CHAPTER 9

Ankylosing Spondylitis
A. Clinical Features

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- Ankylosing spondylitis (AS) is the prototypical form of seronegative spondyloarthropathies, a group of disorders that involves chronic inflammation of the sacroiliac joints and spine as well as extraspinal lesions involving the eye, bowel, and heart.
- The prevalence of AS ranges from 0.1% to 6.0% across different populations, with figures for most populations near the lower end of that range.
- Human leukocyte antigen (HLA)-B27 is a strong genetic risk factor for AS. However, this gene is neither necessary nor sufficient to cause the disease.
- The principal musculoskeletal lesions associated with AS are sacroiliitis, synovitis, and enthesitis (inflammation at the site of tendinous insertions into bone).
- Sacroiliitis, the most common initial feature, causes pain in the buttocks, typically alternating in severity between the left and right sides.
- When synovitis is present, the hips, knees, ankles, and metatarsophalangeal joints are affected most commonly.
- Acute anterior uveitis, characteristically unilateral, is the typical ocular lesion. Patients present with a red, painful, photophobic eye.
- A sizable minority (10%–15%) of patients with AS have full-blown inflammatory bowel disease.
- Conventional radiographs of the sacroiliac joints are usually the most helpful diagnostic test. In earlier cases, findings on magnetic resonance imaging may also be diagnostic.

Ankylosing spondylitis (AS) is a chronic inflammatory disease of the sacroiliac joints and spine that may be associated with a variety of extraspinal lesions involving the eye, bowel, and heart. AS usually begins in young adulthood. The natural history of AS involves progressive stiffening of the spine, with ankylosis (fusion of some or all spinal joints) occurring after some years of disease in about two thirds of the patients. Patients with long-standing severe disease are at increased risk of premature death, but overall the life span of individuals with AS appears to be normal. AS shares many features with the arthritides associated with psoriasis, inflammatory bowel disease, and reactive arthritis. Together, these conditions comprise the spondyloarthritis family and are sometimes termed the *seronegative spondyloarthropathies* ("seronegative" because they are not associated with rheumatoid factor) (1). Typical spondylitis may be present in each of the other spondyloarthritides.

EPIDEMIOLOGY

The prevalence of AS in different populations varies from 0.1% in some African and Eskimo populations, through 0.5% to 1.0% among white populations in the United Kingdom and United States, to around 6% in the Haida Native Americans in Northern Canada. The prevalence generally, but not exclusively, reflects the prevalence of human leukocyte antigen (HLA)-B27 in the different populations. Because few population surveys have been undertaken, much of the available data have been drawn from selective hospital-based surveys and from information on other related spondyloarthritides.

Ankylosing spondylitis is more common in men, with a male : female ratio of approximately 2 : 1. Expression of disease may vary slightly between men and women, but earlier reports exaggerated this disparity to the under-estimation of women with AS, many of whom experienced unnecessary delays in diagnosis (2). Some investigators have suggested that the true sex ratio is closer to unity if based on population data.

ETIOLOGY

In spite of dramatic advances in recent years, the etiology of AS remains unclear. A strong multigenic inherited component is evident, although HLA-B27 remains the strongest association in almost all populations (3).

Animal and laboratory studies suggest that the HLA-B27 molecule itself plays a key role, and that involvement of class I major histocompatibility complex (MHC) antigens in the presentation of microbial peptides is central to the pathogenic mechanism (4).

Infective mechanisms also have been proposed. However, aside from the occurrence of spondylitis in some patients with another form of spondyloarthropathy—reactive arthritis—no clear evidence implicates infection in the etiology of AS. *Klebsiella aeruginosa* has been implicated on the basis of molecular mimicry with HLA-B27 and clinical studies, although its true significance remains unclear. Subclinical mucosal inflammation in the large and small bowel undoubtedly is present in many individuals with AS; this finding could provide the basis for an immune or infective mechanism for the spinal disease.

CLINICAL FEATURES

The principal musculoskeletal lesions associated with AS are enthesitis and synovitis, with sacroiliitis also involving adjacent bone. Inflammatory eye lesions, myocardial changes, gut mucosal lesions, and skin lesions are inconsistent but characteristic features of AS.

PRESENTING FEATURES

Spinal features of AS seldom appear before the age of 16 to 18 years. Before this age, children and teenagers may develop oligoarthritis—typically a swollen knee or metatarsophalangeal (MTP) joint—sometimes associated with iritis and/or enthesitis (5). Juvenile AS is remarkable because it does not involve the spine. For many, symptoms begin early in the third decade of life; the average age at onset is 26 years. Although the disease rarely begins after the age of 40 years, it is not uncommon for the diagnosis to be made only years later, well after that age. Earlier symptoms often are mild, ignored, or not recognized as being part of AS.

The usual presenting symptom is inflammatory back pain that is insidious in onset, persistent for more than 3 months, worsened by rest and improved by exercise. Night pain is a frequent symptom. Sacroiliitis, the most common initial feature, causes pain in the buttocks, typically alternating between right and left in severity. This pain sometimes radiates down the thighs but never below the knee. Although clinical examination is unreliable as a means of diagnosing sacroiliitis, pain in the buttocks may be elicited in some patients by pushing firmly with both hands on the sacrum when the patient is prone. A minority of patients present with oligoarthritis or enthesitis that particularly affects the heel, or hip pain due to aggressive synovitis. Fatigue, a common and troublesome symptom, may be caused in large part by impaired sleep caused by pain and stiffness. Other constitutional features may include fever and weight loss. Overt or subclinical depression, accompanied by a loss of libido and reduced capacity for work, also may contribute to lack of well-being.

Spinal discomfort and stiffness typically ascend the spine over a period of years, producing progressive spinal pain and restriction. One of the first clinical signs is the disappearance of the lumbar lordosis. This progression affects the costovertebral joints, reducing respiratory excursion, and the cervical spine, limiting neck movement. Thoracic spine involvement may be associated with anterior chest pain and sternal/costal cartilage tenderness, which can be particularly distressing for patients. Osteoporosis (which may be prevented by appropriate therapy) may lead to vertebral and other fractures later in life (6). Spinal fractures are more common in patients who have severe involvement with rigidity. Aseptic spondylodiscitis may occur in patients with AS, especially in the thoracic spine.

Enthesitis

The central feature of AS is inflammation at entheses, the sites where tendons and ligaments attach to bone. These inflammatory lesions initially lead to radiographic appearances of osteopenia or lytic lesions, but subsequently reactive bone forms a new, more superficial enthesis, which develops into a radiologically detectable bony overgrowth or spur (7). In the spine, enthesitis occurs at capsular and ligamentous attachments and discovertebral, costovertebral, and costotransverse joints, with involvement also at bony attachments of interspinous and paravertebral ligaments.

Enthesitis accounts for much of the pain, stiffness, and restriction at sacroiliac and other spinal joints. The phenomenon also occurs at extraspinal sites, producing potentially troublesome symptoms. Such lesions most commonly affect the plantar fascia and Achilles tendon insertions to the calcaneus, leading to disabling heel pain. Plantar fasciitis typically leads to the formation of fluffy calcaneal spurs visible on heel radiographs after 6 to 12 months. Similar lesions may occur around the pelvis, costochondral junctions, tibial tubercles, and elsewhere, causing marked local tenderness. More widespread diffuse lesions lead to insidious stiffness and generalized discomfort. Sternal and costochondral pain also reflect a combination of local enthesitis and referred pain from the thoracic spine. This development frequently produces chest pain that must be distinguished from myocardial ischemia.

Sacroiliitis

Inflammation of the sacroiliac joints develops most frequently in the late teens or in the third decade of life,

producing bilateral or occasionally, unilateral buttock pain, usually worse after inactivity and sometimes aggravated by weight bearing. Changes principally affect the lower anterior (synovial) portion of the sacroiliac joints and are associated with juxta-articular osteopenia and osteitis. This condition leads to radiographic appearances of widening of the sacroiliac joint. Endochondral ossification as a consequence of the osteitis gives the radiographic appearance of erosion along the lower part of the sacroiliac joints. Osteitis appears as increased water content of adjacent bone, as seen on magnetic resonance imaging (MRI). MRI is a valuable imaging modality for assessment of inflammation in both the sacroiliac joints and the spine. This can frequently be an important aid in establishing an early diagnosis. Capsular enthesopathy also occurs over the anterior and posterior aspect of the joint throughout its length, leading to sheets of ossification that ultimately obscure the joint completely on standard radiographs, depicted as ankylosis of the sacroiliac joint.

FIGURE 9A-1

Acute anterior uveitis in AS, typically unilateral and associated with redness, pain, and photophobia.

Synovitis

Peripheral synovitis in AS is distinctive because of by the distribution of joints affected rather than because of distinct histological changes. Synovitis is indistinguishable histologically and immunohistochemically from typical rheumatoid disease. Peripheral joint synovitis may precede, accompany, or follow the onset of spinal symptoms. Hips, knees, ankles, and MTP joints are affected most commonly. With the exception of the shoulders, upper limb joints are almost never involved in AS, particularly in the absence of psoriasis. In further contrast to rheumatoid arthritis, peripheral joint synovitis usually is oligoarticular, often asymmetrical, and frequently episodic rather than persistent. Joint erosions, especially at the MTP joints, may lead to subluxation and deformity. Peripheral joint involvement is indistinguishable from that seen in the other spondyloarthritides. Temporomandibular joints may be affected, leading to reduced mouth opening and discomfort on chewing. Dactylitis may lead to pain in one or more toes that lasts many months.

Eye Lesions

Acute anterior uveitis (iritis) develops at some time during the course of the disease in approximately one third of patients with AS, and may be recurrent (Figure 9A-1). The typical pattern is alternating, unilateral eye inflammation associated with pain, redness, lacrimation, photophobia, and blurred vision. The occurrence of uveitis typically does not coincide with flares of arthritis. Untreated or inadequately treated iritis may lead rapidly to considerable scarring, irregularity of the pupil, and visual impairment. Red, sore, gritty eyes or blurring of vision in a patient with AS require urgent ophthalmologic examination.

