disease.¹⁵ Increased T-cell and macrophage concentrations as well as enhanced expression of proinflammatory cytokines, including TNF, are characteristic findings.⁴ The inflammatory reactions are responsible for distinguishing characteristics of the disease, including enthesopathies, cortical bone erosions, and new bone formation.^{1,4}

What are the prevalent clinical features observed in AS?

Sacroiliitis is the hallmark feature of AS³ and the earliest, most consistent findings are traceable to effects of sacroiliitis and enthesitis. Inflammation of the discovertebral, apophyseal, costovertebral, and costotransverse joints of the spine, and paravertebral ligamentous structures are frequently associated with AS. After many years, chronic inflammation can cause bony ankylosis.¹

Chronic low back pain and stiffness, which typically worsens following a period of prolonged inactivity (eg, morning stiffness), are common presentations.³ Over time, lumbar spine mobility becomes restricted in all planes and posture becomes abnormal because of flattening of the lumbar spine and accentuated dorsal spine kyphosis. Radiographic findings in advanced disease include erosions, sclerosis of adjacent bones, pseudo-widening of the sacroiliac joint space, calcification, interosseous bridging, and ossification of the sacroiliac joints. Extraskelatal manifestations are also frequently part of the clinical picture.¹ Table 2 shows skeletal and extraskelatal clinical features seen in AS.

Table 2: Clinical Features of AS

Skeletal	Axial arthritis, eg, sacroiliitis and spondylitis Arthritis of 'girdle joints' (hips and shoulders) Peripheral arthritis uncommon Others: enthesitis, osteoporosis, vertebral fractures, spondylodiscitis, pseudoarthrosis
Extraskelatal	Acute anterior uveitis Cardiovascular involvement Pulmonary involvement Cauda equina syndrome Enteric mucosal lesions Amyloidosis, miscellaneous

Khan MA. Spondyloarthropathies. In: Hunder GG, ed. *Atlas of Rheumatology*. 3rd ed. Philadelphia, Pa: Lippincott Williams & Wilkins; 2002.

What classification criteria are used in AS?

Table 3 presents three sets of classification criteria and the year that each was published. The Modified New York Criteria for AS are now widely used to diagnose the disease. Radiographic evidence of sacroiliitis is heavily relied on to diagnose AS. Diagnosis may be missed early on, though, because routine pelvic radiographs may not clearly demonstrate sacroiliitis in the initial stages of AS.³

Table 3: Classification Criteria for Spondylitis

ROME, 1961

Clinical Criteria

1. Low back pain and stiffness for more than 3 mo, not relieved by rest
2. Pain and stiffness in the thoracic region
3. Limited motion in the lumbar spine
4. Limited chest expansion
5. History or evidence of iritis or its sequelae

Radiologic Criterion

Roentgenogram showing bilateral sacroiliac changes characteristic of ankylosing spondylitis (this would exclude bilateral osteoarthritis of the sacroiliac joints)

Definite ankylosing spondylitis if:

1. Grade 3-4 bilateral sacroiliitis with at least one clinical criterion
2. At least four clinical criteria

NEW YORK, 1966

Diagnosis

1. Limitation of motion of the lumbar spine in all three planes: anterior flexion, lateral flexion, and extension
2. Pain at the dorsolumbar junction or in the lumbar spine
3. Limitation of chest expansion to 2.5 cm or less measured at the level of the fourth intercostal space

Grading of Radiographs

Normal, 0; suspicious, 1; minimal sacroiliitis, 2; moderate sacroiliitis, 3; ankylosis, 4

Definite ankylosing spondylitis if:

1. Grade 3-4 bilateral sacroiliitis with at least one clinical criterion
2. Grade 3-4 unilateral or grade 2 bilateral sacroiliitis with clinical criterion 1 or with both clinical criteria 2 and 3

Probable ankylosing spondylitis if:

Grade 3-4 bilateral sacroiliitis with no clinical criteria

MODIFIED NEW YORK, 1984

Criteria

1. Low back pain of at least 3 mo duration improved by exercise and not relieved by rest
2. Limitation of lumbar spine in sagittal and frontal planes
3. Chest expansion decreased relative to normal values for age and sex

Radiologic Criterion

1. Bilateral sacroiliitis, grade 2-4
2. Unilateral sacroiliitis, grade 3-4

Grading

1. *Definite ankylosing spondylitis if:*
Unilateral grade 3 or 4, or bilateral grade 2-4 sacroiliitis and at least one clinical criterion
2. *Probable ankylosing spondylitis if:*
 - a. Three clinical criterion present
 - b. Radiologic criterion present but no signs or symptoms associated with clinical criteria

Van der Linden, et al. *Arthritis Rheum.* 1984;27:361-368.

Van der Linden S. Ankylosing spondylitis. In: Kelley WN, Harris ED, Ruddy S, Sledge CB, eds. *Textbook of Rheumatology.* 5th ed.

What instruments and/or criteria are recommended to assess disease activity and disability in patients with AS?

Complete agreement does not exist with regard to the specific instruments that should be used to measure disease activity; however, a questionnaire directed at specialists in the field of AS indicates that many experts prefer the Bath AS Disease Activity Index (BASDAI) and/or the Bath AS Functional Index (BASFI).^{13,16} The ASsessment in Ankylosing Spondylitis Improvement Criteria (ASAS-IC), a composite of four domains, have also been evaluated recently and were concluded to be strict in defining response and highly specific as well.¹⁷ Summaries of the three instruments are listed in Tables 4a, 4b, and 4c.

Table 4a: The Bath Ankylosing Spondylitis Activity Index (BASDAI)

- Visual Analog Scale of disease activity
- Questions several areas of involvement, including levels of:
 - fatigue
 - neck/back/hip pain
 - morning stiffness and duration
 - tender/swollen joints

Garrett S. *J Rheumatol.* 1994;21:2286-2291.

