Update on Spondyloarthropathies

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Spondyloarthropathies are a cluster of interrelated and overlapping chronic inflammatory rheumatic diseases that primarily include ankylosing spondylitis, reactive arthritis, and the arthritis associated with psoriasis and inflammatory bowel diseases. The primary pathologic sites are the entheses (the sites of bony insertion of ligaments and tendons); the axial skeleton, including the sacroiliac joints; the limb joints; and some nonarticular structures, such as the gut, skin, eye, and aortic valve. Although spondyloarthropathies are not associated with rheumatoid factor, they show a strong association with HLA-B27; however, this association varies markedly among various spondyloarthropathies and among ethnic groups. The most widely used classification criterion, from the European Spondyloarthropathy Study Group, encompasses the currently recognized wider disease spectrum, with a sensitivity and specificity that generally exceed 85%. Spondyloarthropathies occur in genetically predisposed persons and are triggered by environmental factors, but the cellular and molecular mechanisms of inflammation are not yet fully understood. Chlamydial and many enterobacterial infections can trigger reactive arthritis, but an infectious trigger for ankylosing spondylitis has not yet been established. HLA-B27 itself is involved in enhancing genetic susceptibility, but the underlying molecular basis is still unknown; additional genes include the putative susceptibility genes for Crohn disease, ulcerative colitis, and psoriasis. A specific susceptibility gene for Crohn disease, *NOD2,* is located on chromosome 16q12, and one of the candidate genes for psoriasis, *PSORS1,* has been mapped to a 60-kb fragment on chromosome 6p, which is telomeric to the HLA-C locus. This paper reviews the efficacy of anti–tumor necrosis factor-α therapy and other therapeutic advances.

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Spondyloarthropathies constitute a cluster of interrelated and overlapping chronic inflammatory rheumatic diseases that includes ankylosing spondylitis (the most typical form of spondyloarthropathy); reactive arthritis; arthritis associated with psoriasis, Crohn disease, and ulcerative colitis; and a form of juvenile chronic arthritis (1–8). Their clinical spectrum is much wider than previously realized, and some additional, less clearly defined types are categorized as undifferentiated spondyloarthritis (9, 10). Clear differentiation among these various forms, especially in their early stages, may not always be possible owing to overlapping clinical features. However, lack of differentiation does not usually affect treatment decisions.

The primary pathologic sites include the entheses, which are the site of bony insertion of ligaments and tendon; the sacroiliac joints and the axial skeleton; the limb joints; and some nonarticular structures, such as the gut, skin, eye, and aortic valve (11–18). The entheses are very widespread, and many sites, predominantly in the axial skeleton and the lower extremities, can be symptomatically involved. Thus, the patient can have tenderness at the insertions of plantar fascia and Achilles tendon into the calcaneum, or patellar tendon insertion into the tibial tubercle. Enthesitis most frequently occurs at sites that bear greater physical stress. Therefore, it has been proposed that tissue-specific modulation of immune response toward fibrosis rather than cell lysis at the sites subjected to stress (for example, the axial skeleton, ascending aorta, anterior uveal tract, and apices of the lungs) may explain the tissue distribution of lesions (19).

Table 1 shows the characteristic features of spondyloarthropathies. These diseases are not associated with rheumatoid factor, but they show a strong association with HLA-B27, an allele of the major histocompatibility complex. However, this association varies markedly among the different forms of spondyloarthropathies and among ethnic groups (1, 20–25).

Table 2 lists the diseases strongly associated with HLA-B27 in white persons. Both men and women are affected, although the disease has an overall male predominance, and familial aggregation may occur. Spondyloarthropathies usually begin in the late teens and early 20s but may also present earlier in childhood or at an older age; they probably account for about 20% of all chronic arthritides seen in pediatric rheumatology (6–10). Juvenile-onset spondyloarthropathies are not covered in this paper.

