JAMA | Review

Axial Spondyloarthritis
A Review

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IMPORTANCE Axial spondyloarthritis is an immune-mediated inflammatory condition involving the sacroiliac joints, spine, and peripheral joints. It affects approximately 1% of adults in the US and is associated with impaired physical function and reduced quality of life.

OBSERVATIONS Inflammatory chronic back pain characterized by gradual onset starting before age 45 years, prolonged morning stiffness, improvement with exercise, and lack of improvement with rest is the most common symptom of axial spondyloarthritis and affects more than 80% of patients. Patients with axial spondyloarthritis may also have inflammatory arthritis in large peripheral joints (most commonly knees) in an oligoarticular, asymmetric fashion; inflammation at tendon insertions (enthesitis); inflammatory eye disease (uveitis); psoriasis; and inflammatory bowel disease. The pathogenesis of axial spondyloarthritis may involve genetic predisposition, gut microbial dysbiosis, and entheseal trauma, with immune cell infiltration of the sacroiliac joints and entheseal insertion areas in the spine. There are currently no diagnostic criteria for axial spondyloarthritis. The diagnosis, often delayed 6 to 8 years after symptom onset, is based on history (ie, inflammatory back pain [sensitivity, 74%-81%; specificity, 25%-44%]), laboratory findings (human leukocyte antigen B27–positive [sensitivity, 50%; specificity, 90%] and elevated C-reactive protein level [sensitivity, 35%; specificity, 91%]), and imaging findings consisting of sacroiliitis on plain radiography (sensitivity, 66%; specificity, 68%) or magnetic resonance imaging (sensitivity, 78%; specificity, 88%). First-line treatments are physical therapy and nonsteroidal anti-inflammatory drugs (NSAIDs). However, less than 25% of patients achieve complete symptom control with NSAIDs. Approximately 75% of patients require biologic drugs (tumor necrosis factor inhibitors [anti-TNF agents], interleukin 17 inhibitors [anti–IL-17 agents]) or targeted synthetic disease-modifying antirheumatic agents (Janus kinase [JAK] inhibitors) to reduce symptoms, prevent structural damage, and improve quality of life. Clinical trials reported that anti-TNF agents significantly improved ASAS20 (measure of pain, function, and inflammation) in 58% to 64% of patients compared with 19% to 38% for placebo. Similar outcomes were attained with anti–IL-17 agents (48%-61%, vs 18%-29% with placebo) and JAK inhibitors (52%-56%, vs 26%-29% with placebo). Anti-TNF agents, anti–IL-17 agents, and JAK inhibitors have been associated with reduced radiographic progression of axial spondyloarthritis.

CONCLUSIONS Axial spondyloarthritis predominantly affects the sacroiliac joints and spine but is also associated with extraskeletal manifestations such as uveitis, psoriasis, and inflammatory bowel disease. Physical therapy and NSAIDs are first-line treatments, but most patients require therapy with biologics (anti-TNF or anti–IL-17 agents) or JAK inhibitors to achieve improvement in signs and symptoms, inflammation control, and reduced progression of structural damage.

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Axial spondyloarthritis is a multisystem inflammatory disease characterized by inflammation of the axial skeleton, including the sacroiliac joints and the spine. Axial spondyloarthritis can also affect the peripheral joints and organs such as the skin, eyes, and gastrointestinal tract. Axial spondyloarthritis encompasses radiographic (known as ankylosing spondylitis) as well as nonradiographic disease.[1] While both entities have similar clinical presentations, the main difference between radiographic and nonradiographic disease is the presence of definitive sacroiliitis on plain radiography (sclerosis, erosions, narrowing of sacroiliac joints, and ankylosis).

In the US, the prevalence of axial spondyloarthritis is approximately 1% among adults, based on the 2009-2010 National Health and Nutrition Examination Survey,[2,3] the most recent nationally representative data available. In the US, the disease prevalence is higher than that of rheumatoid arthritis (0.6%).[4] The global prevalence is not well defined, ranging from 0.3% to 1.4%.[5] While axial spondyloarthritis symptoms typically develop before age 45 years, an uncommon late-onset disease, defined as age of onset after age 45 years, may occur.[6,7]

This review focuses on the epidemiology, clinical manifestations, diagnosis, and treatment of axial spondyloarthritis.