Table 4b: The Bath Ankylosing Spondylitis Functional Index (BASFI)

- 10 cm –VAS
- Mean score of 10 questions
- Questions level of functional disability, including:
 - ability to bend at the waist and perform tasks
 - looking over your shoulder without turning your body
 - standing unsupported for 10 minutes without discomfort
 - rising from a seated position without the use of an aid
 - exercising and performing strenuous activity
 - performing daily activities of living
 - climbing 12-15 steps without aid

Calin A. *J Rheumatol.* 1994;21:2281-2285.

Table 4c: ASsessment in Ankylosing Spondylitis (ASAS)

- **ASAS 20:** An improvement of $\geq 20\%$ and absolute improvement of ≥ 10 units on a 0-100 scale in ≥ 3 of the following 4 domains:
 - patient global assessment (by VAS global assessment)
 - Pain assessment (the average of VAS total and nocturnal pain scores)
 - Function (represented by BASFI)
 - Inflammation (the average of the BASDAI's last two VASs concerning morning stiffness intensity and duration)
- Absence of deterioration in the potential remaining domain (deterioration is defined as $\geq 20\%$ worsening)

van Tubergen A, van der Heijde D, Anderson J, et al for the ASAS Working Group. *Ann Rheum Dis.* 2003;62:215-221.

Why are new therapies needed for the treatment of patients with AS?

Nonsteroidal anti-inflammatory drugs (NSAIDs) and cyclo-oxygenase-2 (COX-2) inhibitors are considered the "gold standard" for AS treatment because they rapidly relieve inflammatory back pain. However patients only experience benefit while the medications are administered; the drugs do not slow or stop the progression of the disease. Disease-modifying antirheumatic drugs (DMARDs) are used as second-line therapy, but their efficacy remains unproven. Thus, agents that alter the natural course of the disease by directly influencing the underlying pathogenic mechanisms and ultimately inhibiting the destructive processes (eg, bony ankylosis) are needed.⁷ Such medications should not only ameliorate the signs and symptoms of AS, but increase physical functioning, decrease disability, and improve quality of life.

What is TNF?

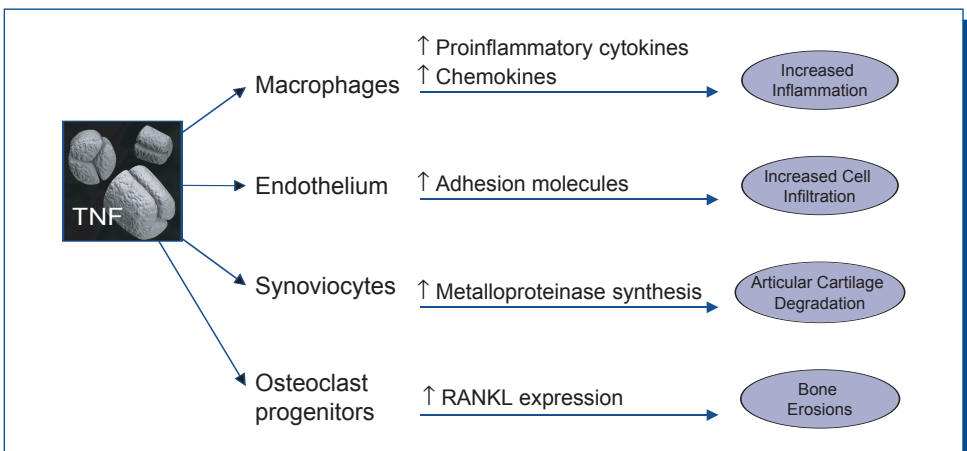
TNF is a proinflammatory cytokine. Its functions include:

- Stimulation of endothelial cells to express adhesion molecules¹⁸
- Recruitment of white blood cells in inflamed synovium and skin¹⁹
- Induction of inflammatory cytokine production (eg, IL-1, IL-6)¹⁹
- Stimulation of synovial cells to release collagenases^{20,21}
- Induction of bone and cartilage resorption²⁰
- Stimulation of fibroblast proliferation²⁰

Why target TNF in AS?

TNF has been identified as a key role player in the pathogenesis of chronic inflammatory diseases, including AS, and appears to have a central role in the pathogenesis of joint destruction as illustrated in Figure 1. In addition, work with anti-TNF agents indicates they are effective in patients with AS that is unresponsive to conventional therapies. In clinical trials, peripheral arthritis, enthesitis, and axial signs and symptoms improved with administration of anti-TNF medications.^{15,22}

Figure 1: AS Immunology



United States Modifications of the ASAS International Guidelines for Use of Anti-TNF Therapy in Patients With AS

John C. Davis, Jr, MD, MPH, MS, FACP, FACR

Recently, a US-based group adapted the ASAS International Guidelines to reflect the realities of clinical practice in America. The group was composed of experts interested in multiple areas of epidemiology, research, treatment, and education on the topic of spondyloarthropathies. The following questions/answers are based on the US modifications of the ASAS International Guidelines.

Which patients with AS are appropriate for anti-TNF therapy?

According to the US modifications of the ASAS International Guidelines, criteria for initiation of treatment, patients must fit into one of the categories below.^{16,23}

- A. Diagnosis of AS according to Modified New York Criteria
 - B. Active disease for 4 weeks or more as defined by both:
 - a. Bath AS Disease Activity Index (BASDAI) score of greater than 4 cm (scale 0 to 10 cm), recorded at two different times, approximately 1 month apart; and
 - b. Physician Global Assessment of 2 or greater on Likert Scale, where 0 = none, 1 = mild, 2 = moderate, 3 = severe, and 4 = very severe
 - C. Treatment failures: patients refractory to an adequate therapeutic trial of conventional therapy defined as follows:
 - a. For patients with all types of AS symptoms (ie, axial symptoms, peripheral arthritis, enthesitis), lack of response or intolerability to at least two NSAIDs for at least 3 months
 - b. For patients with symptomatic peripheral arthritis, a lack of response or intolerability to therapy with more than one DMARD agent, preferably sulfasalazine
- Of note, steroid injections are not required
 - Methotrexate may be considered as a DMARD.