Spondyloarthropathies are now recognized as being more prevalent than previously thought. The European Spondyloarthropathy Study Group classification criterion is the one most widely used, because it encompasses

Table 1. **Features of Spondyloarthropathies**

Radiographic sacroiliitis with or without accompanying spondylitis
Variable inflammatory peripheral arthritis, enthesitis, and dactylitis
Association with chronic inflammatory bowel disease
Association with psoriasis and other mucocutaneous lesions
Tendency for anterior ocular inflammation
Increased familial incidence
Occasional aortitis and heart block
No association with rheumatoid factor
Strong association with HLA-B27

the wider disease spectrum. This criterion has been validated in various groups, and its sensitivity and specificity generally exceed 85% (**Table 3**) (26–30). Studies from western Europe indicate that ankylosing spondylitis in its full spectrum is much more common than previously realized, and its overall prevalence may be similar to that of rheumatoid arthritis (**Table 4**) (31–33). Moreover, the prevalence of spondyloarthropathies as a whole may be approximately twice as high as was thought previously; this is especially the case in Eskimo and Inuit persons, among whom the prevalence of HLA-B27 is 25% to 40% (1, 21, 27). Conversely, spondyloarthropathies are relatively rare among Japanese persons, who have a very low (<1%) prevalence of HLA-B27 (30).

The undifferentiated forms of spondyloarthropathies, which are frequently underdiagnosed, include isolated clinical syndromes, such as HLA-B27–associated seronegative oligoarthritis or polyarthritis, mostly of the lower extremities. This arthritis has no recognizable preceding bacterial infectious trigger, extraarticular clinical features, or associated inflammatory bowel disease or psoriasis (1–3, 8–10). Patients with undifferentiated spondyloarthropathy may have dactylitis ("sausage digits") and enthesitis, especially at the heel (Achilles tendonitis and plantar fasciitis) (10). Others may present with an episode of acute anterior uveitis (acute iritis) or have a syndrome of aortic incompetence plus heart block (1–3, 34–39). This cardiac syndrome and acute anterior uveitis may occur in patients with no signs of arthritis or may accompany or precede the onset of spondyloarthropathy. In one Scandinavian study, more than 88% of male patients without arthritis and with aortic incompetence and severe cardiac conduction disturbance were positive for HLA-B27 (39). Approximately 50% of patients with acute anterior uveitis test positive for HLA-B27, and more than half of the HLA-B27–positive patients with acute anterior uveitis have some form of spondyloarthropathy (34, 35).

Routine HLA-B27 testing is not clinically helpful, because spondyloarthropathies can occur in the absence of the allele. HLA-B27 is present in 8% of healthy white persons, of whom about 90% will never develop these diseases (1–4, 20–22). However, the risk for spondyloarthropathies among HLA-B27–positive persons who have a first-degree relative with ankylosing spondylitis is increased threefold (30% instead of 10%). No preventive or curative therapy is available that would justify testing unaffected or asymptomatic relatives for HLA-B27 status (1–3).

ANKYLOSING SPONDYLITIS

Ankylosing spondylitis is thought to be the most common and most typical form of spondyloarthropathy. It is two to three times more common in men than women. Ankylosing spondylitis usually begins with back pain and stiffness in adolescence and early adulthood, but diverse presentations may antedate back symptoms in some patients (1–4, 40). It is very rare for ankylosing spondylitis to first begin after 45 years of age, but disease is diagnosed at an older age in many patients, in part because symptoms over the years have been minimal (8–10, 41).

The diagnosis of ankylosing spondylitis is clinical, but the classic features suggestive of chronic inflammatory back pain—insidious onset before 45 years of age, worsening with inactivity, and improvement with physical exercise (**Table 3**)—are on their own not very specific (42). A history of acute anterior uveitis, a positive family history of ankylosing spondylitis or related spon-

Table 2. **Association of Spondyloarthropathies with HLA-B27 in White Persons***

Disease	Approximate Prevalence of HLA-B27, %
Ankylosing spondylitis	90
Reactive arthritis	40–80
Juvenile spondyloarthropathy	70
Enteropathic spondyloarthritis	35–75
Psoriatic spondyloarthritis	40–50
Undifferentiated spondyloarthropathy	70
Acute anterior uveitis (acute iritis)	50
Aortic incompetence with heart block	80

* Persons of western European extraction. The prevalence in the general healthy population is approximately 8%.