Inflammatory Bowel Disease

Sacroiliitis occurs in 6% to 25% of people with Crohn's disease or ulcerative colitis. Patients with Crohn's disease or ulcerative colitis frequently have unilateral sacroiliitis, and may also suffer from peripheral arthritis and enthesitis. Similarly, inflammatory bowel disease may be present or develop in people with preexisting AS. Indeed, approximately 60% of people with AS have subclinical changes in the small or large bowel (8). There is speculation that these changes may relate to the pathogenesis of AS, but their true significance is unknown. Even though some AS lesions closely resemble those of Crohn's disease, the great majority of such lesions never become symptomatic. Only about 10% to 15% of the patients with AS have overt ulcerative colitis or Crohn's disease. The link between AS and inflammatory bowel disease appears to be indirect, as variations in inflammatory activity of each disease appear to occur independently. However, in a patient with AS altered bowel habits with diarrhea and abdominal discomfort, with or without passage of blood or mucus, requires investigation.

In a minority of people with colitis and peripheral arthritis, peripheral joint disease may diminish substantially after total colectomy. Conversely, however, many

patients complain of a disorder resembling fibromyalgia that produces mild but widespread discomfort after colectomy. Active inflammatory bowel disease increases the risk and severity of osteoporosis. Crohn's disease with extensive small bowel involvement also may lead to impaired vitamin D absorption and osteomalacia, producing ill-defined musculoskeletal pain and difficulty with walking.

Cardiovascular Involvement

Cardiac conduction abnormalities and myocardial dysfunction have been recorded in a significant minority of people with AS (9). Aortitis with dilatation of the aortic valve ring and aortic regurgitation has been demonstrated in approximately 1% of patients. The risk of occurrence of aortic insufficiency and cardiac conduction abnormalities increase with age, disease duration, presence of HLA-B27, and peripheral joint involvement.

Pulmonary Involvement

Approximately 1% of patients develop progressive upper lobe fibrosis of the lungs (10). Rigidity of the chest wall results in the inability to extend the chest fully and to mild restrictive lung function impairment, but rarely leads to ventilation insufficiency due to the compensation by increased diaphragmatic contribution.

Neurologic Lesions

Neurologic deficits are associated most often with cord or root lesions following spinal fracture. Nerve root pain may arise from the cervical spine, especially when there is marked flexion deformity. Long-tract signs, including quadriplegia, may follow spinal fracture dislocation after relatively minor trauma and complicate spontaneous atlantoaxial subluxation. Subluxation also may lead to severe occipital headache. Weakness of the legs occasionally occurs in association with a cauda equina syndrome. This syndrome is particularly associated with the development of dural ectasia demonstrable on MRI.

Skin Involvement

In various series, between 10% and 25% of the patients with typical AS have concomitant psoriasis lesions.

Renal Consequences

Although rarely seen today, secondary amyloidosis caused by longstanding AS is well described.

IMAGING

Radiographic damage of the spine and axial joints is a key characteristic of patients with AS. By definition, all patients fulfilling the modified New York criteria show signs of sacroiliitis on radiographs. However, about 30% of the patients do not develop damage of the spine visible on radiographs. If patients show no spinal damage after a certain disease duration (about 10 years), it is unlikely that the patient will develop radiographic abnormalities of the spine at all. On the other hand, patients who have spinal damage are prone to develop more damage.

The most widely used imaging technique is conventional radiography. However, MRI and ultrasound are being used more frequently. Characteristic features on radiographs of the sacroiliac joints are pseudowidening of the joint space, sclerosis, erosions, and ankylosis (Figure 9A-2). At late stages, there is complete ankylosis of the joint. The sacroiliac joint has a complicated, irregular anatomy; computed tomography (CT), which provides views through slices of the joint space, can be helpful when the presence of sacroiliitis is in question. Many AS-related changes can be seen in the spine; squaring of the vertebrae, sclerosis, erosions, syndesmophytes, bony bridging, and spondylodiscitis are the most relevant (Figures 9A-3 and 9A-4).

Syndesmophytes are characterized by axial growth that may lead to bridging phenomena. For making a diagnosis, conventional radiography is still the preferred option. However, if the radiographs are persistently normal in the setting of high disease suspicion, MRI of the sacroiliac joints and spine can add information. In contrast to conventional radiographs, MRI has the potential to demonstrate inflammation, not merely the end results of inflammation on bone. Among MRI

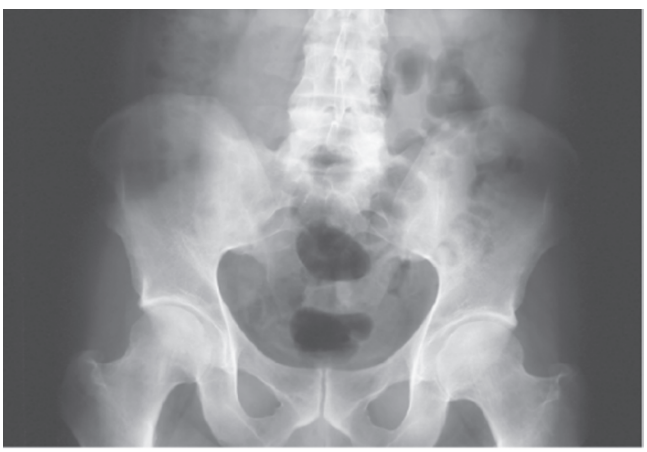

FIGURE 9A-2

Anteroposterior radiographs of the pelvis showing complete ankylosis of both sacroiliac joints and syndesmophyte formation in the lower lumbar vertebrae.

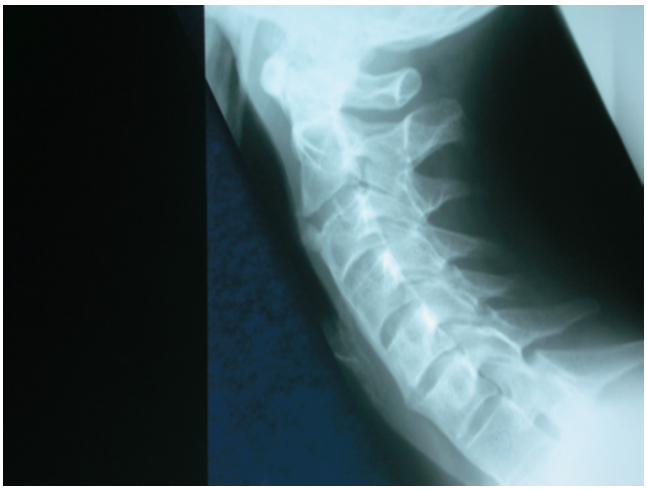

FIGURE 9A-3

Radiograph of the lateral cervical spine, demonstrating the formation of extensive bridging syndesmophytes that involve almost the entire cervical spine.

techniques for delineating inflammation, the short tau inversion recovery (STIR) technique is preferred (Figure 9A-5). MRI is also useful in visualizing enthesitis, for example, of the heel or Achilles tendon insertion.

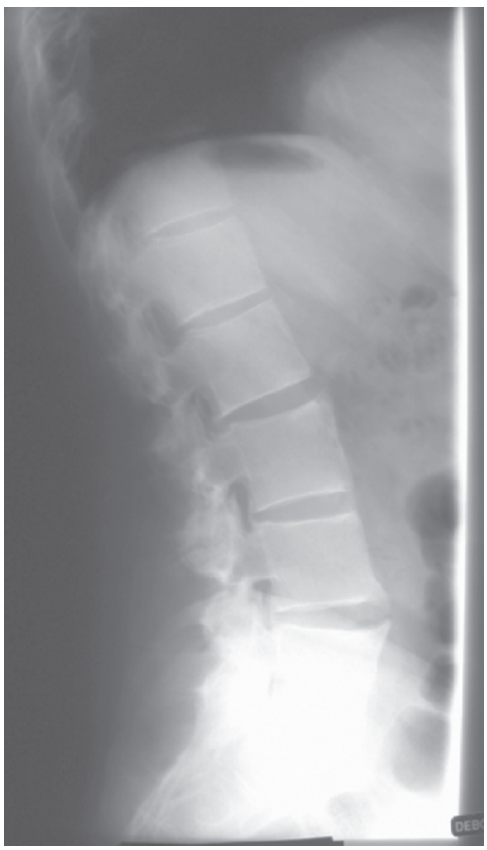

FIGURE 9A-4

Radiograph of the lateral lumbar spine with squaring of L1 and syndesmophyte formation from L3 to L5.

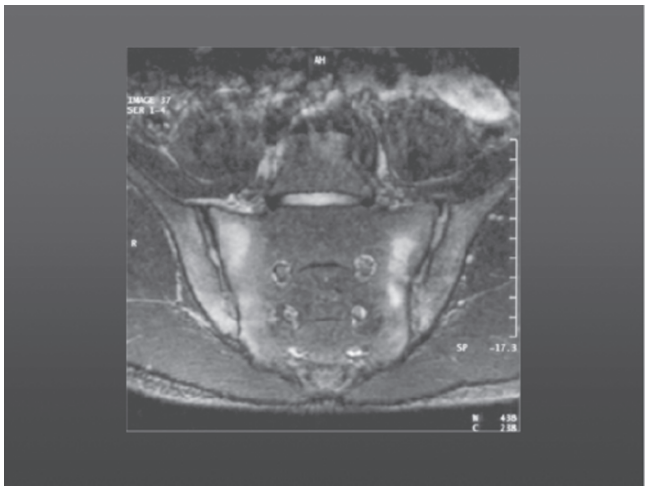

FIGURE 9A-5

Short tau inversion recovery (STIR) image of the sacroiliac joints revealing extensive inflammation (*white*) involving both the sacral and iliac sides of the joints bilaterally.

MAKING THE DIAGNOSIS

As in many other diseases in which the etiology is not clearly defined (e.g., by the isolation of a specific causative pathogen), the diagnosis of AS must rest on the combination of clinical features, radiological findings, and laboratory results. There are no established diagnostic criteria for AS. On the other hand, classification criteria, used for the purpose of categorizing patients in research studies, are available. The most widely used classification criteria for AS are the modified New York criteria (Table 9A-1) (11). Although the New York criteria are useful in established disease, their heavy reliance on the demonstration of radiographic sacroiliitis diminishes their applicability in patients with early disease.

TABLE 9A-1. MODIFIED NEW YORK CRITERIA FOR ANKYLOSING SPONDYLITIS.

Criteria

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

4a. Unilateral sacroiliitis grade 3–4.
4b. Bilateral sacroiliitis grade 2–4.

Definite ankylosing spondylitis if (4a OR 4b) AND any clinical criterion (1–3)

SOURCE: From Van der Linden et al., Arthritis Rheum 1984;27:361–368, with permission of *Arthritis and Rheumatism*.

Classification criteria for spondyloarthritis, although clearly not intended for diagnostic purposes, are used frequently in clinical practice aids to the identification of atypical or undifferentiated cases. Amor's criteria (Table 9A-2) (12) and the European Spondyloarthropathy Study Group criteria (Table 9A-3) (13) are often employed in this manner. Ongoing studies are designed to evaluate the use of classification criteria for the purpose of diagnosis when applied to patients at early stages of disease.