Which patients should not be prescribed anti-TNF therapy?

There are no AS-specific exclusions, but anti-TNF therapy is contraindicated in patients with a history of current or recurrent infections, tuberculosis, multiple sclerosis, lupus, or malignancy. Pregnant and lactating females should also not be administered the agents. For specific drug regimens, the package insert as well as recommendations from professional societies should be referenced for a complete listing of precautions and exclusion criteria.¹⁶

What precautions should be followed to minimize risk of tuberculosis with administration of anti-TNF agents?

Members of the US-based group recommend that healthcare providers heed the guidelines set forth by the American Thoracic Society for tuberculosis screening and treatment. Diagnostic standards and classification were published by the American Thoracic Society in the *American Journal of Respiratory and Critical Care Medicine* (2000;161:1376-1395). They are available online at <http://www.cdc.gov/nchstp/tb/pubs/pdf/1376.pdf>. In an official joint statement, the American Thoracic Society, the Centers for Disease Control and Prevention, and the Infectious Diseases Society of America published treatment guidelines in the *American Journal of Respiratory and Critical Care Medicine* (2003;167:603-662). The guidelines can also be found online at: <http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5211a1.htm>.

What are the general recommendations for monitoring disease activity in patients with AS?

The use of the ASAS core set of outcome parameters for clinical practice is recommended for monitoring patients. The core set consists of the following components: physical function (Bath AS Functional Index [BASFI] or Dougados Functional Index), pain, spinal mobility, patient's global assessment, stiffness, peripheral joints and entheses, acute phase reactants, and fatigue.¹⁶

How to monitor response during therapy?

Patients who do not meet the criteria for minimal clinically important improvement during the initial reassessment at 6 to 8 weeks should discontinue treatment. Response criteria are defined as reduction of 2 or more units on the BASDAI score and improvement of more than 1 on the Physician Global Assessment.²³

Anti-TNF Therapies in AS

John D. Reveille, MD

What anti-TNF agents are approved for treatment of active ankylosing spondylitis?

Etanercept is the only US Food and Drug Administration (FDA)-approved anti-tumor necrosis factor (TNF) agent.²⁴ Adalimumab is currently under investigation. In Europe, infliximab has been approved for use in patients with active AS.²⁵

What are the pharmacologic characteristics that differentiate etanercept from infliximab?

Etanercept and infliximab possess distinct pharmacologic properties that translate to two medications in the same class, but with different efficacy and safety profiles. Etanercept is a fusion protein²⁴ while infliximab is a monoclonal antibody.²⁶ Table 5 provides a comparison of additional characteristics of etanercept and infliximab.

Table 5: Etanercept vs Infliximab: Differentiating Characteristics

	Etanercept	Infliximab
Mechanism of TNF inhibition	"Decoy" receptor for TNF	Binds to TNF and inhibits it from binding with its TNF receptor
Terminal half-life	4.25 +/- 1.25 days (mean +/- SD)	8 to 9.5 days (median values)
In vitro lysis of cells expressing transmembrane TNF	No	Yes
Mode of administration	Subcutaneous	IV infusion (over 2 to 3 hours)

Lee J-H, Slifman NR, Gershon SK, et al. Life-threatening histoplasmosis complicating immunotherapy with tumor necrosis factor α antagonists infliximab and etanercept. *Arthritis Rheum.* 2002;46:2565-2570.

For the treatment of AS, what are the recommended dosing regimens of etanercept and infliximab?

Recommended dosing for etanercept is 50 mg per week as two 25 mg subcutaneous injections on the same day or 3 - 4 days apart.²⁴ For infliximab, the suggested dosing is 5 mg/kg administered intravenously every 6 to 8 weeks after initial injections at 0, 2, and 6 weeks as in the treatment algorithm.²³

For the treatment of other spondyloarthropathies, do clinical differences exist between etanercept and infliximab?

Differences in treating spondyloarthropathies do exist as noted by the current indications for the two medications. Etanercept is indicated for the treatment of patients with psoriatic arthritis, rheumatoid arthritis, juvenile rheumatoid arthritis, and AS.²⁴ Infliximab is indicated for Crohn's disease as well as rheumatoid arthritis in conjunction with methotrexate.²⁶ Infliximab is under investigation for use in the psoriatic arthritis population.

Safety differences also exist as determined by the risk of tuberculosis (TB) and histoplasmosis infections. As of 2002 with more than 117,000 patients dosed with etanercept, postmarketing surveillance has confirmed 20 cases of tuberculosis.²⁷ Analysis of infliximab postmarketing reports for the approximately 147,000 patients who received infliximab worldwide—mainly for treatment of Crohn’s disease and rheumatoid arthritis—revealed 70 cases of TB following therapy. Infliximab was not only associated with increased risk of reactivating TB, but also with atypical patterns of disease. The atypical cases, which tend to be particularly virulent, occurred at higher rates than predicted for non-HIV-associated community TB.²⁸

Rates of histoplasmosis were also tabulated using the FDA’s surveillance database. A total of 10 cases of histoplasmosis were reported: nine associated with infliximab and one with etanercept. Infliximab may be disproportionately associated with histoplasmosis because the agent causes lysis of various tumor necrosis factor (TNF) expressing cells, including macrophages, which protect against infection.²⁹ Ultimately, the overall ability to ward off infection may become impaired. Of note, additional, as-yet-unidentified reasons may still explain differences in infection rates, but at this time, until further investigations are completed, healthcare professionals should be vigilant and aware of the potential for infection with both medications.