Table 3. **The European Spondyloarthropathy Study Group Criteria**

Criterion	Definition
Inflammatory spinal pain with at least four of the following five components: At least 3 months in duration Onset before 45 years of age Insidious (gradual) onset Improved by exercise Associated with morning spinal stiffness	History of or current symptoms of spinal pain (low, middle, and upper back, or neck region)
Synovitis	Past or present asymmetric arthritis, or arthritis predominately in the lower limbs
Spondyloarthropathy	Presence of inflammatory spinal pain OR synovitis AND one or more of the following conditions: 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 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 planter 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).

dyloarthropathies, or impaired spinal mobility or chest expansion further supports the clinical diagnosis (1–3, 26, 35, 40, 43). Other clinical indicators are the presence of enthesitis, with resultant tenderness over the sacroiliac joints and the spine and sometimes at other sites, such as the heels, iliac crest, and anterior chest wall (26, 44, 45). The modified New York criteria for ankylosing spondylitis are now commonly used for disease classification (**Table 5**) (46).

The clinical diagnosis is supported by radiologic evidence of sacroiliitis, which is still considered to be the radiographic hallmark of ankylosing spondylitis. Anteroposterior radiography of the pelvis is usually sufficient. However, in patients in whom clinical suspicion of early disease is high but standard radiography of the sacroiliac joints is normal or shows only equivocal changes, magnetic resonance imaging, especially with gadolinium enhancement, produces excellent radiation-free evidence of sacroiliitis and enthesitis (17, 47, 48). Magnetic resonance imaging is especially valuable in identifying sacroiliitis in children and adolescents (6, 48). However, the test is expensive.

The diagnosis is usually delayed by 5 to 6 years, especially in patients with an early or incomplete clinical picture (8, 9, 49–51). Multiple referrals of such patients for the same symptoms often do not yield a correct diagnosis, and during this prolonged diagnostic delay, many unnecessary and invasive investigations are performed (49). In a comparison study, ankylosing spondylitis was more frequently detected in a specialized clinic than in a community setting (50). A normal erythrocyte sedimentation rate does not exclude active disease (52).

Some patients may have mild constitutional symptoms, such as malaise, loss of appetite, or mild fever, in the early stage of the disease. One or more episodes of acute anterior uveitis (acute iritis or iridocyclitis) are a prominent extraarticular feature of ankylosing spondylitis, occurring in 25% to 40% of patients; these episodes are less common among persons lacking HLA-B27 (1–4, 53). Painful, inflamed, or gritty eye, with or without blurring of vision, needs urgent ophthalmologic examination to exclude acute anterior uveitis (34). This disorder is typically unilateral and tends to recur, sometimes in the contralateral eye. Other, uncommon extraarticular features are aortic incompetence and associated cardiac conduction disturbances or heart block (36–39).

Spinal osteoporosis is frequently observed, especially in patients with severe ankylosing spondylitis of long duration. Spinal osteoporosis occurs in part because of ankylosis and lack of mobility, but it can also occur in a relatively early stage of the disease, perhaps as a result of proinflammatory cytokines (54–56). Assessment of biochemical markers of bone metabolism has shown that diminished bone formation and enhanced bone resorp-

Table 4. **Recent Prevalence Studies of Ankylosing Spondylitis and Related Spondyloarthropathies**

Ethnic Group or Region	Frequency of HLA-B27 in Population	Prevalence of Ankylosing Spondylitis in Adults		Prevalence of Spondyloarthropathies (Including Ankylosing Spondylitis) in Adults	
		General Population	HLA-B27–Positive Persons	General Population	HLA-B27–Positive Persons
	←		%		→
Eskimos (Alaska)	40	0.4		2.5	
Eskimos (Alaska and Siberia) and Chukchi	25–40		1.6	2–3.4	4.2
Sami	24	1.8	6.8		
Northern Norway	10–16	1.4			
Mordovia	16	0.5			
Western Europe	8	0.2	2		
Germany (Berlin)	9	0.9	6.4	1.9	13.6

tion are involved (55). Osteoporosis may contribute to spinal fractures and progressive spinal deformity. Patients with ankylosed spine, especially when the ankylosis also involves the neck, are prone to spinal fractures that can happen even after trivial trauma and are easily overlooked (57–60). Transverse displaced fractures, especially of the neck, can result in quadriplegia or paraplegia, and morbidity and mortality rates are high.