The optimal role of HLA-B27 in establishing the diagnosis of AS remains under investigation. For many years, HLA-B27 was not recommended for use as a diagnostic test. In certain clinical situations, however, when moderate to high suspicion of spondyloarthritis exists, HLA-B27 testing may play an important role (14). At present, only radiographic sacroiliitis is included in the various criteria sets. However, MRI studies confirming the presence of inflammation even before the occurrence of radiographically evident joint damage may contribute to earlier diagnosis.

TABLE 9A-2. AMOR'S CLASSIFICATION CRITERIA FOR SPONDYLOARTHRITIS.

A	CLINICAL SYMPTOMS OR HISTORY OF	SCORING
1	Lumbar or dorsal pain at night or morning stiffness of lumbar or dorsal pain	1
2	Asymmetrical oligoarthritis	2
3	Buttock pain If alternate buttock pain	1 2
4	Sausagelike toe or digit	2
5	Heel pain or other well-defined enthesopathy	2
6	Iritis	1
7	Nongonococcal urethritis or cervicitis within 1 month before the onset of arthritis	1
8	Acute diarrhea within 1 month before the onset of arthritis	1
9	Psoriasis, balanitis, or inflammatory bowel disease (ulcerative colitis or Crohn's disease)	2
B	**RADIOLOGICAL FINDINGS**	
10	Sacroiliitis (bilateral grade 2 or unilateral grade 3)	3
C	**GENETIC BACKGROUND**	
11	Presence of HLA-B27 and/or family history of ankylosing spondylitis, reactive arthritis, uveitis, psoriasis, or inflammatory bowel disease	2
D	**RESPONSE TO TREATMENT**	
12	Clear-cut improvement within 48 hours after NSAIDs intake or rapid relapse of the pain after their discontinuation	2

SOURCE: From Amor B et al., Rev Rheum Mal Ostéoart 1990;57:85–89, by permission of *Revue du rheumatisme et des maladies ostéo-articulaires.*
ABBREVIATIONS: NSAIDs, nonsteroidal anti-inflammatory drugs.
A patient is considered as suffering from a spondylarthropathy if the sum is ≥6.

TABLE 9A-3. THE EUROPEAN SPONDYLARTHROPATHY STUDY GROUP CRITERIA.

Inflammatory spinal pain

OR

Synovitis (asymmetric, predominantly in lower extremities)

AND one or more of the following:
- Family history: first- or second-degree relatives with ankylosing spondylitis, psoriasis, acute iritis, reactive arthritis, or inflammatory bowel disease
- Past or present psoriasis, diagnosed by a physician
- Past or present ulcerative colitis or Crohn's disease, diagnosed by a physician and confirmed by radiography or endoscopy
- Past or present pain alternating between the two buttocks
- Past or present spontaneous pain or tenderness at examination of the site of the insertion—the Achilles tendon or plantar fascia (enthesitis)
- Episode of diarrhea occurring within 1 month before onset of arthritis
- Nongonococcal urethritis or cervicitis occurring within 1 month before onset of arthritis
- Bilateral grade 2–4 sacroiliitis or unilateral grade 3 or 4 sacroiliitis [grades are 0, normal, 1, possible, 2, minimal, 3, moderate, 4, completely fused (ankylosed)]

SOURCE: From Dougados M et al., Arthritis Rheum 1991;34:1218–1230, by permission of *Arthritis and Rheumatism* and Wiley Periodicals, Inc.

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CHAPTER 9

Ankylosing Spondylitis
B. Pathology and Pathogenesis

JUERGEN BRAUN, MD

- Human leukocyte antigen (HLA)-B27 is the major genetic risk factor for ankylosing spondylitis (AS), reactive arthritis, psoriatic arthritis, spondyloarthropathy associated with inflammatory bowel disease, and isolated acute anterior uveitis.
- These diseases are linked by the frequency of inflammation involving the entheses (the sites where tendons and ligaments join to bones) and the axial skeleton, and the common finding of micro- or macroscopic gut inflammation, even in patients without overt gastrointestinal symptoms.
- HLA-B27 transgenic rats develop a spondyloarthropathy.
- HLA-B27 is present in >90% of patients with AS, as well as 50% to 75% of patients with other forms of spondyloarthritides. In contrast, only 5% to 15% of the general population is HLA-B27 positive.
- The contribution of HLA-B27 to AS susceptibility is estimated to be 30%.
- Fewer than 5% of HLA-B27–positive individuals develop SpA.
- Among the HLA class B molecules that determine the antigen binding cleft, HLA-B27 has a unique B pocket that likely influences the peptide repertoire.
- The subtypes of HLA-B27, of which there are more than 30, differ in part only by single amino acids. Only a few HLA-B27 subtypes are associated with AS.
- Intracellular misfolding of HLA-B27 may lead to aberrant expression of B27 homodimers on the cell surface, with possible influences on antigen presentation.

Ankylosing spondylitis (AS) and other spondyloarthritides (SpA) are characterized by inflammation and new bone formation in the axial skeleton and entheses. Peripheral joints and other organs, such as the eye, skin, heart, and gut, may also be involved. Details of the pathogenesis of AS and other SpA remain unresolved, but much has been learned in the three decades since the discovery of HLA-B27, a major histocompatibility complex (MHC) class I allele that is the major genetic factor in these interrelated diseases. HLA-B27 is present not only in most patients with AS, but also in many with other forms of SpA: reactive arthritis (ReA), psoriatic SpA, inflammatory bowel disease (IBD)–associated SpA, and isolated acute anterior uveitis.

Some important considerations related to the origin of AS and related diseases stem from clinical observations. First, the entheses and the axial skeleton are affected much more strongly in patients with SpA than in other rheumatic diseases. Second, microscopic and macroscopic gut inflammation are more frequent in patients with SpA than in other rheumatic diseases (1). The gastrointestinal immune response to pathogens and even normal flora may play a role in causing these disorders.

Several interesting features of the HLA-B27 molecule itself may contribute to disease pathogenesis in the SpA. The following points are explored in further detail in this chapter:

1. Among the HLA class B molecules that determine the antigen binding cleft, HLA-B27 has a unique B pocket that likely influences the peptide repertoire.
2. There are more than 30 subtypes of HLA-B27, which differ in part only by single amino acids. Only a few HLA-B27 subtypes are associated with AS.
3. Intracellular misfolding of HLA-B27 may lead to aberrant expression of B27 homodimers on the cell surface, with possible influences on antigen presentation.
4. HLA-B27 itself can be presented by HLA class II as an autoantigen, and could be recognized by CD4+ T cells.
5. HLA-B27 transgenic rats develop an SpA-like disease.
6. Data suggest that intracellular handling of microbes by HLA-B27 transfected cell lines is altered.

Both genetic and nongenetic factors contribute to AS. In addition to HLA-B27 and other MHC-related genetic factors, current hypotheses implicate both innate and adaptive immune responses. *Chlamydia*, *Yersinia*,

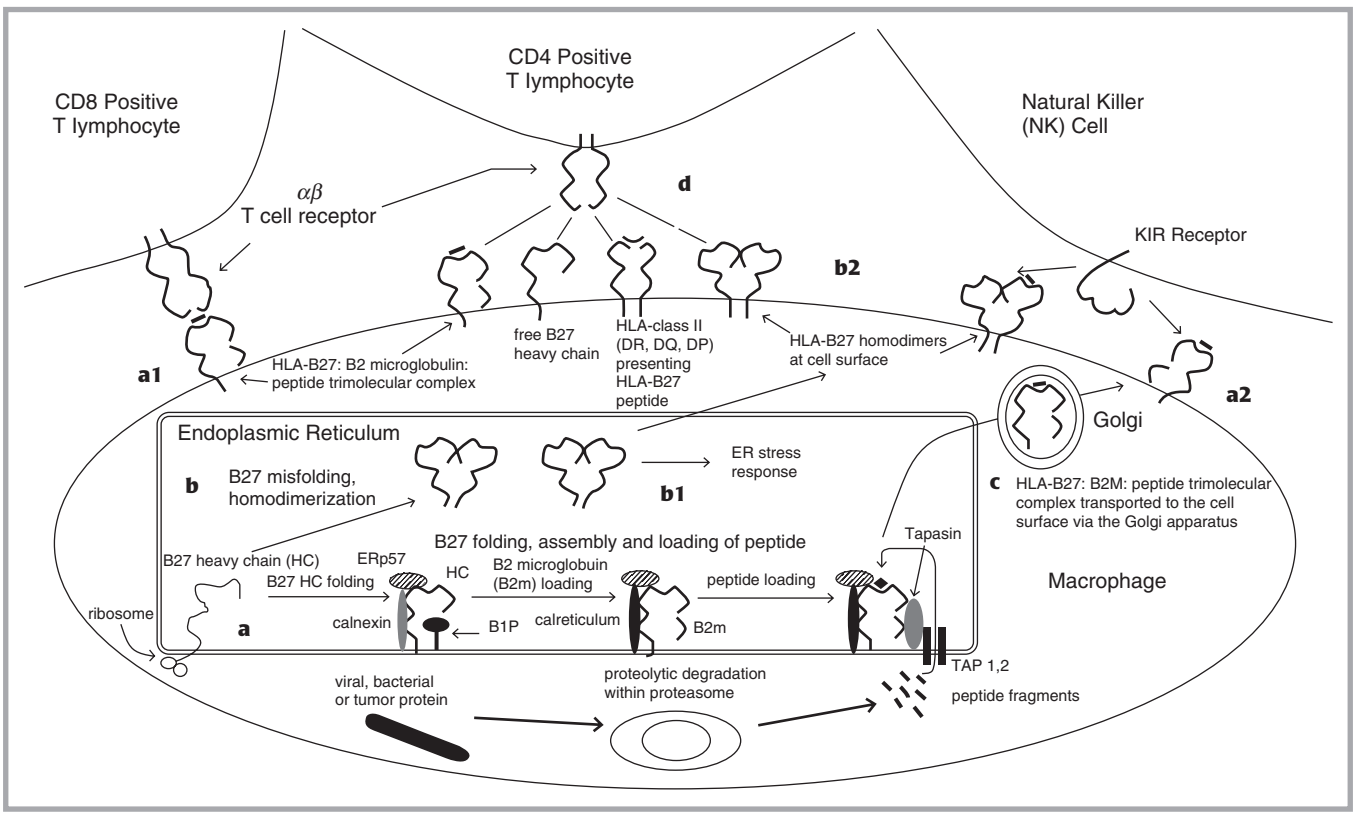
Salmonella, and other species contribute directly to the etiology of ReA, for example, and autoantigens such as the G1 domain of aggrecan have been linked to AS.