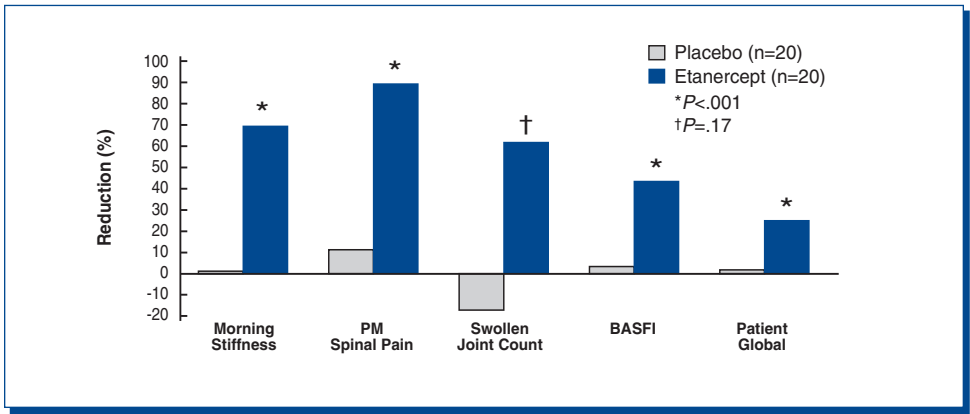
What clinical studies have evaluated etanercept for the treatment of AS?

An overview of some key clinical trials designed to assess administration of etanercept to patients with active AS follows:

- Marzo-Ortega and colleagues performed a longitudinal study in 10 patients with spondyloarthritis to determine the effect of etanercept, 25 mg, administered twice weekly, on clinical manifestations of the disease and on MRI-observed enthesal lesions. Assessment measures included enthesal count, visual analog scale scores for spinal pain and enthesal pain, Bath AS Functional Index (BASFI), Bath AS Disease Activity Index (BASDAI), Ankylosing Spondylitis Quality of Life questionnaire, and MRI scans of the sacroiliac joints, lumbar spine, and affected peripheral joints at baseline and 6 months. Significant improvement in all clinical and functional parameters was observed at 6 months. A total of 86% of MRI-detected enthesal lesions regressed completely or improved, and no new lesions developed.³⁰
- Marzo-Ortega and colleagues assessed efficacy of etanercept, 25 mg, twice weekly in the prevention of bone loss in 10 patients with AS and spondyloarthropathies. Results of the etanercept-treated group were compared with findings from a group of patients with equivalent disease activity treated with nonsteroidal anti-inflammatory drugs (NSAIDs) (n=8) and sulfasalazine (n=2). Of note, two conventionally treated patients also received corticosteroid injections. The investigators found that mean hip and spine bone mineral density, measured at baseline and following 24 weeks of treatment, increased over the treatment period in the etanercept-treated group, but decreased in the conventionally treated group.³¹
- Gorman and colleagues randomly assigned 40 patients with active AS to receive either etanercept, 25 mg, or placebo twice weekly over a 4-month period. The primary outcome measure was the ASsessment in Ankylosing Spondylitis 20% (ASAS 20), a composite treatment response, defined as 20%-or-greater improvement in at least three of the following five measures of disease activity and no worsening of any component: morning stiffness (must improve), nocturnal spinal pain (must improve), the BASFI, patient’s global assessment of disease activity, and joint swelling. NSAIDs, oral corticosteroids, and disease-modifying antirheumatic drugs (DMARDs) were allowed during the trial. At 4 months, 80% of etanercept-treated patients and 30% of placebo-

treated patients demonstrated a treatment response ($P=.004$). Treatment response was rapid and did not decrease over time. Primary outcome responses for the individual efficacy measures are illustrated in Figure 2.¹⁵

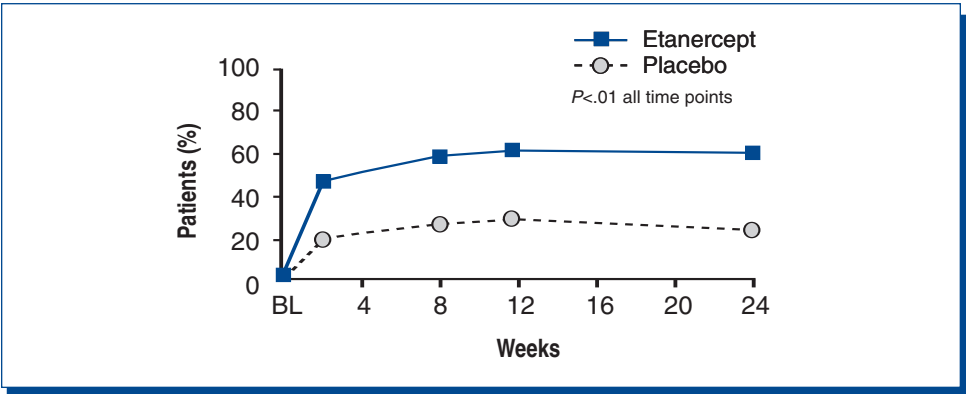
Figure 2: Primary Outcome Response at 4 Months: Etanercept vs. Placebo



Gorman JD, Sack KE, Davis JC Jr. *N Engl J Med.* 2002;346:1349-1356.