Reactive Arthritis

Reactive arthritis is an episode of aseptic peripheral arthritis occurring within 1 month of a primary infection elsewhere in the body, usually genitourinary infection with *Chlamydia trachomatis* or enteritis due to gram-negative enterobacteria, such as *Shigella, Salmonella, Yersinia,* or *Campylobacter* species (**Table 6**) (61–66). It can also follow local injection of bacille Calmette-Guérin (BCG) into the site of bladder cancer (67, 68) but not bacille Calmette-Guérin inoculation that is used in some countries to decrease the risk for tuberculosis. It has been suggested that respiratory tract infection with *Chlamydia pneumoniae* may also trigger reactive arthritis, but the evidence is not conclusive (69).

Genitourinary tract infection with *Chlamydia trachomatis* is the more commonly recognized initiator of reactive arthritis in developed countries, whereas infections with enterobacteria are the more common triggers in developing parts of the world. Urethritis and cervicitis can accompany arthritis after acute bacterial diarrhea; conversely, the psoriasiform lesions over the external genitalia (circinate balanitis and circinate vulvitis) can occur in the absence of genitourinary infection. In about one quarter of cases, the triggering organism is unknown.

Reactive arthritis is typically acute, asymmetric, and oligoarticular and is frequently associated with one or more characteristic extraarticular features, such as ocular inflammation (conjunctivitis or acute iritis); enthesitis (Achilles tendonitis and plantar fasciitis); dactylitis ("sausage digits"); mucocutaneous lesions; urethritis; and, on rare occasions, carditis (61–66). Conjunctivitis occurs in one third of patients with reactive arthritis, usually at the same time as flares of arthritis, and acute anterior uveitis may occur at some time in about 5% of patients. The triad of arthritis, conjunctivitis, and urethritis has been called the Reiter syndrome, but most patients with reactive arthritis do not present with this triad (61).

The average duration of the arthritis is 4 to 5 months, but two thirds of patients have mild musculoskeletal symptoms that persist for more than 1 year (61, 62, 70). Recurrent attacks are more common in patients with chlamydia-induced reactive arthritis. Approxi-

Table 5. **The Modified New York Criteria for Ankylosing Spondylitis**

Criteria components
1. Low back pain of at least 3 months' duration that improved by exercise and was not relieved by rest
2. Limited lumbar spinal motion in sagittal (sideways) and frontal (forward and backward) planes
3. Chest expansion decreased relative to normal values for sex and age
4. Bilateral sacroiliitis grade 2–4 or unilateral sacroiliitis grade 3 or 4

Definite ankylosing spondylitis if criterion 4 and any one of the other criteria is fulfilled

Table 6. **Bacteria That Trigger Reactive Arthritis***

Chlamydia trachomatis
Shigella flexneri
Salmonella species
Yersinia enterocolitica
Y. pseudotuberculosis
Campylobacter fetus jejuni
Clostridium difficile
Intravesical injection of bacille Calmette–Guérin to treat bladder cancer
Chlamydia pneumoniae†

* Cases of oligoarthritis and reactive arthritis not associated with HLA-B27 have also been observed after many bacterial, viral, and parasitic infections and in association with intestinal bypass surgery, acne, hidradenitis suppurative, and cystic fibrosis.
† Unconfirmed.

mately 15% to 30% of patients develop chronic or recurrent arthritis or sacroiliitis or spondylitis, and most of these patients have a positive family history for spondyloarthropathies or are positive for HLA-B27 (61–63).