Human Leukocyte Antigen-B27

The discovery of the link between HLA-B27 and AS was a major contribution to understanding the pathogenesis of this disease (2). HLA-B27 is present in >90% of patients with AS, as well as 50% to 75% of patients with other forms of SpA. In contrast, only 5% to 15% of the general population is HLA-B27 positive, with variations based on ancestry. The overall contribution of HLA-B27 to AS susceptibility is estimated to be 30%, but the gene is neither necessary nor sufficient to cause the disease. Fewer than 5% of HLA-B27–positive individuals develop SpA, but the individual risk is higher in the setting of a positive family history of SpA (Figure 9B-1) (3). The dominant effect of HLA-B27 in AS

FIGURE 9B-1

Unique intracellular and extracellular functions of HLA-B27 that may affect susceptibility to spondyloarthritis. (a) The HLA-B27 heavy chain is transcribed off ribosomes in macrophages, and retained in the endoplasmic reticulum (ER) by the molecular chaperone calnexin and ERp57. The latter is a protein disulfide isomerase that reduces and oxidizes disulfide bonds. HLA-B27 is then folded into its tertiary structure and bound to beta-2-microglobulin. Calnexin releases the complex, which becomes associated with calreticulum, which in turn chaperones the formation of the peptide loading onto the complex of heavy chain, beta-2-microglobulin and antigenic peptide, via the TAP proteins and tapasin. Thence the trimolecular peptide complex (HLA-B27 heavy chain, beta-2-microglobulin, and peptide) travels to the cell surface, where the antigenic peptide is presented either to CD8+ T lymphocytes or to natural killer (NK) cells. (b) The HLA-B27 heavy chain misfolds in the endoplasmic reticulum, forming B27 homodimers and other misfoldings, where they either (b1) accumulate causing an proinflammatory ER stress response; or (b2) migrate to the cell surface, where they become antigenic themselves or present peptide to receptors on other inflammatory cells. (c) Intracellular impairment of peptide processing or loading into HLA-B27 by viruses or intracellular bacteria causes a selective impairment of the immune response. (d) Either the trimolecular complex presents processed peptide to CD4+ T lymphocytes, or free HLA-B27 heavy chains or HLA-B27 homodimers are recognized as antigenic by the T-cell receptor thence, or processed antigenic fragments of HLA-B27 are presented to the T-cell receptor of CD4−positive T lymphocytes.



makes this disease rather unique among rheumatic conditions. It is clear, however, that other genes also contribute to the risk of AS.

Human leukocyte antigen-B27 is an MHC class I molecule and, as such, participates in antigen presentation. HLA-B27 binds an accessory molecule—beta-2 microglobulin—that helps the heavy chain maintain its proper conformation. Genetic evidence from humans and data from animal models suggest that HLA-B27 has one or more unique characteristics that can promote inflammation. Among individuals with HLA-B27, the protein is expressed ubiquitously but most abundantly on antigen-presenting cells such as macrophages and dendritic cells (DC). HLA-B27 expression is upregulated by proinflammatory stimuli. The peptides displayed by HLA-B27 and related MHC class I molecules are normally derived from self-proteins, but when cells are infected with microbes such as viruses or other intracellular pathogens, foreign peptides are presented.

Peptide-loaded MHC class I molecules are recognized by receptors on several different types of immune cells. T-cell receptors (TCRs) on cytotoxic CD8+ T cells recognize MHC class I complexes. The ability of TCRs on CD8+ T cells to recognize MHC class I molecules and distinguish different alleles or different peptides displayed by the same allele (e.g., viral vs. self-peptide) plays a critical role in the adaptive immune response to viruses.

Hypotheses about the role of HLA-B27 in AS can be considered in terms of two distinct paradigms: one invokes immunological recognition of HLA-B27 expressed on the cell surface, either as classic trimolecular complexes of heavy chain/peptide/beta-2 microglobulin, or beta-2-microglobulin free forms of the heavy chain that exist as dimers or perhaps monomers. The other paradigm posits that intracellular effects of HLA-B27 are responsible for influences on bacterial killing, either due to HLA-B27 misfolding (4) or some other as yet unrecognized consequence of its expression (Table 9B-1). Potential links to pathogenesis from misfolding include endoplasmic reticulum (ER) stress and activation of the unfolded protein response, while enhanced bacterial survival may lead to persistent infection. These concepts also differ in terms of whether the fundamental abnormality is one of adaptive (arthritogenic peptides) or innate immunity (immune receptor recognition, misfolding, altered bacterial survival).

TABLE 9B-1. OVERVIEW OF THE FOUR MAIN THEORIES ON THE PATHOGENESIS OF SPONDYLOARTHRITIDES RELATED TO HLA-B27.

The Arthritogenic Peptide Hypothesis
HLA-B27 binds a unique set of antigenic peptides, bacterial or self, which gives rise to an HLA-B27–restricted cytotoxic T-cell response to such peptides which are presented by disease-associated HLA-B27 subtypes but not by other HLA class I molecules.
Self-Association of the HLA-B27 Molecule
A unique property of HLA-B27 is that its heavy chains can form homodimers in vitro that are dependent on disulfide binding through their cysteine-67 residues in the alpha-1 domain. These homodimers occur as a result of B27 misfolding within the endoplasmic reticulum. The accumulation of misfolded protein may result in a proinflammatory intracellular stress response. Alternatively, B27 homodimers can migrate to the cell surface where they either become antigenic themselves or present peptide to other inflammatory cells.
Alteration of Intracellular Handling of Microbes Due to HLA-B27
HLA-B27 leads to a less effective elimination of microbes, such as salmonella, in conjunction with an upregulated production of cytokines.
Recognition of HLA-B27 as an Autoantigen
HLA-B27 itself can be recognized by CD4+ T cells, when presented by HLA class II (DR, DQ, and DP) heterodimers as an autoantigen. This was also part of the classic molecular mimicry hypothesis, wherein homology of peptides from the HLA-B27 molecule shared striking sequence homology with those from bacterial sources.

Arthritogenic Peptides

The basis for this concept is essentially that of molecular mimicry; that is, self-peptides displayed by folded HLA-B27 heavy chain/beta-2 microglobulin complexes are targeted by autoreactive $CD8^+$ T cells because they resemble microbial peptides (5). In this model, the cytotoxic T cells and the unique peptide binding specificity of HLA-B27 are the main causes of the chronic inflammation. HLA-B27-restricted CD8+ T-cell clones with specificity for bacteria or possibly self-peptides have been detected in both the synovial fluid and peripheral blood of patients with ReA and AS. With regard to ReA, several HLA-B27–binding *Yersinia*- and *Chlamydia*-derived peptides have been identified in synovial fluid that may account for the CD8+ T-cell response. Whether these immune responses are beneficial or detrimental to the patient remains unclear. Autoreactive self-peptides that might be targeted by these T cells have not been defined.

Indirect evidence that antigens might be driving the inflammation comes from analyses of the TCR beta chain (TCRB) repertoire using TCRB CDR3 size spectratyping: HLA-B27+ twin pairs who were concordant for AS exhibited increased T-cell oligoclonality in both CD8+ and CD4+ T-cell subsets, suggesting a role for conventional T-cell antigens in AS pathogenesis.

Although triggering bacterial infections have as yet not been identified in AS, several HLA-B27–binding candidate peptides have been studied. The peptide LRRYLENGK, for example, known to be part of both the HLA-B27 heavy chain and proteins from entero-

bacteriae, was recognized more often by HLA-B27–restricted CD8+ T cells from AS patients compared to controls.

Aberrant Cell Surface Heavy Chains

Human leukocyte antigen-B27 heavy chains exist in aberrant forms on the cell surface. Purified HLA-B27 molecules can refold in vitro without beta-2 microglobulin, for which the formation of disulfide-linked dimers through the unpaired Cys 67 residue (Cys^{67}) is functional. Such dimers form when cell surface heavy chains lose beta-2 microglobulin and undergo endosomal recycling. Furthermore, relatively stable monomeric HLA-B27 heavy chains exist on the cell surface (6). Thus, MHC class I receptors on leukocytes might recognize aberrant forms of HLA-B27 in a specific manner, leading to modification of leukocyte function. The extent to which other alleles form cell surface dimers is less clear.

Enhanced Bacterial Survival

The strong relationship between HLA-B27 and ReA leads to the question of whether HLA-B27 might influence the invasion and the handling of intracellular bacteria. Enhanced survival of intracellular *Salmonella* has been reported in monocytic cells and fibroblasts that express HLA-B27 after DNA transfection. The effect of HLA-B27 seems to depend on the Glu^{45} residue, which may be a major determinant of HLA-B27 misfolding. Data on this point are not conclusive, however, as other experiments have failed to demonstrate an effect of HLA-B27 expression on synoviocytes on the clearance of *Salmonella*.

Protein Misfolding and Endoplasmic Reticulum Stress

Evidence of abnormalities in HLA-B27 folding was first reported a few years ago. HLA-B27 heavy chains, even those expressed under normal physiologic conditions, were described as undergoing ER-associated degradation (ERAD) shortly after synthesis. ERAD is a quality control pathway that cells use to dispose of proteins that do not fold efficiently. Abnormally folded HLA-B27 complexes have been found in the ER, with abnormalities relating to aberrant inter- and intrachain disulfide bonds.

In normal cells, the dimers that form in the ER do not contribute to the cell surface population. About 25% of newly synthesized HLA-B27 heavy chains form disulfide-linked complexes in the ER, whereas only about 6% become disulfide-linked on the cell surface. Another critical feature of misfolding is prolonged binding of the heavy chain to the ER chaperone BiP. Misfolding has not been seen in other MHC class I alleles. HLA-B27 misfolding and cell surface dimerization are distinct processes.

The tendency of HLA-B27 to misfold is a consequence of residues that comprise the B pocket of the peptide-binding groove. The B pocket renders HLA-B27 inefficient at loading peptides because of resistance to the peptide-induced conformational change that promotes folding. Prolonged retention of the HLA-B27 heavy chain in the ER in an unfolded conformation results in aberrant disulfide bond formation, with possible involvement of the unpaired Cys at position 67 (Cys^{67}). Aberrant disulfide bond formation may contribute to the accumulation of heavy chains bound to BiP. The amino acid residue in HLA-B27 most detrimental to efficient folding, not surprisingly, is Glu^{45} in the B pocket. Some proteins that misfold are not eliminated efficiently and may lead to stress in the ER by activating a process known as the unfolded protein response.