Methods

We searched PubMed from January 1, 2003, through July 1, 2024, and restricted the search to clinical trials, observational studies, and systematic reviews/meta-analyses published in English using the terms *axial spondyloarthritis* or *ankylosing spondylitis*. We also reviewed the most recent evidence-based guidelines published by the American College of Rheumatology (ACR), the Spondyloarthritis Research and Treatment Network (SPARTAN), and the Spondylitis Association of America (SAA)[8] and guidelines published by the Assessment of Spondyloarthritis International Society and the European Alliance of Associations for Rheumatology (EULAR).[9] Of 1819 articles identified, 102 were included, consisting of 8 systematic reviews and/or meta-analyses, 8 national/international guidelines, 16 reviews, 28 cohort studies, and 42 clinical trials.

Pathophysiology and Pathogenesis

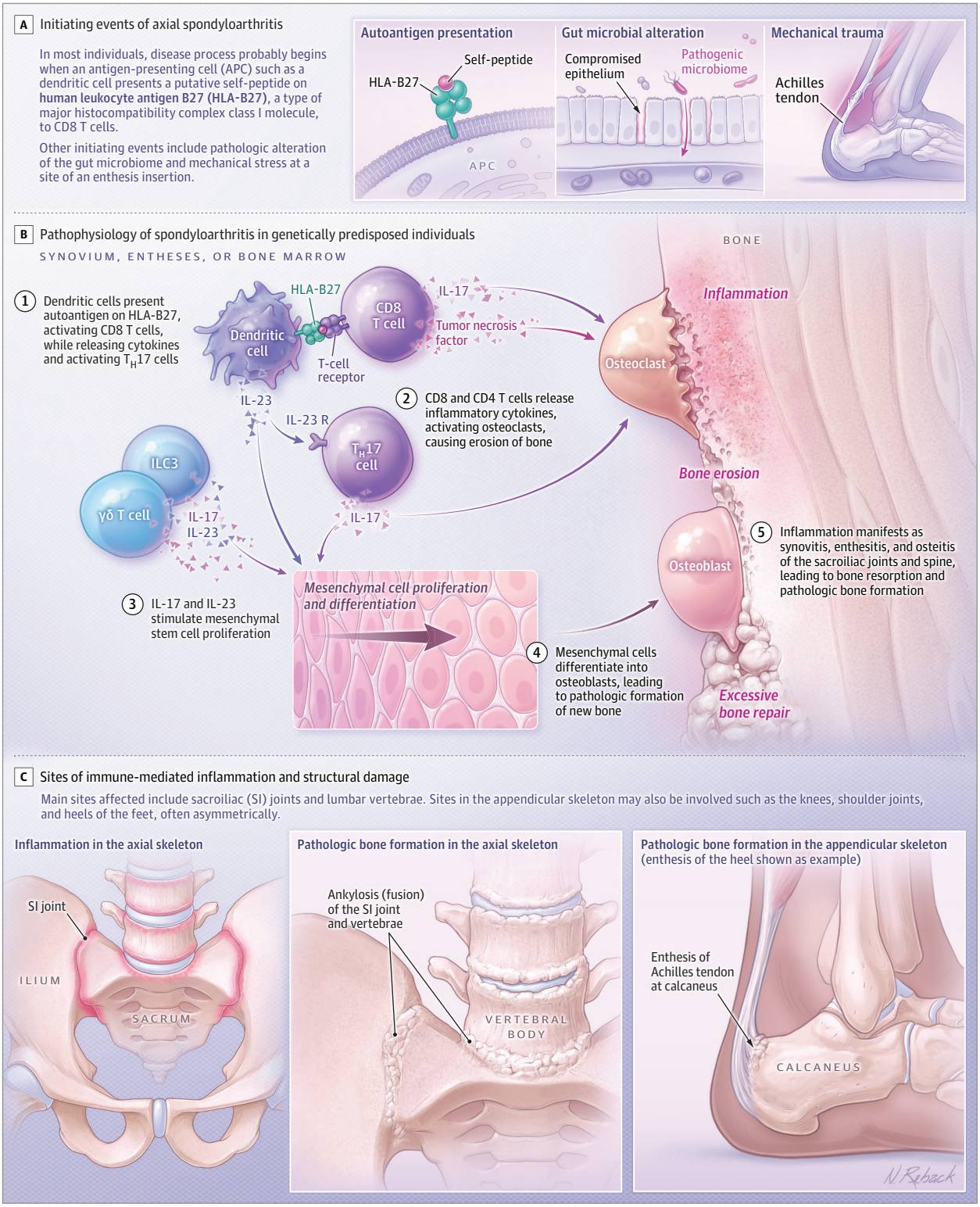
A characteristic feature of axial spondyloarthritis is inflammation-induced bone loss that occurs simultaneously with abnormal new bone formation at specific sites in the skeleton such as the sacroiliac joints, at entheses in the spine, and in the peripheral skeleton. Immune cells (lymphocytes, neutrophils, and dendritic cells) infiltrating the synovium (synovitis), the entheses (enthesitis), and the bone marrow (osteitis) of the sacroiliac joints and spine lead to release of proinflammatory cytokines (tumor necrosis factor [TNF], interleukin [IL] 23, IL-17), which activates osteoclasts and causes bony erosions. Interleukin 23 and IL-17 stimulate mesenchymal stem cells to differentiate into osteoblasts, leading to pathologic new bone formation in the sacroiliac joints, spine, and peripheral entheses (termed enthesophytes).[10] Enthesitis and inflammatory granulation tissue has been described in biopsy specimens of the paravertebral connective tissue at the junction of the annulus fibrosus and vertebral bone in patients with axial spondyloarthritis.[11,12] The outer annular fibers of the vertebral disk can erode and are eventually replaced by bone, forming a syndesmophyte (a bony outgrowth from the spinal ligaments as they attach to adjacent vertebral bodies). The syndesmophyte then grows by osteoblast proliferation, ultimately bridging the adjacent vertebral bodies, resulting in ankyloses (bony fusion). These discoveries have led to development of new therapeutic agents targeting TNF, IL-17, and intracellular kinases (Janus kinase [JAK]), which have demonstrated efficacy in clinical trials.