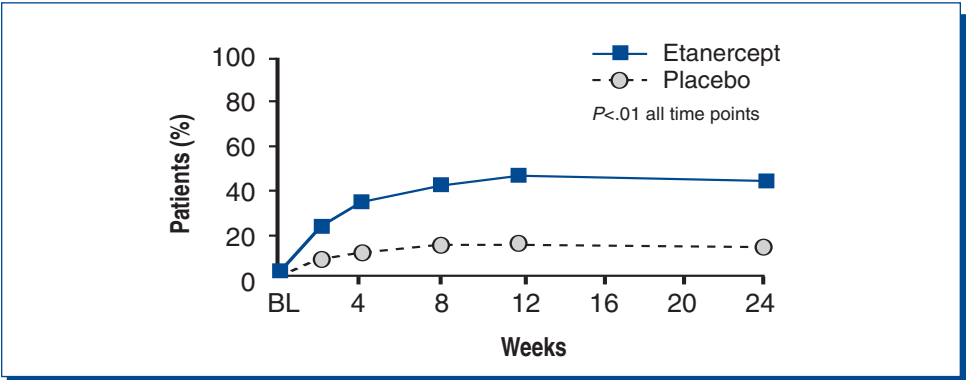
- Gorman and colleagues completed an open-label extension of the last study discussed. The 38 patients who entered were given etanercept for an additional 6 months. Again, the primary endpoint was the ASAS 20. The ASAS 50 and ASAS 70 were also measured. After 10 months of treatment, 84% of the placebo/etanercept group and 95% of the etanercept/etanercept group achieved the ASAS 20. Once the groups were combined, an overall response of 83%, 80%, and 60% was achieved on the ASAS 20, ASAS 50, and ASAS 70, respectively.³²
- Brandt and colleagues evaluated 30 patients with active AS in a double-blind, placebo-controlled study design, and randomized them to receive etanercept (n=14) or placebo (n=16) over a 6-week period. DMARDs and corticosteroids were disallowed, but NSAIDs could be continued. Following the 6-week phase, all patients were given etanercept; those initially in the placebo group received the medication for 12 weeks, while those in the original etanercept group received 6 more weeks of treatment. Patients and investigators were unblinded at week 12 to determine who would continue to receive the additional 6 weeks of therapy. All patients entered a post-treatment observational phase for 24 weeks. The primary endpoint was at least 50% improvement on the BASDAI, which was observed in 57% of etanercept-treated patients and only 6% of placebo-treated patients. Once the placebo group was switched to etanercept, 56% improved. In both groups, improvements ceased once etanercept therapy was discontinued.³³
- Davis and colleagues demonstrated that therapy with etanercept caused dramatic improvement in patients with AS. The primary efficacy variable for this double-blind, placebo-controlled trial was the percentages of patients achieving the ASAS 20 response at weeks 12 and 24. Additional outcome measures were the percentage of patients achieving higher ASAS responses (ie, ASAS 50 and ASAS 70). A total of 277 subjects were randomly assigned to receive etanercept, 25 mg, or placebo twice weekly for 24 weeks. Significantly more patients achieved the ASAS 20 in the etanercept group (57%) compared with the placebo group (22%) at week 24 ($P<.0001$).³⁴ Results for the ASAS 20, ASAS 50, and ASAS 70 are graphically depicted in Figures 3a, 3b, and 3c.

Figure 3a: ASAS 20 Results



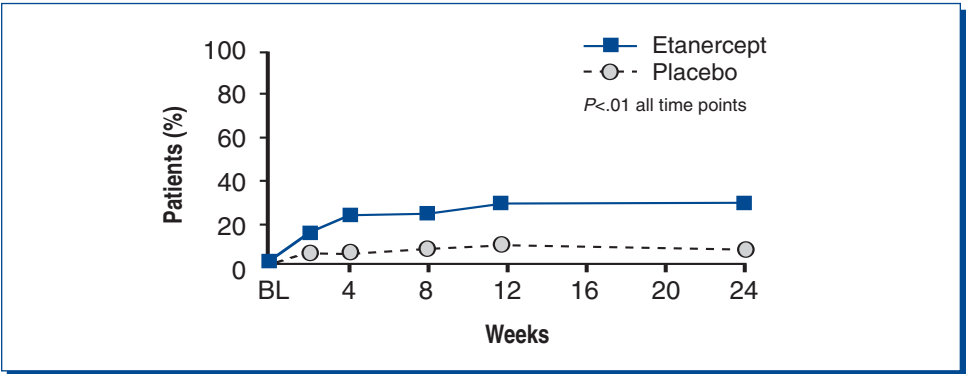
Davis JC Jr, van der Heijde D, Braun J, et al for the Enbrel Ankylosing Spondylitis Study Group. *Arthritis Rheum.* 2003;48:3230-3236.

Figure 3b: ASAS 50 Results



Davis JC Jr, van der Heijde D, Braun J, et al for the Enbrel Ankylosing Spondylitis Study Group. *Arthritis Rheum.* 2003;48:3230-3236.

Figure 3c: ASAS 70 Results



Davis JC Jr, van der Heijde D, Braun J, et al for the Enbrel Ankylosing Spondylitis Study Group. *Arthritis Rheum.* 2003;48:3230-3236.

What is the safety and tolerability profile of etanercept?

Table 6 presents the adverse-event data for etanercept. Most events were mild or moderate in intensity and only injection-site bruising, upper respiratory infections, and accidental injury occurred significantly more frequently with etanercept than with placebo. Incidence of adverse events in the AS population was similar to those observed in clinical trials with rheumatoid arthritis and psoriatic arthritis patient populations.³⁵

Serious infections and sepsis, mainly in patients predisposed to infections caused by immunosuppressive therapy or underlying illness, have been described in postmarketing reports. Etanercept should be discontinued in patients with serious infection, never begun in the presence of sepsis or infection—both chronic and localized—used with caution in those predisposed to infection (eg, patients with poorly controlled diabetes).²⁴

The causal relationship to etanercept is unclear, but cases of CNS demyelinating disorders, including transverse myelitis, optic neuritis, and multiple sclerosis, have been reported. Therefore, caution is advised when considering use of etanercept in patients with these conditions. Similar caution must be exercised in patients with a history of hematologic abnormalities as rare cases of pancytopenia, including aplastic anemia, have occurred. Again, a causal relationship to etanercept is unclear.^{24,36} Administration of etanercept may also result in formation of autoantibodies or in the rare development of a lupus-like syndrome. Discontinue treatment and carefully monitor the patient if symptoms suggestive of a lupus-like syndrome are observed.²⁴

The use of etanercept in the treatment of heart failure was evaluated in two large clinical trials. Although the trials were terminated early due to lack of efficacy, one study suggested higher mortality in patients treated with etanercept compared to placebo. However, results from the second study were not in agreement with the first. Postmarketing reports of worsening congestive heart failure in patients treated with etanercept have been noted. In addition, rare cases of new onset congestive heart failure in patients with and without pre-existing cardiovascular disease have been observed. Some of these patients were under the age of 50 years. Therefore, caution and careful monitoring are advised if etanercept is prescribed to a patient with heart failure.²⁴