Human Leukocyte Antigen-B27: A Causative Factor for Disease in Animal Models

The immunologic function of HLA-B27 is to bind peptides derived from proteins degraded in the cytosol and display them on the cell surface, where they can be recognized by CD8+ T cells. In transgenic animal models, HLA-B27 and human beta-2-microglobulin were expressed in mice without producing inflammatory joint disease. In other HLA-B27 transgenic mice models, a higher frequency of ankylosing enthesopathy was reported, but this phenotype occurs also in wild-type mice.

The strongest experimental evidence that HLA-B27 plays a direct role in disease pathophysiology comes from transgenic rats, where overexpression of HLA-B27 and human beta-2-microglobulin results in spontaneous inflammation in the gastrointestinal tract and joints (7). The skin and nail lesions in this transgenic rat model resemble those seen in psoriasis HLA-B27/human beta-2-microglobulin transgenic (B27-Tg) rats, which develop colitis initially and subsequently manifest inflammation in other locations. Expression of the disease phenotype depends on the specific genetic background of the rat. When raised under entirely germ-free conditions, B27-Tg rats do not develop disease. Colonization of the gastrointestinal tract with normal gut flora, however (e.g., *Bacteroides* sp.), is sufficient to trigger inflammation. B27-Tg rats do not provide a precise phenocopy of human AS because they do not develop ankylosis of the axial skeleton. Further, the colitis observed in the B27-Tg rats is more prominent than that which occurs in human AS patients.

THE ROLE OF MICROBES AND THE GUT

Several gastrointestinal or genitourinary pathogens have been implicated as triggers of HLA-B27–associated ReA in humans, including *Campylobacter*, *Chlamydia*, *Salmonella*, and *Shigella*. DNA from these organisms can be detected by polymerase chain reaction (PCR) in synovial samples, and the lipopolysaccharide (LPS) of *Salmonella*, *Yersinia*, and *Shigella* has also been found. The presence of bacterial products in joints provides a potential link between gut infection and joint inflammation in ReA (1). More than two thirds of patients with SpA have microscopic lesions of the gut: polymorphonuclear infiltration of ileal villi and crypts, and granulocytes, lymphocytes, and plasma cells in the lamina propria. Patients who develop overt inflammatory bowel disease are more likely to have symptoms of active AS, and SpA patients with gut inflammation have a higher risk of developing AS.

In juvenile AS patients without gastrointestinal symptoms, radionuclide labeling of lymphocytes indicate homing to the gut in almost half of the patients. Positive scans are in patients with active joint disease and correlate with nonspecific mucosal inflammatory changes on biopsy. Thus, subclinical gut inflammation may be important in disease pathogenesis. In this regard, CD163+ macrophages are overrepresented in the gut mucosa of patients with SpA and Crohn's disease, but not ulcerative colitis. These findings have underscored the close relationship between gut inflammation and arthritis in the SpA.

Human Leukocyte Antigen-B27 SUBTYPES

Human leukocyte antigen-B27 constitutes the greatest known risk factor for AS. However, HLA-B27 is not just one molecule: more than 30 different subtypes have now been described (http://www.ebi.ac.uk/imgt/hla/). Most of these subtypes only differ by a few amino acids, but these differences may be sufficient to alter the peptide binding properties of the molecule.

*Human leukocyte antigen-B*2705*, found in all populations, appears to be the original or parent HLA-B27 molecule. Most of the other subtypes have probably evolved from three pathways, defined by the pattern of amino acid substitutions in the first (alpha-1) and second (alpha-2) domains (Figures 9B-2 and 9B-3). The finding of particular HLA-B27 subtypes in populations tends to have strong geographic patterns. The most common subtypes—*HLA-B*2705, -B*2702, -B*2704, -B*2707*—are clearly associated with SpA.

The HLA-B27 subtypes are distributed unevenly around the world. Whereas HLA-B*2709 is found primarily in Sardinia and regions of mainland Italy, -B*2706 is common in native Indonesians. Although neither -B*2709 nor -B*2706 appears to be associated with AS, B*2709 has been reported in patients with undifferentiated forms of SpA (uSpA).

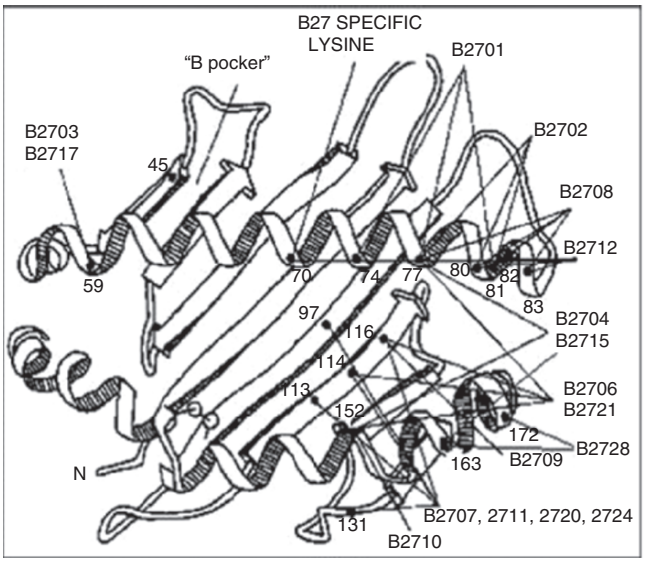


FIGURE 9B-2

The crystallized HLA-B27 molecule, indicating positions of amino acid substitutions in selected HLA-B27 subtypes.

Variations in the clinical phenotype associated with HLA-B27 subtypes likely relate to amino acid differences in the B pocket of the antigen binding cleft, which could alter the nature of the peptides presented by these HLA-B27 subtypes. The only xdifference between these subtypes and the major AS-associated subtypes is the exchange at position 116 of an aspartate for a histidine residue. Position 116, located within the peptide binding groove at the floor of the F pocket, plays a pivotal role in anchoring the C-terminal peptide residue. Other subtypes of HLA-B27 are too rare to have had their clinical associations established, but cases of AS have occurred in carriers of *-B*2701, *2703, *2704, *2707, *2708, *2710, *2714, *2715*, and **2719*.

Until recently, the only known differences between these subtypes was their peptide binding specificity, which has been used to support the concept that disease pathogenesis is a consequence of peptide display differences. For the $VIP1R_{400–408}$ peptide, this is clearly not the case because it is presented by both -B*2705 and -B*2709. However, there are interesting differences between -B*2706 and other disease-associated alleles. Comparing -B*2704, -B*2705, -B*2706, and -B*2709, -B*2706 is the only subtype that does not interact appreciably with the peptide loading complex (8). The -B*2706 heavy chain also folds faster than other subtypes. This raises the possibility that the -B*2706 heavy chain might show a diminished capacity to misfold and cause ER stress because mutations that enhance the

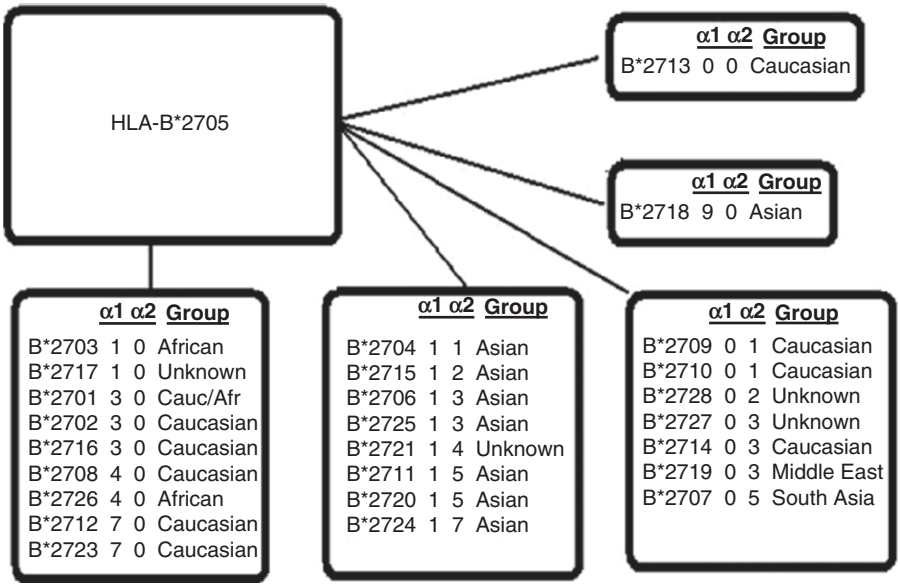


FIGURE 9B-3

Possible evolutionary pathway of HLA-B27 subtypes from the parent *HLA-B*2705.* The three major families of HLA-B27 subtypes are denoted in relationship to the parent subtype *HLA-B*2705* (*HLA-B*2713* and *B*2718* are assumed to have evolved separately). The numbers of amino acid substitutions from B*2705 in the first (alpha-1) and second (alpha-2) domains are indicated, as well as the predominant ethnic group in which the subtype was described. For example, *HLA-B*2704* differs from HLA-B27 by one amino acid substitution in the alpha-1 and one amino acid substitution in the alpha-2 domain. Of note, at the time of this writing, we are unable to find the sequences of four HLA-B27 subtypes that have been described only in the past few months (*B*2729–B*2732*).

rate of -B*2705 folding reduce misfolding. If this is responsible for the lack of association with disease, then another explanation would be necessary for -B*2709.

OTHER MAJOR HISTOCOMPATIBILITY COMPLEX GENES AND ANKYLOSING SPONDYLITIS SUSCEPTIBILITY

Human leukocyte antigen-B27 constitutes only part of the overall risk for SpA. Fewer than 5% of HLA-B27–positive individuals in the general population develop an SpA. In contrast, up to 20% of HLA-B27–positive relatives of AS patients will develop an SpA in time. Family studies have shown that HLA-B27 contributes less than 40% of the overall genetic risk for SpA. The entire effect of the MHC, on the other hand, is about 50%.

Identifying other MHC genes that may be involved in AS susceptibility is generally complicated because of the tight linkage disequilibrium found within the MHC. However, there is some evidence from studies of individual MHC genes that other non-B27 MHC genetic effects are present in patients with AS. These genes are listed in Table 9B-2.