Although the etiology of axial spondyloarthritis is not fully elucidated, genetics and environmental factors are thought to play a role (**Figure 1**). First, in the genetic hypothesis, human leukocyte antigen B27 (HLA-B27), a major histocompatibility class I molecule expressed on antigen-presenting cells such as monocytes and macrophages, present a self-peptide from the joint to $CD8^+$ T cells, initiating a T-cell–mediated inflammatory response.[13] Second, gut microbial alteration, termed *dysbiosis*, is thought to play a role in the pathogenesis of axial spondyloarthritis. Human studies have shown translocation of gut bacteria and bacterial products through a disrupted intestinal barrier (due to microscopic intestinal inflammation) to distant axial as well as peripheral articular and entheseal sites, which precipitates an inflammatory arthritis response.[14,15] A third hypothesis involves repetitive mechanical trauma at the entheses in a genetically predisposed individual, which leads to recruitment of neutrophils from the bone marrow to the entheseal site, producing neutrophilic inflammation and activation of proinflammatory cytokines such as IL-23, IL-17, and TNF.[10,16] The pathogenic mechanisms underlying extramusculoskeletal manifestations such as uveitis are currently not well understood. Clinical features that increase the likelihood for spondyloarthritis are listed in **Box 1**.

Epidemiology

Radiographic axial spondyloarthritis is more common among men than women, with a male to female ratio of 3:1.[17] However, with use of magnetic resonance imaging (MRI) to diagnose early stages of axial spondyloarthritis (nonradiographic disease), axial spondyloarthritis has a similar prevalence between males and females.[18] The prevalence of axial spondyloarthritis increased in the US between 2006 and 2014. The prevalence increased from 4.39 to 6.52 cases per 10 000 and from 1.33 to 2.21 cases per 10 000, based on Medicare and MarketScan data, respectively.[19] This is likely due to increased recognition by clinicians. While the population prevalence (diagnosed and undiagnosed patients in the general population) is approximately 1% based on data from the National Health and Nutrition Examination Survey,[2,3] recent electronic health record studies reported the diagnostic prevalence (diagnosed patients in a defined cohort) to be approximately 0.2%.[20] This difference between the population prevalence vs diagnostic prevalence reported in real-world data from electronic health records suggests that this condition is underdiagnosed by clinicians. In a systematic review and meta-analysis[21] of 64 observational studies of 28 947 patients, the pooled mean delay from symptom onset to diagnosis of axial spondyloarthritis was 6.7 years (95% CI, 6.2-7.2), with high levels of heterogeneity among the included studies. Diagnostic delay has the potential to lead to disease progression and structural damage to the spine, due to delayed treatment.[22] Advanced disease and spinal fusion can limit patients' range of motion, reduce physical function, increase disability, and worsen quality of life.[22,23] A cohort study of 644 patients with axial spondyloarthritis who were followed up for 5 years reported a positive association

Figure 1. Pathophysiology of Axial Spondyloarthritis



Multiple mechanisms play a role, including HLA-B27, gut microbiome, and mechanical stress. The interaction between dendritic cells and $CD8^+$ T cells, as well as the activation of $CD4^+$ T cells, promote an inflammatory cascade characterized by the production of several cytokines including interleukin (IL) 23, IL-22, IL-17, and tumor necrosis factor. With chronic inflammation, new bone formation will occur. This is thought to be due to mesenchymal cell proliferation leading to osteoblast differentiation, mediated by multiple signaling pathways including Wnt, bone morphogenetic protein, and hedgehog.