Severe arthritis or an illness resembling typical reactive arthritis, psoriatic arthritis, or undifferentiated spondyloarthropathy can occur in some patients infected with HIV (71–74), but these conditions seem to have become less common in developed countries since more effective antiviral therapies have become available. Since the advent of the current HIV epidemic, reactive arthritis, psoriasis, psoriatic arthritis, and related spondyloarthropathies, except ankylosing spondylitis, have become more common in sub-Saharan Africa, where these diseases used to be rare. For example, the prevalence of spondyloarthropathies in Lusaka, Zambia, is now calculated to be approximately 180 per 100 000 in HIV-infected persons, a rate 12 times higher than that in persons not infected with HIV (73). Patients with HIV infection are also prone to bone and joint infections owing to their low $CD4^+$ T-cell count.

Psoriatic Arthritis

Moll and Wright (75) broadly defined psoriatic arthritis as an "inflammatory arthritis associated with psoriasis, which is usually negative for rheumatoid factor" and proposed different subtypes: monoarthritis and oligoarthritis, polyarthritis, arthritis of distal interphalangeal joints with nail changes, arthritis mutilans, and spondylitis. However, the distinction among these subtypes becomes less clear with time, and there are no internationally agreed-on criteria for the diagnosis of psoriatic arthritis (76–78). A search for psoriasis should not be limited to the extremities but should also include the scalp, ears, umbilicus, pelvic area, perineum, natal cleft (perianal area), palms, soles, and nails. Nail involvement is often a useful clue in diagnosis of psoriatic arthritis.

Psoriasis is a common skin disease among white persons (1% to 3% prevalence) and is more common (5% to 10%) in the northernmost regions of Norway and Russia. The disease is uncommon in persons from some other ethnic groups, such as black persons and Native Americans (0% to 0.3%) (78). It affects men and women equally. More than 10% of patients with psoriasis have associated inflammatory arthritis, including sacroiliitis and spondylitis (78). Psoriasis usually antedates the appearance of arthritis. The arthritis usually begins between 30 to 50 years of age, but it can also begin in childhood, and it may precede the onset or diagnosis of psoriasis in up to 15% of patients.

Psoriasis has many types, such as guttate, pustular, or plaque psoriasis, and may or may not be associated with nail pitting, dystrophy, or onycholysis. Mucosal psoriatic lesions may affect the buccal mucosa, tongue, and genitalia. Type 1 psoriasis tends to be familial, with an early age of onset (<40 years) and a strong association with major histocompatibility complex. Type 2 psoriasis has a later age of onset and tends to be nonfamilial (78).

The evolution of mild psoriasis to a widespread erythrodermic pattern with associated flare-up of arthritis may raise the possibility of HIV infection. The incidence of psoriasis and psoriatic arthritis has increased dramatically in sub-Saharan Africa in association with the current epidemic of HIV infection (73, 74, 78). Of 702 patients with inflammatory arthritis in Zambia, 28 had psoriatic arthritis and all but 1 (96%) were positive for HIV (73). This finding suggests that every patient with newly diagnosed psoriatic arthritis in sub-Saharan Africa should be tested for possible HIV infection.

Enteropathic Arthritis

The term *enteropathic arthritis* describes the occurrence of inflammatory arthritis in patients with ulcerative colitis or Crohn disease. This disorder is more common than previously reported: Thirty-nine percent of 103 consecutive patients with ulcerative colitis or Crohn disease, regardless of the extent of the bowel disease, had enteropathic arthritis, and most (90%) fulfilled the classification criteria for spondyloarthropathy (79).

An additional 18% of the patients had asymptomatic sacroiliitis. Sacroiliitis, whether symptomatic or asymptomatic, was related to the duration of disease. Inflammatory back pain was present in 30% of the 103 patients, 10% had synovitis, 7% had a peripheral enthesitis, and 10% fulfilled the criteria for ankylosing spondylitis.