NON–MAJOR HISTOCOMPATIBILITY COMPLEX GENES AND ANKYLOSING SPONDYLITIS SUSCEPTIBILITY

The strength of the association of B27 and of the linkage of the MHC with AS has obscured the role of other genetic factors for decades. The concordance rate for B27-positive dizygotic (DZ) twin pairs (23%), considerably lower than that of monozygotic (MZ) twin pairs (63%), points clearly to the presence of non-B27 susceptibility factors (9).

The total number of genes involved in susceptibility to AS is unknown, but family recurrence risk modeling suggests that the number is limited. The reduction of disease concordance with distant relatives of patients is determined by the number and the interactions of the involved genes. In AS, an oligogenic model appears to be operative, with multiplicative interactions between loci.

Non-major histocompatibility complex genetic effects appear to also have significant influence on disease severity, as demonstrated by a complex segregation study (10). A high degree of familiality was observed

TABLE 9B-2. GENES POSSIBLY INVOLVED IN THE PATHOGENESIS OF ANKYLOSING SPONDYLITIS.

Major histocompatibility complex (MHC)
HLA-B27
HLA-B60
HLA-B38,-B39
MICA
MHC class II alleles including HLA-DRB1*01 and DRB1*04
TAP alleles
Low molecular weight proteosome (LMP) -2 and -7
Tumor necrosis factor (TNF) alpha (TNF-308 polymorphism)
Non–major histocompatibility complex
Interleukin 1 complex
Interleukin 6
Interleukin 10
Transforming growth factor (TGF) beta
Alpha/beta T-cell receptor (TCR)
Cytochrome P450 gene debrisoquine 4-hydroxylase (CYP2D6)
CARD15
Vascular endothelial growth factor (VEGF) polymorphisms
TLR4, CD14, NFKB1, MMP3, PTPN22, alpha-1-antitrypsin, secretor status, and immunoglobulin allotypes
Ank (extracellular inorganic pyrophosphates)

for disease activity and function, with heritability estimated at 51% and 68%, respectively. High heritability of radiographic severity was demonstrated. The heritability observed was clearly due to non-B27 factors because all patients in the study were HLA-B27 positive.

Genomewide linkage studies in AS and SpA have detected strong suggestions of linkage at chromosome 16q (11). Other regions achieving moderate evidence of linkage have been identified on chromosomes 3, 10, and 19. On chromosome 3, peak linkage was seen at 202 cM, and on chromosome 10, at 127 cM. Loci previously associated with AS on chromosome 2q (the *IL-1* gene cluster) and 22q (*CYP2D6*) had nominal linkage in a meta-analysis (12), providing further statistical support for their involvement in susceptibility to AS.

In a genomewide study of 151 affected sibling pair families, linkage with disease activity was observed on chromosomes 11q, 16p, 18p, and 20q, with age of symptom onset on chromosome 11q, and with function on chromosome 2q (12). Five regions on chromosomes 3p, 11p and 11q, 16p and 18p were linked to more than one phenotype studied, making the likelihood of chance findings low. MHC genes were associated with susceptibility to SpA, but not with disease severity or age of onset.

Association studies in different populations have shown that implicated variations in *IL-1* gene family members are associated with susceptibility to AS. The interleukin 1 complex on chromosome 2 includes the genes encoding IL-1 alpha, IL-1 beta, and their naturally occurring inhibitor, IL-1 receptor antagonist (IL-1RA), along with six other homologous genes named *IL-1F5–10*. These cytokines, all strong candidates for involvement in inflammatory diseases, lie directly below the 2q peak found in AS linkage studies. The agreement of some large studies implicates *IL-1A/B* variants strongly in the etiology of AS, but key variants remain to be identified. Observational studies of IL-1 inhibition with anakinra in patients with AS have shown conflicting results. Based on the results of genetic studies to date, however, rigorous investigations of this therapy in AS would seem appropriate.

HISTOPATHOLOGY IN ANKYLOSING SPONDYLITIS

The most common sites of inflammation in AS include sacroiliac joints, entheses, vertebral bodies adjacent to intervertebral disks, peripheral joints, gastrointestinal tract, and the eye. Many of these lesions are poorly accessible, so information on their histopathology is limited. In immunohistologic studies on early sacroiliitis in SpA, synovitis with myxoid-appearing bone marrow, pannus formation, and granulation tissue have been described. CD4+ and CD8+ T cells and CD68+ macrophages are accompanied by proliferating fibroblasts and neovascularization. Overexpression of tumor necrosis factor alpha (TNF-alpha) and expression of transforming growth factor beta (TGF-beta) mRNA were found. Destroyed bone is partly replaced, and endochondral ossification results in bony ankylosis.

In studies of peripheral synovitis (not restricted to patients with AS), increased vascularity, endothelial cell activation, and expression of adhesion molecules and chemotactic factors have been observed. Infiltrating cells include activated T lymphocytes, with CD4+ T cells often predominating over CD8, natural killer (NK) cells, B lymphocytes, and CD68+ macrophages. Although the total numbers of CD68+ macrophages are similar in SpA, macrophages expressing the hemoglobin scavenger receptor CD163 are increased in both synovial tissues and the colonic mucosa of patients with SpA. The cell surface expression of CD163 defines a cell population that produces more TNF-alpha and less IL-10, indicating a T-cell helper (Th1) response.

Enthesitis, a hallmark of SpA, is characterized by erosive, inflammatory lesions associated with an abundance of osteoclasts and infiltration of the bone marrow. Lymphocytic infiltration of CD8+ and CD4+ T cells is found in established disease. In earlier enthesitis, CD68+ macrophages predominate.

With regard to joint inflammation, there are more similarities than differences between the SpA and other forms of inflammatory arthritis. Macrophages appear to play an important role in early disease, but T cells are clearly involved. Both innate and adaptive immune

responses may have a role in SpA. The observation that TNF-alpha is overexpressed in sacroiliac joints provided a strong rationale for the use of TNF inhibitors, which are very efficacious in SpA.

CYTOKINE EXPRESSION IN ANKYLOSING SPONDYLITIS

The inflammation associated with AS and SpA has also been examined by assessing cytokine production. Enzyme-linked immunosorbent assay (ELISA) techniques have been used to measure serum cytokine levels, and fluorescent-activated cell sorting (FACS) technology to assess the percentage of cells producing cytokines in peripheral blood. Serum cytokines are difficult to measure because their half-lives are short and differ between cytokines. Although the measurement of TNF-alpha serum levels does not seem useful in clinical practice, IL-6 levels are increased in AS patients, correlate with other measures of disease activity, and reflect responses to therapy.

Studies examining T cells in SpA have mostly shown a decrease in Th1 cytokine-producing cells. The T cells of HLA-B27+ patients with AS and healthy HLA-B27+ individuals produce less TNF-alpha and interferon gamma (IFN-gamma) than do those of healthy HLA-B27+ controls. An impaired Th1 response could hinder elimination of intracellular pathogens and lead to a chronic infection. However, a primary Th1 deficit in all HLA-B27+ individuals seems unlikely, and its presence in the majority of active SpA patients is unclear. The presumed Th1 deficit improved after treatment with certain TNF inhibitors, but not others (13).

Cytokine production by antigen-presenting cells, such as macrophages and dendritic cells (DCs), plays a critical role in directing adaptive immune responses. One important recognition system is the family of Toll-like receptors (TLR), which induces cytokine production such as TNF-alpha and IL-6 by activation of NF-κB. Thus, TLRs sit at the crossroads of innate and adaptive immunity, where microbial invasion is translated from nonspecific to antigen-specific inflammatory responses. This may be critical for the pathogenesis of SpA.

NEW BONE FORMATION

The remodeling of bone leading to the squaring of the vertebral bodies in AS is the result of acute and chronic spondylitis. The inflammatory process leads to the destruction and simultaneous rebuilding of both the cortex and the spongiosa of the vertebral bodies. The development of square vertebral bodies is based on a combination of a destructive osteitis and repair. The process of joint ankylosis partially recapitulates embryonic endochondral bone formation in a spontaneous model of arthritis in DBA/1 mice. Bone morphogenetic protein (BMP) signaling is a key molecular pathway involved in this pathology. Systemic gene transfer of noggin, a BMP antagonist, is effective both as a preventive and a therapeutic strategy in this mouse model, interfering with enthesial progenitor cell proliferation (14). Immunohistochemical staining for phosphorylated smad1/5 in entheseal biopsies of SpA patients reveals active BMP signaling in similar target cells. This suggests a role for BMPs in the pathogenesis of AS.

Ankylosing spondylitis patients frequently are treated with nonsteroidal anti-inflammatory drugs (NSAIDs), including selective cyclooxygenase (COX)-2 inhibitors. COX-2 is an inducible enzyme that converts arachidonic acid to prostaglandin E2, a modulator of bone metabolism. The inhibition of radiographic progression by continuous intake of NSAIDs may be explained by the inhibition of prostaglandins by NSAIDs. Several animal and in vitro studies demonstrated impaired bone healing in the presence of NSAIDs. The steps involved in bone healing include an inflammatory response, bone resorption, and new bone formation. Prostaglandins have been shown to elicit and participate in inflammatory responses, enhance osteoclast activity and subsequent bone resorption, and increase osteoblast activity and new bone formation. By inhibiting COX and the subsequent production of prostaglandins, NSAIDs act in an anti-inflammatory mode and may inhibit new bone formation simultaneously.

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CHAPTER 9

Ankylosing Spondylitis
C. Treatment and Assessment

JOHN C. DAVIS, JR., MD, MPH

- Multiple modalities for the therapy of ankylosing spondylitis (AS) are available, including physical therapy and patient education, nonsteroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, disease-modifying antirheumatic drugs (DMARDs), and anti–tumor necrosis factor (TNF) agents.
- Combination approaches to therapy are often required to relieve symptoms, improve function, and potentially modify disease progression.
- In assessing patient outcomes in clinical trials, disease activity is measured by the Bath Ankylosing Disease Activity Index (BASDAI), which includes six patient-oriented questions based on fatigue, overall back and hip pain, peripheral arthritis, entheses, and the duration and intensity of morning stiffness.
- Physical therapy and stretching exercises are cornerstones of AS treatment, regardless of which other therapies are employed.
- Indomethacin is the most commonly prescribed NSAID for AS treatment, but other NSAIDs are comparable to indomethacin in efficacy and safety.
- Tumor necrosis factor inhibitors (etanercept, infliximab, and adalimumab) demonstrate striking efficacy in the majority of patients with AS.
- For patients with AS and concomitant inflammatory bowel disease, a monoclonal antibody approach to the inhibition of TNF (i.e., either infliximab or adalimumab) is preferred.