Table 6: Etanercept Adverse Events

Events in > 5% of Patients	Placebo % (n=139)	Etanercept % (n=138)
Injection site reaction	9	30*
Injection site bruising	17	21
Upper respiratory infection	12	20 [†]
Headache	12	14
Accidental injury	4	12 [‡]
Diarrhea	9	8
Rash	7	11
Rhinitis	7	6
Abdominal pain	5	6
Dizziness	2	6
Flu syndrome	7	4

* $P < .001$ † $P < .0500$ ‡ $P < .0200$

Davis JC Jr, van der Heijde D, Braun J, et al for the Enbrel Ankylosing Spondylitis Study Group. Recombinant human tumor necrosis factor receptor (etanercept) for treating ankylosing spondylitis: a randomized controlled trial. *Arthritis Rheum.* 2003;48:3230-3236.

Summary of Etanercept for the Treatment of AS

The introduction of etanercept for the treatment of AS answers an unmet therapeutic need for a disease inadequately treated with NSAIDs and DMARDs. Presence of elevated levels of TNF in AS implies that an anti-TNF therapy such as etanercept would be effective. Moreover, etanercept was already known to control symptoms of psoriatic arthritis, another inflammatory spondyloarthropathy, and rheumatoid arthritis. Therefore, it was not surprising that clinical trial results support similar benefits and tolerability in patients with AS. Of note, etanercept is well tolerated, but caution is advised when administering to patients with certain conditions, such as heart failure.

What clinical trials have evaluated infliximab in patients with AS?

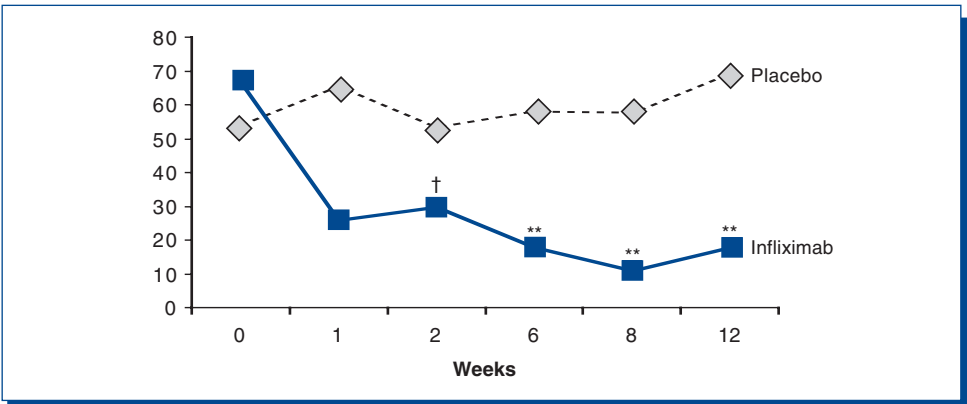
A summary of several published clinical trials designed to assess administration of infliximab in patients with AS follows:

- Stone and colleagues enrolled 21 patients with AS into an open-label study to (1) evaluate whether infliximab is an effective treatment for patients who failed conventional AS treatment, and (2) determine if clinical response correlated with gadolinium-enhanced MRI imaging. Patients were treated with infliximab, 5 mg/kg, intravenously over two hours at weeks 0, 2, and 6. Outcome measures included nine functional indices (eg, the BASDAI and BASFI). At 6 weeks, improvement of more than 60% was observed in the BASDAI, BASFI, patient global assessment, physician global assessment, spinal pain, and total body pain, and Health Assessment Questionnaire scores. At 14 weeks, improvement was greater than 75% in these same measures. Improvement on the imaging studies was observed in all patients who underwent pre- and post-infusion MRI scans. Overall, infliximab was effective, but within varying degrees of response.³⁷
- Maksymowych and colleagues investigated the efficacy of infliximab in a prospective observational study of 21 patients with NSAID-refractory AS. Infliximab was dosed 3 mg/kg intravenously at weeks 0, 2, and 6 and every 2 months over an 18-month period. Bath AS indexes were used to evaluate the patients at baseline, 14 weeks, and one year. Of the 17 patients for whom data were available at 14 weeks, significant mean improvement on BASDAI was observed. Significant mean reduction in BASFI, Bath AS Global Index, erythrocyte sedimentation rate, and C-reactive protein (CRP) was also found ($P < .001$ all parameters except CRP, $P = .01$). At 1 year, data on eight patients demonstrated sustained efficacy.³⁸
- Brandt and colleagues completed an open-label, observational, 12-week trial in six patients with active and severe spondyloarthropathies to evaluate efficacy of infliximab. Patients were administered an infusion of infliximab, 3 or 5 mg/kg, at weeks 0, 2, and 6. Efficacy variables were the BASDAI, BASFI, pain on visual analog scale, Bath AS Metrology Index (BASMI), and quality of life (SF-36). Five patients experienced significant improvement after the first infusion, which lasted until week 12. Those receiving the higher dose demonstrated 50% or greater improvement in outcome variables; the 3 mg/kg group experienced 15% or greater improvement.²²
- Braun and colleagues randomized 35 patients with AS to receive infliximab, 5 mg/kg, and 35 to receive placebo, both administered at weeks 0, 2, and 6. The primary efficacy variable was regression of disease activity of at least 50%. BASDAI, BASFI, BASMI, and quality of life (SF-36) were also assessed. At week 12, 53% of infliximab-treated patients

and 9% of placebo-treated patients had a regression of disease activity of 50% or more ($P<.0001$). Function and quality of life also significantly improved with infliximab treatment compared to placebo treatment ($P<.0001$).³⁹