Arthritis of peripheral (limb) joints tends to occur much more frequently with enteropathic arthritis than with primary ankylosing spondylitis, but it is usually self-limited and nondeforming. About one fourth of patients with enteropathic arthritis have axial disease (sacroiliitis alone or with classic clinical and radiographic features of ankylosing spondylitis) that does not fluctuate with bowel disease activity (79–81). Conversely, an increased frequency of subclinical inflammatory lesions in the gut (20% to 70%) is observed on colonoscopic mucosal biopsy in patients with spondyloarthropathy who have no gastrointestinal symptoms or clinically obvious inflammatory bowel disease. Follow-up studies of such patients indicate that 6% will develop inflammatory bowel disease, and of those with histologically "chronic" inflammatory gut lesions, 15% to 25% will develop clinically obvious Crohn disease. This suggests that the latter patients initially had a subclinical form of Crohn disease when they presented with arthritis (81).

PATHOGENESIS

Spondyloarthropathies are multifactorial diseases that occur in genetically predisposed persons and are triggered by environmental factors (66). The cellular and molecular mechanisms of inflammation are not yet fully understood. Characteristics are increased numbers of T cells and macrophages and greater expression of proinflammatory cytokines (interleukin-1β, tumor necrosis factor-α, and interferon-γ) at the sites of inflammation (82). The inflammatory process gradually progresses to cortical bone erosions and new bone formation but can also cause substantial loss of bone mass in relatively early stages of active disease in some patients (54, 55). Unlike rheumatoid arthritis, in which synovitis is the initial or primary lesion, the synovitis of spondyloarthropathy may be a secondary event after enthesitis, at least in some joints (83).

No definite evidence exists of an infectious trigger for ankylosing spondylitis, despite the persistent claim by one group for the past 25 years that carriage of *Klebsiella pneumoniae* in the gut is such a trigger (84). The bacterial triggers of postinfectious reactive arthritis (**Table 6**) share the characteristics of being invasive of the mucosal surface and being able to replicate intracellularly. Moreover, their outer membrane contains lipopolysaccharides. Chlamydia is an obligate intracellular pathogen that primarily resides in the epithelial cells but can infect other cell types, such as macrophages (64).

Spondyloarthropathies seem to have an immune-mediated pathogenesis. The arthritogenic peptide hypothesis suggests that the arthritis is triggered by a T-cell response to specific antigenic peptides derived from the triggering bacteria and that these T cells then cross-react with self-antigen–derived peptides (16–19, 66, 85–90). Increased oligoclonal expansion of $CD8^+$T cells has been observed in the affected joints of some patients with spondyloarthropathy; the types of microbial or self-antigens responsible for this expansion are being investigated (12, 66, 87–91).

Microbial antigenic components or nonreplicating bacteria may reach regional lymph nodes or be transported by macrophages to the joints and other sites of inflammation. They have been found in the synovial tissue or synovial fluid of some patients with reactive arthritis, and they can persist in the joint and drive the local immune response. However, despite many attempts, no organisms have been successfully cultured from the inflamed joints of patients with spondyloarthropathies. Chlamydia has unusual biological properties in synovial tissue or fluid, which may explain why culture of joint materials is negative for *C. trachomatis* (64).

The cartilage proteoglycans versican and aggrecan and the link protein are being studied as possible autoantigens in ankylosing spondylitis and related spondyloarthropathies. These substances share considerable molecule homology and induce arthritis resembling spondyloarthropathy in BALB/c mice (89).

A potential association between psoriatic arthritis and trauma in the 3 months preceding disease onset has been reported, but only in 8% to 9% of patients (compared with 1% to 2% of controls with rheumatoid arthritis). This effect may result from psychological stress rather than from direct physical trauma to a joint, although the Koebner phenomenon, a recognized feature of skin psoriasis, may also occur in peripheral joints (deep Koebner phenomenon) (91).

GENETIC ASPECTS

Family and twin studies suggest that a few genes determine susceptibility to spondyloarthropathies (66, 92–97). Different combinations of such genes and environmental factors may predispose to variation in disease expression, and variable sets of susceptibility alleles at different loci may produce the same disease phenotype, resulting in clinical misclassification. Moreover, not everyone with a set of susceptibility allelles will develop disease (that is, penetrance is variable).