Ankylosing spondylitis (AS) is the prototype of chronic inflammatory diseases of the spine known as the spondyloarthropathies (SpA). Patients present with significant inflammatory back pain and may progress, in severe forms, to fusion of the entire spine. AS may also involve peripheral joints, entheses, and non-articular structures (such as the gut and anterior chamber of the eye). Accordingly, these manifestations should be taken into account when assessing and treating the patient. Recently, the treatment goal in AS has evolved from providing only symptomatic relief to inducing major clinical responses and potentially disease-modifying benefits. Multiple modalities are available, including physical therapy and patient education, nonsteroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, disease-modifying antirheumatic drugs (DMARDs), and anti–tumor necrosis factor (TNF) agents (Table 9C-1). No single modality treats all manifestations of a patient with AS. Combination approaches to therapy are often required to relieve symptoms, improve function, and potentially modify disease progression.

DISEASE ACTIVITY AND CLINICAL ASSESSMENT

Other than a complete medical history and physical examination, a core set of domains and instruments has been recommended by the Assessments in Ankylosing Spondylitis Working group (ASAS) for monitoring patients in the clinical setting (Table 9C-2) (1). These include measures of physical function, pain, spinal mobility, patient's global assessment, duration of morning stiffness, involvement of peripheral joints and entheses, acute phase reactants, and fatigue. Overall disease activity should be measured by the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), which includes six patient-oriented questions based on fatigue, overall back and hip pain, peripheral arthritis, entheses, and the duration and intensity of morning stiffness (Table 9C-2). In addition, a physician global assessment, taking into account available clinical, laboratory, and imaging data, should be performed using either a visual analog scale or a numeric ranking scale.

TABLE 9C-1. SUMMARY OF THERAPIES FOR ANKYLOSING SPONDYLITIS.

TREATMENT	EFFICACY
NSAIDs	Provide symptom relief, may reduce inflammation May influence radiographic progression
Muscle relaxants	May reduce stiffness, but not evaluated in clinical trials
Glucocorticoids	Oral: useful for treatment of peripheral arthritis Injected glucocorticoids may be useful for spine disease, enthesitis, and peripheral arthritis Topical: effective in AAU
MTX	Limited/no evidence of efficacy
SSZ	Limited effectiveness, decrease in ESR and morning stiffness; peripheral arthritis possible benefit
Thalidomide	Provides clinical improvement in small clinical trials
Pamidronate	Provides clinical improvement in small clinical trials
Etanercept	Supported by clinical trials, may impact disease progression; MRI/DXA
Infliximab	Supported by clinical trials, may impact disease progression; MRI/DXA
Adalimumab	Supported by clinical trials, impact on disease progression under study
Leflunomide	No evidence of efficacy
Anakinra	No evidence of efficacy

ABBREVIATIONS: AAU, acute anterior uveitis; DXA, dual-energy x-ray absorptiometry; ESR, erythrocyte sedimentation rate; MRI, magnetic resonance imaging; MTX, methotrexate; NSAIDs, nonsteroidal anti-inflammatory drugs; SSZ, sulfasaliazine.

PHYSICAL THERAPY, EXERCISE, AND PATIENT EDUCATION

The cornerstone of therapy for all patients includes physical therapy, exercise, and patient education in conjunction with any pharmacologic intervention. There are, however, limited and conflicting data on which specific approach is most appropriate (2). In a meta-analysis, group exercise in a hospital setting was reported to be more effective than a home-based program (3). Spa therapy programs used in addition to standard medications and group physical therapy programs have been reported to add additional benefit in terms of clinical response and cost savings (4,5). Decreased range of motion and kyphosis of the spine are significant contributors to morbidity, and a regular, individualized exercise program is important for maintenance of function and posture. Extended periods of immobility, including car and plane travel, should be minimized and interrupted with breaks to permit frequent stretching. Sleeping with a thin pillow and lying in a straight position are preferred. Deep breathing exercises and avoidance or discontinuation of smoking should be emphasized. Patient support groups such as the Spondylitis Association of America (http://www.spondylitis.org) are of tremendous benefit in terms of education and additional resources available to patients.

TABLE 9C-2. ASSESSMENT OF DISEASE ACTIVITY.

ASAS CORE SET FOR DAILY PRACTICE

Domain	Recommended instrument
Physical function	BASFI or Dougados Functional Index
Pain	VAS—total back pain and nocturnal back pain over the past week
Spinal mobility	Chest expansion, Schober Test, occiput to wall, and lateral lumbar flexion
Patient global assessment	VAS—over the past week
Stiffness	Duration of morning stiffness over last week
Peripheral joints and entheses	Number of swollen joint counts, enthesitis score such as developed in San Francisco, Maastricht, or Berlin
Acute phase reactants	ESR or CRP
Fatigue	VAS or fatigue question on BASDAI
BASDAI	Calculated by averaging questions 5 and 6 and then averaging this sum with questions 1–4 VAS overall level of fatigue/tiredness VAS overall level of AS neck, back, or hip pain VAS overall level of pain/swelling in joints other than neck, back, or hips VAS overall discomfort from any areas tender to touch or pressure VAS overall level of morning stiffness from time of awakening Duration and intensity of morning stiffness from time of awakening (up to 120 minutes)

ABBREVIATIONS: ASAS, Assessments in Ankylosing Spondylitis Working Group; BASDAI, Bath Ankylosing Spondylitis Functional Index (BASFI); CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; VAS, visual analog scale (VAS can be replaced with a numeric rating scale).

PHARMACOLOGIC MODALITIES

Tricyclic Antidepressants and Muscle Relaxants

Sleep disturbances and fatigue are common symptoms of AS. Amitriptyline was studied over a 2-week period in a small randomized trial (6). The authors reported improvement in sleep and reduced disease activity, with minimal side effects. Patients with a significant degree of stiffness and muscle spasm may respond to a combination of NSAIDs (see below), analgesics, and muscle relaxants, particularly when initiating physical therapy.

Nonsteroidal Anti-Inflammatory Drugs

Nonsteroidal anti-inflammatory drugs, commonly prescribed as first-line therapy, have been proven effective in relief of axial and peripheral symptoms (including arthritis and enthesitis). A rapid response to NSAIDs (within 48 hours) has also been included in classification criteria for SpA. Indomethacin is the most commonly prescribed NSAID for AS treatment, but other NSAIDs are comparable to indomethacin in efficacy and safety. (As is true with the use of NSAIDs in other disorders, patients may develop individual choices regarding which NSAID is most effective for them.) A randomized trial of the cyclooxygenase-2 (COX-2) selective agent celecoxib showed similar efficacy to the nonselective agent ketoprofen and superiority to placebo in both global and spinal pain measurements (7). In addition, a post hoc analysis of patients in this study treated with continuous versus on-demand celecoxib reported a small decrease in radiographic progression (8). Adequate doses of at least two different NSAIDs should be tried for several weeks before concluding that a patient's response to NSAIDs has been suboptimal. For patients with moderate-to-severe disease, the high frequency of adverse effects and a lack of efficacy in limiting disease progression may require that other agents be used in conjunction with NSAIDs. Selective COX-2 inhibitors should be reserved for those who have contraindications to conventional NSAIDs and no cardiovascular risk factors.

Glucocorticoids

Oral glucocorticoids have limited efficacy in the treatment of AS. Both axial and peripheral joint pain and swelling may respond in the short term to oral glucocorticoids, but long-term use is associated with significant morbidities, including osteoporosis and vertebral fracture. Intravenous methylprednisolone (either 375 mg/day or 1000 mg/day) for 3 days has been reported to produce improvement in morning stiffness, back pain, and spinal mobility for up to 21 months, but trials to date have been uncontrolled and no difference in response has been noted between the two doses (9,10). Local glucocorticoid injections of joints and, less frequently, entheses can provide temporary relief of symptoms but may cause side effects such as tendon rupture. (Glucocorticoid injections of tendons are *not* advised.) Injections are preferable to systemic glucocorticoids for treatment of oligo- or monoarticular arthritis. Fluoroscopic or computer tomography (CT)-guided glucocorticoid injections of the sacroiliac joints was shown to provide symptomatic relief in a double-blind study (11). Acute anterior uveitis (AAU) is the one manifestation of AS that responds effectively to topical glucocorticoids. Prompt evaluation and treatment of AAU with a combination of glucocorticoid eyedrops and a mydriatic agent are critical for the prevention of ocular sequelae (synechiae formation between the iris and lens).

Pamidronate and Thalidomide

Pamidronate is an intravenously administered bisphosphonate. Several studies reported the effects of bisphosphonates on bone metabolism, inflammation, and immune regulation (12–14). In both open-label and blinded studies, monthly infusions of pamidronate decreased disease activity and produced improvement in the functional, outcomes global measures, and spinal mobility (15,16). The most common side effects of therapy were musculoskeletal complaints following the first infusion and transient lymphopenia.

Thalidomide is a glutamic acid derivative that produces anti-inflammatory and immunomodulatory effects, including a reduction in TNF production (17). Early reports of its use in AS came from a study from France demonstrating reductions in clinical symptoms and a reduction in acute phase reactants (18). Two open-label studies reported on a total of 43 patients (19,20). In a year-long study of 30 patients, 80% showed a clinical response (20% in several parameters) (20). Secondary outcomes, including reductions in acute phase reactants, were also observed. Maximum beneficial effects of thalidomide were observed following 6 to 12 months of therapy, and relapse occurred 3 months after discontinuation. In a 6-month study of patients with severe, refractory AS, 4 of 10 patients achieved significant improvement and 4 of 10 patients achieved a moderate response (19). The tolerability and side effects of thalidomide vary significantly between studies and

may represent differences in dosing regimens. Commonly reported side effects include drowsiness, constipation, dizziness, headache, nausea/vomiting, and paresthesias. Peripheral neuropathy (often irreversible) is an important long-term concern with thalidomide.

Sulfasalazine

Sulfasalazine (SSZ), a salicyclic acid derivative created by covalent linkage of 5-amino-salicyclic acid (5-ASA) to sulfapyridine, is cleaved by bacteria in the colon. The 5-ASA absorption is limited to the colonic wall, where the drug is effective in inflammatory bowel disease. The sulfapyridine moiety, absorbed through the gastrointestinal wall, acts as systemic effects in several autoimmune diseases (21). A meta-analysis of five randomized, controlled trials involving a total of 272 patients was published in 1990 (22). Doses ranged from 2 to 3 g/day for 3 to 11 months. Benefit was demonstrated in clinical and laboratory parameters, including the severity and duration of morning stiffness and the severity of pain. General well-being, acute phase reactants, and spinal mobility measurements showed nonsignificant trends in favor of SSZ. Only one of the five trials in this meta-analysis evaluated response rates in axial versus peripheral symptoms, with a nonstatistically significant trend favoring response of peripheral symptoms (23).