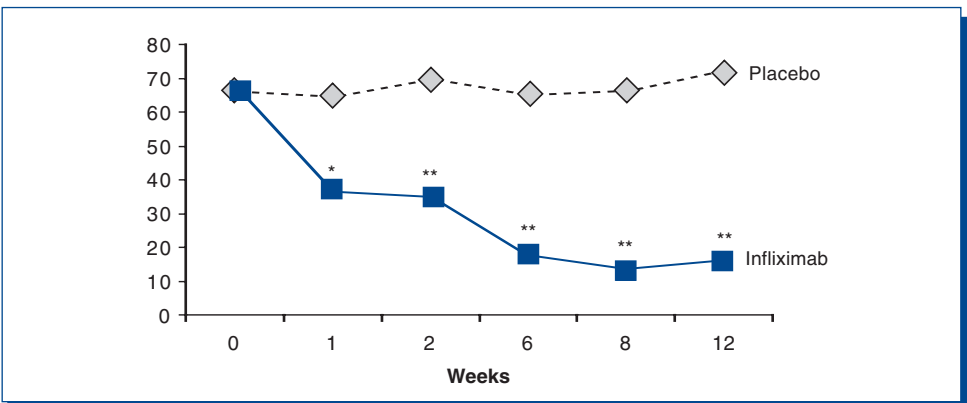
- Van den Bosch and colleagues performed a placebo-controlled trial to evaluate efficacy of infliximab for the treatment of patients with AS. A total of 40 patients were randomly assigned to receive either infliximab, 5 mg/kg, or placebo. Both treatment groups received intravenous infusions at weeks 0, 2, and 6. Primary endpoints were the improvement in patient and physician global assessments of disease activity on a 100-mm visual analog scale. At week 12, patients in the infliximab group improved significantly compared with baseline values while no improvement was observed in the placebo group. Significant differences between the infliximab and placebo groups were also observed in the outcome variables beginning at week 2 and lasting through completion of the 12-week study.⁴⁰

Figure 4a: Patient Global Assessment



* $P\leq.01$, [†] $P\leq.05$, ^{**} $P\leq.001$ vs placebo.
Van den Bosch F, Kruithof E, Baeten D, et al. *Arthritis Rheum.* 2002;46:755-765.

Figure 4b: Physician Global Assessment



* $P\leq.01$, [†] $P\leq.05$, ^{**} $P\leq.001$ vs placebo.
Van den Bosch F, Kruithof E, Baeten D, et al. *Arthritis Rheum.* 2002;46:755-765.

What is the safety and tolerability profile of infliximab?

Overall, infliximab is well tolerated. Table 7 presents the adverse effects observed in patients administered infliximab for the treatment of rheumatoid arthritis. Because infliximab is not yet approved for treatment of AS in the United States, a summary of side effects in that patient population is not available in the prescribing information.²⁶ However, the rates of adverse events are likely comparable to those of the rheumatoid arthritis population.

Table 7: Infliximab Adverse Events

Events in ≥ 5% of Patients	Placebo % (n=81)	Infliximab % (n=430)
Acute infusion reaction	10*	20*
Upper respiratory infection	35	40
Headache	21	29
Diarrhea	19	19
Rash	7	18
Rhinitis	14	14
Abdominal pain	12	17
Fatigue	9	13
Arthralgia	7	13

Remicade [package insert]. Malvern, Pa: Centocor, Inc; 2003.

Serious infections and sepsis have been reported in patients administered infliximab. Many cases were in individuals on concomitant immunosuppressive therapy, and some proved to be fatal. Infliximab is contraindicated in patients with serious active infection, and patients should be monitored for signs and symptoms of illness while on or after use of the medication. Discontinue infliximab if the patient develops a serious infection.²⁶

Rare cases of optic neuritis, seizure, and new onset or exacerbation of CNS demyelinating disorders have been reported with infliximab administration. Caution is advised in prescribing infliximab in patients with these conditions. A lupus-like syndrome due to the formation of autoantibodies may also occur, though incidence is rare. Should symptoms develop, discontinue treatment.²⁶

Other therapy options should be considered in patients with heart failure as an association between infliximab and adverse outcomes has been reported in this patient population. Post-marketing reports indicate worsening heart failure, with and without identifiable precipitating factors. It is rare, but new onset of heart failure has been observed, and in some cases patients were under 50 years of age without known pre-existing cardiovascular disease. Closely monitor patients with heart failure if infliximab is administered.²⁶

Summary of Infliximab for the Treatment of AS

Although not FDA-approved for treatment of AS, infliximab demonstrates efficacy in this patient population. Infliximab is also generally well tolerated, but caution is advised when administering to patients with certain conditions, such as heart failure. Infliximab is currently indicated for treatment of rheumatoid arthritis and Crohn's disease; potential to improve outcome in the AS patient population is supported by clinical trials. Future widespread administration will definitively determine the degree with which infliximab may influence symptoms of AS.

Summary of Anti-TNF Therapy in AS

The advent of anti-TNF agents means that AS treatment is no longer a discouraging endeavor. The medications target the underlying inflammatory process, potentially altering disease progression,³⁰ as they provide symptomatic relief.² Etanercept, currently the only FDA-approved biologic for treatment of AS, is recommended after a trial of NSAIDs. Please refer to the enclosed treatment algorithms for specific recommendations on incorporating anti-TNF agents into an effective approach for managing AS.

To date, the safety and tolerability profiles of the anti-TNF agents are encouraging. Long-term data are still needed, however, to further evaluate the medications and ensure that toxicity does not develop over time. Although the administration of such medications has proven benefits, in an era of healthcare cost containment, the high cost of the drugs is an issue. It is therefore important to have criteria for judicious use of anti-TNF therapies to overcome healthcare/health insurance barriers and make certain that proper treatment is provided to appropriate patients. It is the author's hope that implementation of the US modifications of the ASAS International Guidelines and treatment algorithms will achieve this goal.