Recent studies have confirmed that HLA-B27 makes the strongest genetic contribution to development of spondyloarthropathies, and findings support the role of additional genes (66, 92, 93, 96, 97) that may also include the putative susceptibility genes for psoriasis and inflammatory bowel diseases (98–101). One of the candidate genes for psoriasis, *PSORS1,* is located somewhere in a 60-kb fragment telomeric to HLA-C locus on chromosome 6p (101). A specific susceptibility gene for Crohn disease, *NOD2,* has been identified in the pericentromeric region (16q12) of chromosome 16 (98–100). The protein encoded by this gene activates nuclear factor (NF)-κB in response to bacterial lipopolysaccharides. A frame-shift mutation in the *NOD2* gene caused by a cytosine insertion confers substantially increased susceptibility to Crohn disease. The wild-type *NOD2,* but not the mutant type, activates NF-κB. These findings implicate *NOD2* in susceptibility to Crohn disease and suggest a link between an innate immune response to bacterial components and development of disease (98–100).

Substantial evidence favors a direct role of HLA-B27 in enhancing genetic susceptibility, but the underlying molecular basis is still unknown despite intensive investigation (66, 92–95). HLA-B27 may play a role by presenting putative arthritogenic peptides to T cells, or it may have unusual cell biology (compared with most other HLA class I molecules) that may have a pathogenic role (19, 85, 102–104). For example, the HLA-B27 molecule can exist in an aberrant form (free heavy chains forming stable homodimers that lack β_2-microglobulin) (19), and it has an increased tendency to misfold in the endoplasmic reticulum (103). However, no single compelling hypothesis fully explains the pathogenic role of HLA-B27 (66).

HLA-B27–transgenic rodents spontaneously develop an inflammatory disease resembling human spondyloarthropathies. Development of this inflammatory disease requires bacterial components and increased expression of HLA-B27 by T cells and antigen-presenting cells (85, 86). Diarrhea and gut inflammation that precede the onset of arthritis require the presence of normal live bowel flora. An increased frequency of subclinical inflammatory lesions in the gut in patients with spondyloarthropathies, and the known association between inflammatory bowel diseases and spondyloarthropathies, support a pathogenic link between gut inflammation and spondyloarthropathies that is independent of HLA-B27 (66, 80, 81).

HLA-B27 is a serologic specificity that encompasses 25 proteins (HLA-B*2701 to HLA-B*2725) that are also called subtypes of HLA-B27 (93, 105). They may have evolved from the most widespread subtype, HLA-B*2705. Occurrence of ankylosing spondylitis or related spondyloarthropathies has been documented in persons possessing various subtypes that have been studied for disease association. However, HLA-B*2706 in southeast Asia and HLA-B*2709 in Sardinia seem not to be associated with ankylosing spondylitis, although rare occurrence of spondyloarthropathy has been observed (88, 93, 105–108). The two major subtypes observed in white persons, HLA-B*2705 and HLA-B*2702, are associated with disease.

MANAGEMENT

The use of nonsteroidal anti-inflammatory drugs at full therapeutic doses during the active phases of the disease and a lifelong program of appropriate regular exercises, including swimming, form the mainstay of management of ankylosing spondylitis (1–3, 109–111). Formal sessions of group physical therapy and hydrotherapy and passive stretching of the joints are generally underutilized. A few randomized, controlled studies have demonstrated the benefits of these therapies in increasing range of movement and improving posture or minimizing deformity (112–115).

Use of splints, braces, and corsets is not helpful and should therefore be avoided. The use of wide rear-view mirrors, seat belt, and proper head support while driving must be emphasized for patients with substantially limited range of motion of the neck. Appropriate counseling and lifestyle modifications include smoking cessation; yearly influenza immunization; avoidance of

physical injury and falls; and workplace and job modification, if necessary. Health education and counseling of patients with chronic arthritis add substantial and sustained benefits to conventional therapy while reducing costs (116–118), and self-help education programs are well accepted by patients and provide improved behavioral and health status outcomes. Management of acute anterior uveitis, psoriasis, and inflammatory bowel disease in patients with spondyloarthropathies is not covered in this article.