METHOTREXATE

The limited studies of methotrexate (MTX) available have shown little benefit in the treatment of AS, in contrast to the proven long-term efficacy and tolerability in rheumatoid arthritis and psoriatic arthritis. In an open-label study of MTX (7.5–15 mg once a week), 9 of 11 patients who had previously demonstrated inadequate response to either NSAIDs or sulfasalazine were evaluated at 24 weeks. The small study reported a reduction in the number of swollen joints in patients with a predominance of peripheral arthritis (24). Two patients with significant extra-articular disease (both with enthesitis and iridocyclitis) discontinued MTX due to continued disease activity. A randomized, placebo-controlled trial of MTX in AS failed to demonstrate significant benefit in either axial or peripheral arthritis, but there was a trend toward a reduction in peripheral symptoms (25). A more recent small study evaluated MTX in a dose of only 7.5 mg/week in patients with AS treated for 24 weeks (26). This study reported a composite response rate of over 50% (n = 17) in those receiving MTX, compared with 17% in the placebo group (despite the relatively low dose of MTX used in the study). Long-term data in MTX-treated patients are not available.

BIOLOGIC AGENTS

There is no evidence that the conventional therapies discussed so far actually modify disease progression. In contrast, there is a growing body of evidence that demonstrates the clinical efficacy of TNF blockade. Multiple studies have demonstrated that TNF-alpha appears to play a key role in promoting inflammation in AS. Increased TNF-alpha expression is found in the sacroiliac joints, peripheral synovial tissue, and serum of patients with AS (27–31). Following a series of randomized, controlled clinical trials, three TNF inhibitors are either approved for the treatment of AS or the subject of ongoing study—etanercept, infliximab, and adalimumab.

Etanercept

Etanercept is a soluble fusion protein containing an Fc fragment of human IgG_1 fused to two extracellular domains of the p75 TNF receptor. The medication's mechanism of action is to bind soluble forms of TNF-alpha, thereby preventing attachment of the cytokine to cell surface receptors. Etanercept is given in doses of 50 mg subcutaneously per week (alternatively 25 mg twice weekly). The efficacy of etanercept in AS was demonstrated in a double-blind, placebo-controlled trial of 40 patients with active spondylitis (32). Patients had moderate-to-severe disease despite stable doses of NSAIDs, DMARDs, or glucocorticoids. Patients randomized to the etanercept group demonstrated a rapid and sustained response in four primary outcome measures: duration of morning stiffness, nocturnal pain, patient's global assessment, and functional index. A number of secondary outcomes also improved, including spinal and chest range of motion, enthesitis, and acute phase reactants. The most frequent side effects were injection-site reactions and minor infections, which did not differ statistically between the two groups. These results were confirmed in a larger randomized, placebo-controlled trial in patients with moderate to severe disease (33). A significant percentage of patients achieved the primary outcome, defined by the ASAS Working Group 20% improvement criteria (ASAS20) compared to placebo at both 12 and 24 weeks. These results were sustained through 2 years (34).

Early evidence of the benefit of etanercept by MRI was published in an uncontrolled study of 10 patients with active spondylitis (35). Repeated MRIs demonstrated a 86% reduction or resolution in acute inflammatory bone lesions over 24 weeks. Moreover, no new bone lesions were identified over this period. These results were confirmed by a larger MRI substudy of the large randomized study that demonstrated significant reduction in inflammatory lesions (36).

Infliximab

Infliximab is a chimeric monoclonal IgG_1 antibody that binds both soluble and cell bound forms of TNF-alpha. In AS, infliximab is usually given at a slightly higher dose than in rheumatoid arthritis patients. Dosing for AS is 5 mg/kg intravenously at baseline, week 2, week 6, and then every 6 weeks thereafter. In an early study, a 3-month randomized study compared infliximab in doses of 5 mg/kg intravenously to placebo in AS patients with active disease (37). A larger proportion of patients experienced a response in terms of the BASDAI than placebo. This has been shown to be sustained to 3 years (38). These results have been confirmed by a larger randomized placebo-controlled trial over 24 weeks (39). A significantly larger proportion of patients achieved an ASAS20 compared to placebo over the 24 weeks. MRI results also demonstrated a significant decrease in inflammatory lesions.

Adalimumab

Adalimumab is a fully humanized IgG_1 monoclonal antibody that inhibits. The usual dose is 40 mg, administered subcutaneously every other week. Results from a small open-label trial in which AS patients were treated with adalimumab showed significant improvement in disease activity, acute phase reactants, pain, and morning stiffness (40). Results from a large, randomized, placebo-controlled study demonstrated a significant clinical response in the ASAS20 as well as many secondary outcome measures when adalimumab was administered over a 24-week period (41).

TREATMENT RECOMMENDATIONS AND BEST PRACTICE GUIDELINES

A systematic literature review and Delphi exercise was performed on all treatment modalities for AS and recently published (Table 9C-3) (42). In addition, treatment recommendations for the use of anti-TNF agents have been published by the ASAS and modified for use in the United States by the Spondyloarthritis Research and Treatment Network (SPARTAN) (Table 9C-4) (43–45). Patients who are symptomatic, regardless of their predominant manifestation (peripheral arthritis, axial arthritis, enthesitis) should be given a trial of at least two NSAIDs. Patients with moderate disease activity or greater [BASDAI score of 4 or above and a physician global score of at least 2 (range, 0–4)], should be given additional therapy. For patients with pronounced peripheral symptoms, a trial of SSZ or MTX should be considered. For patients with purely axial manifestations, no trial of SSZ or MTX is required and an anti-TNF agent should be prescribed. For those with concomitant inflammatory bowel disease, a monoclonal antibody is preferred. Strict adherence to screening and treatment of latent tuberculosis infection is required prior to the initiation of anti-TNF therapy. In

TABLE 9C-3. SUMMARY OF APPROVED ANTI–TUMOR NECROSIS FACTOR AGENTS USED IN THE TREATMENT OF PATIENTS WITH ANKYLOSING SPONDYLITIS.

AGENT	DESCRIPTION	DOSING	CLINICAL RESPONSE	DISEASE-MODIFYING PROPERTIES
Etanercept	Dimeric fusion protein of the TNF-alpha receptor linked to the Fc portion of human IgG1	Subcutaneous injection of 50 mg once a week or 25 mg twice weekly	ASAS 20/50/70 BASDAI 50 ASAS 5/6 Partial remission	DXA improvement in lumbar spine Reduction in acute MRI changes Limited plain radiographic data
Infliximab	Monoclonal IgG1 anti-TNF antibody with a mouse variable region	Intravenous infusion of 5 mg/kg at 0, 2, and 6 weeks and then every 6 weeks	ASAS 20/50/70 BASDAI 50 ASAS 5/6 Partial remission	DXA improvement in lumbar spine and hip Improvement in cartilage and bone metabolism measures Reduction in acute MRI changes Limited radiographic data Effective in patients with IBD
Adalimumab	Fully humanized monoclonal antibody directed against TNF-alpha	Subcutaneous injection of 40 mg every other week	ASAS 20/50/70 BASDAI 50 ASAS 5/6 Partial remission	Reduction in acute MRI changes Limited data on efficacy in patients with IBD

ABBREVIATIONS: ASAS, Assessments in Ankylosing Spondylitis Working Group; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; DXA, dual-energy x-ray absorptiometry; IBD, inflammatory bowel disease; MRI, magnetic resonance imaging; TNF, tumor necrosis factor.
Data from References 33 and 39.

TABLE 9C-4. BEST CLINICAL PRACTICE GUIDELINES FOR THE USE OF ANTI–TUMOR NECROSIS FACTOR AGENTS IN ANKYLOSING SPONDYLITIS.

Patient acceptance including and understanding of risk and benefits of long-term or potentially lifelong anti-TNF therapy and unknown effects on pregnancy/lactation.
Diagnosis and/or associated features
Modified NY Criteria or other evidence of SpA, including inflammatory back pain, persistently elevated acute phase reactants, baseline radiographic damage and/or rapid radiographic progression, spinal inflammation on imaging modality including MRI and ultrasound.
Suggested disease activity
BASDAI Score of ≥4 (0–10). Physician global assessment of at least moderate disease activity based upon either a score of ≥2 on a Lickert scale (0–4) or VAS score of ≥4 (0–10).
Clinical presentation and extra-articular features
Three clinical presentations: axial, peripheral arthritis (excluding hip), and entheseal. Predominant feature guides the previous treatment requirements. For axial, peripheral, and entheseal presentations–failure of at least two NSAIDs either due to inefficacy or toxicity. For peripheral features–arthritis or ethesitis: NSAID failure and failure of methotrexate or sulfasalazine at maximally tolerated doses for 3 months. For axial predominance: NSAID failure and no DMARD failure required. Intra-articular or entheseal injections of glucocorticoids as clinically indicated.
Response
Reduction in BASDAI score and physician global score of at least 50%.
Timing of response
Response expected within 12 weeks of initiation of treatment.
Agents
Etanercept 50 mg/wk sq Infliximab 5 mg/kg at 0, 2,and 6 weeks, then every 6 weeks intravenously. Adalimumab 40 mg every other week sq
Precautions/contraindications
Active or recurrent infection including untreated evidence of latent TB or recent TB exposure. SLE or MS symptom/history. Other per package insert.

ABBREVIATIONS: BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; DMARD, disease-modifying antirheumatic drug; MRI, magnetic resonance imaging; MS, multiple sclerosis; NSAIDs, nonsteroidal anti-inflammatory drugs; SLE, systemic lupus erythematosus; SpA, spondyloarthropathies; TB, tuberculosis; TNF, tumor necrosis factor; VAS, visual analog scale.
Data from References 43 through 45.

addition, if during treatment there are signs/symptoms of infection or recent contact, screening and evaluation should be pursued.

SURGICAL INTERVENTION

Advances in orthopedic surgery have also proven to be highly effective in patients with disabling manifestations (in particular, severe pain) of AS. The disease commonly involves the hip joint, a finding that portends more severe disease and a worse prognosis. Additionally, kyphosis can lead to significant loss of function and disability. Surgical intervention—total hip arthroplasty and osteotomy and fixation—may greatly improve a patient's level of mobility and quality of life. Appropriate referrals should be made to an orthopedist.

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