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CME Evaluation Form

Title: Guidelines in Rheumatology:
The Diagnosis and Management of Ankylosing Spondylitis

To ensure processing of your application, the sponsoring institution requires your evaluation of this activity entitled *Guidelines in Rheumatology: The Diagnosis and Management of Ankylosing Spondylitis*. Please complete this questionnaire, and return it to the accrediting institution. Thank you for your comments.

Date of Release: March 2004 Date of Completion: _____

How well did the objectives relate to the overall purpose of this program?

- Excellent Good Fair Poor

Comments:

How do you like the teaching strategies used in this activity?

- Excellent Good Fair Poor

How do you rate the expertise of the authors?

Muhammad Asim Khan, MD, MACP, FRCP

- Excellent Good Fair Poor

John C. Davis, Jr, MD, MPH, MS, FACP, FACR

- Excellent Good Fair Poor

John D. Reveille, MD

- Excellent Good Fair Poor

To what extent did you achieve each objective of this activity?

Rate your ability to do the following:

1. Effectively manage patients with ankylosing spondylitis through patient evaluation, assessment of clinical data, and expert treatment recommendations.

- Excellent Good Fair Poor

2. Recognize barriers to therapeutic compliance.

- Excellent Good Fair Poor

3. Understand comorbid conditions related to disease and medication regimens in patients with AS and implement effective management of those conditions.

- Excellent Good Fair Poor

4. Identify treatment regimens as well as strategies to improve patient outcomes.

- Excellent Good Fair Poor

Is there any subject matter you would like included in future activities?

- Yes No

Comments:

Did the commercial support of this activity in any way influence the balance, objectivity, and scientific rigor of the information presented?

- Yes No

Comments:

As a result of your participation in this activity, do you plan to make any changes in your practice? Yes No

Please give two examples: _____

Application for CME Credit

This is to attest that I have participated in the Albert Einstein College of Medicine, Montefiore Medical Center, and the Spondylitis Association of America activity entitled: *Guidelines in Rheumatology: The Diagnosis and Management of Ankylosing Spondylitis*.

To ensure processing, please print clearly.

Last Name: _____

First Name: _____

Degree: _____

Address: _____

City: _____

State: _____ Zip: _____

E-mail: _____

Phone Number: () _____

When used and completed as designed, *Guidelines in Rheumatology: The Diagnosis and Management of Ankylosing Spondylitis* is designated for 2 category 1 credits toward the AMA Physician's Recognition Award. Each physician should claim only those credits that he/she actually spent in the activity. (Valid through June 2005. No credit will be given after this date.)

Signature: _____ Date: _____

To ensure processing of your application, the sponsoring institution requires your evaluation of this activity along with your posttest. Please complete this form, along with the CME PreTest and CME Posttest, and fax to: (718) 798-2336

Or mail to:

The Albert Einstein College of Medicine Center for Continuing Medical Education
3301 Bainbridge Avenue, Bronx, NY 10467

The fee for this activity has been waived by the Albert Einstein College of Medicine.

1.	a	b	c	d	e
2.	a	b	c	d	e
3.	a	b	c	d	e
4.	a	b	c	d	e
5.	a	b	c	d	
6.	a	b	c	d	e
7.	a	b	c	d	
8.	a	b	c	d	e
9.	a	b	c	d	
10.	a	b			

CME Self-Assessment Posttest Answer Grid

Estimated time to complete this activity is 1 hour. Valid through June 2005.

Circle the one best answer for each of the questions on the following page on the Answer Grid below. You must answer at least 70% of the questions correctly to receive credit. Return this answer sheet with your CME Evaluation Form and completed Application for Credit (above) to Albert Einstein College of Medicine, Bronx, NY.

CME Self-Assessment Posttest Questions

1. According to current clinical trends, what is the male/female ratio for the prevalence of AS?
a. 1:1 b. 1:3.5 c. 1:5 d. 2.5:1 e. 4:1
2. What is the average delay between the time of disease onset and diagnosis of AS?
a. 6 months b. 2.7 years c. 5.9 years d. 7.2 years e. 8.9 years
3. A survey of patients with AS revealed that all of the following are common quality-of-life concerns except:
a. Pain b. Fatigue c. Headaches d. Stiffness e. Sleep problems
4. All of the following are functions of tumor necrosis factor (TNF) except:
a. Induces inflammatory cytokine production
b. Inhibits release of collagenases by synovial cells
c. Stimulates fibroblast proliferation
d. Inhibits synthesis of proteoglycans in cartilage
e. Recruits white blood cells in inflamed synovium
5. Which patients qualify for initiation of anti-TNF therapy according to US modifications of ASAS Guidelines?
a. Patients with axial symptoms and a lack of response to 3 NSAIDs for 3 months, and a BASDAI score of 4 or more.
b. Patients with a BASDAI score of 2.
c. Patients with peripheral arthritis symptoms and intolerance to 2 NSAIDs for 2 months.
d. Patients with a Physician Global Assessment of 1.
6. Anti-TNF therapy is contraindicated in patients with the following conditions except:
a. Tuberculosis b. Multiple sclerosis c. Diabetes d. Lupus e. Malignancy
7. Following 6 to 8 weeks of anti-TNF treatment, what defines a response to therapy?
a. Reduction of 1 or more units on the BASDAI and improvement of more than 1 on the Physician Global Assessment.
b. Increase of 1 or more units on the BASDAI and improvement of more than 1 on the Physician Global Assessment.
c. Reduction of 2 or more units on the BASDAI and improvement of more than 1 on the Physician Global Assessment.
d. Increase of 2 or more units on the BASDAI and improvement of more than 1 on the Physician Global Assessment.
8. Which is not an FDA-approved treatment indication for etanercept?
a. Psoriatic arthritis
b. Ankylosing spondylitis
c. Rheumatoid arthritis
d. Crohn's disease
e. Juvenile rheumatoid arthritis
9. According to the AS treatment algorithm, how long is an adequate trial of NSAIDs?
a. 2 weeks b. 3 months c. 6 months d. 1 year
10. Levels of TNF are elevated in ankylosing spondylitis.
a. True b. False

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