Local injection of corticosteroids for recalcitrant enthesitis and persistent synovitis of peripheral joints can be helpful. Addition of enteric-coated sulfasalazine to control peripheral arthritis or to treat concurrent psoriasis or inflammatory bowel disease may be needed in patients who do not respond adequately or cannot tolerate nonsteroidal anti-inflammatory drugs (109). Methotrexate may be helpful for patients with persistent synovitis of peripheral joints, but the first randomized, controlled study of severe ankylosing spondylitis demonstrated no significant benefit of this agent compared with placebo, even in patients with peripheral arthritis (119). Amitriptyline in doses of up to 30 mg at bedtime can help improve sleep (120).

Antibiotics are not effective (121–124), although prolonged (>3 months) treatment of severe, persistent chlamydia-induced reactive arthritis with tetracycline (lymecycline) provided some improvement in one study (125). Moreover, prompt and effective treatment of chlamydial infections reduced the risk for sexually acquired reactive arthritis in a Greenland Inuit population that had a high prevalence of both HLA-B27 and chlamydial infections (126).

Efficacy of Anti–Tumor Necrosis Factor-α and Other New Therapies

Patients with ankylosing spondylitis, psoriatic arthritis, or enteropathic arthritis that is unresponsive to conventional therapies have received anti–tumor necrosis factor-α therapy with infliximab (Remicade, Centocor, Inc., Malvern, Pennsylvania) or etanercept (Enbrel, Immunex Corp., Seattle, Washington). This treatment rapidly improved peripheral arthritis, enthesitis, and axial signs and symptoms (127–133). Open-label and randomized, double-blind, placebo-controlled trials of infliximab given intravenously in a dose of 5 mg/kg of body weight on three occasions (weeks 0, 2, and 6) have demonstrated a quick therapeutic response and a statistically significant improvement in most patients with ankylosing spondylitis (127–130). These and other studies have used the newly developed and recently renamed WHO/ILAR/OMERACT core sets to evaluate the efficacy of drug therapy and physical therapy in patients with ankylosing spondylitis (134, 135). These core sets are also designed for clinical record keeping in daily practice.

Statistically significant efficacy of etanercept (25 mg subcutaneously twice weekly) in patients with severe psoriasis and psoriatic arthritis was reported in a randomized, double-blind, placebo-controlled trial (131). This therapy substantially reduced the use of methotrexate and corticosteroids in these patients. Etanercept is also very effective in children with juvenile arthritis, including juvenile spondyloarthropathy (133). A controlled study of etanercept in ankylosing spondylitis has also demonstrated statistically significant efficacy (136).

As in rheumatoid arthritis, therapy for spondyloarthropathies must be continued because disease activity returns a few weeks after administration of anti–tumor necrosis factor-α is stopped. Studies are under way to find the optimum long-term dose to maintain remission in patients with spondyloarthropathies. High cost and potentially serious adverse effects, including predisposition to bacterial infections, reactivation of tuberculosis, and demyelination, are some of the disadvantages of this therapy (128–133, 137).

Experimental drugs under study for treatment of ankylosing spondylitis include pamidronate, a bisphosphonate that requires intravenous infusion (138, 139), and thalidomide (140, 141). The therapeutic effects of pamidronate may result from its anti-inflammatory effect and not from its effect on bone resorption. Oral bisphosphonates used to treat osteoporosis have no such documented anti-inflammatory effect. The therapeutic efficacy of thalidomide may result in part from its known mild anti–tumor necrosis factor-α activity due to an increase in the degradation rate of tumor necrosis factor messenger RNA (140–142). Its major risks are teratogenicity, somnolence, and peripheral neuropathy.

In conclusion, spondyloarthropathies are a cluster of interrelated and overlapping chronic inflammatory rheumatic diseases that occur in genetically predisposed persons and are triggered by environmental factors. HLA

genes are involved in enhancing genetic susceptibility, but the underlying molecular basis is still unknown (143). Additional genes include the putative susceptibility genes for psoriasis and inflammatory bowel diseases. Significant new therapeutic advances have been made, including anti–tumor necrosis factor-α therapy. Advances in surgical management of ankylosing spondylitis and related spondyloarthropathies are not covered in this article.

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