Box 1. What Clinical Features Increase the Likelihood for Spondyloarthritis?

- Inflammatory back pain (see definition in **Table 1**)
- Peripheral inflammatory arthritis (typically oligoarticular [≤4 joints], involving large joints, asymmetric, greater in lower limbs than in upper limbs)
- Heel enthesitis (inflammation of the insertion of the Achilles tendon or plantar fascia to the calcaneum)
- Dactylitis (sausage digits)
- Acute anterior uveitis (iritis)
- Psoriasis
- Inflammatory bowel disease
- Positive for human leukocyte antigen B27
- Elevated C-reactive protein level
- Family history of spondyloarthritis (axial spondyloarthritis, bxpsoriatic arthritis, inflammatory bowel associated arthritis, or reactive arthritis)
- Good response to nonsteroidal anti-inflammatory drugs

Table 1. Key Symptomatic Differences Between Inflammatory and Mechanical Back Pain

Characteristics of inflammatory back pain[a]	Characteristics of mechanical back pain
Chronic (>3 mo) gradual onset	Acute or chronic
Significant morning stiffness ≥30 min	Morning stiffness <30 min
Improves with activity	Worsens with activity
Does not improve (or worsens) with rest	Improves with rest
Awakens patient from sleep; typically second half of the night	Sleep disturbance is uncommon
Good response to nonsteroidal anti-inflammatory drugs (>50% symptom relief in 48 h with full dose of the drug)	Fair to poor response to nonsteroidal anti-inflammatory drugs

[a] All features may not be present at the same time in a patient; up to 80% of patients with axial spondyloarthritis present with inflammatory back pain. Only 15% of patients with inflammatory back pain develop axial spondyloarthritis.

Figure 2. Dactylitis of the Left Second Toe

between disease activity scores and disability assessed using a validated outcome measure, the Health Assessment Questionnaire for Ankylosing Spondylitis (adjusted β, 0.205 [95% CI, 0.187-0.222]).[24] This association was also reported between spinal mobility and disability (adjusted β, 0.087 [95% CI, 0.069-0.105]).[24] Diagnostic delay may occur more commonly in females compared with males; 1 study of 2846 unselected patients participating in the European Map of Axial Spondyloarthritis study reported that compared with males, females reported a longer diagnostic delay (mean, 6.1 [SD, 7.4] years vs 8.2 [SD, 8.9] years; $P < .001$).[21,25]

Clinical Manifestations

Patients with axial spondyloarthritis often present with what is commonly known as *inflammatory back pain*. Although this term is a misnomer, since it describes specific symptomatic characteristics of the back pain without objective evidence of inflammation, it may suggest the presence of an immune-mediated cause for a patient's back pain. Typical inflammatory back pain observed in axial spondyloarthritis is characterized by prolonged morning stiffness [≥30 minutes], improvement with exercise, and failure to improve with rest, with a gradual onset typically starting before age 45 years (**Table 1**). In a study that included 180 patients with axial spondyloarthritis, the prevalence of inflammatory back pain was 81%.[26] However, the presence of inflammatory back pain alone is insufficient to diagnose axial spondyloarthritis (sensitivity, 74%-81%; specificity, 25%-44%).[26] Moreover, only 15% of patients with inflammatory back pain will develop axial spondyloarthritis.[3]

Approximately 20% of patients with axial spondyloarthritis have symptoms affecting joints or organs in addition to the axial skeleton, such as peripheral arthritis, enthesitis, or uveitis.[27] Peripheral inflammatory arthritis typically affects the large joints such as knees and shoulders in an asymmetric, oligoarticular fashion (<4 joints), mostly involving lower extremities (30%-40%),[18] enthesitis in 30% to 40%,[18] and dactylitis or "sausage digits" (5%-7%) (**Figure 2**).[18] Acute anterior uveitis, experienced by up to 45% of patients with axial spondyloarthritis in their lifetime, commonly presents with ocular pain, erythema, blurry vision, and photophobia and may be associated with floaters and vision loss.[28] Extramusculoskeletal manifestations, which may be the presenting symptom of axial spondyloarthritis, include psoriasis, which affects 10% to 15% of patients[18] and inflammatory bowel disease (Crohn disease and ulcerative colitis), which affects 8% of patients.[28] Because sacroiliitis or spondylitis may be observed in both psoriatic and inflammatory bowel disease (IBD)–associated arthritis, it can sometimes be difficult to identify whether the disease is primarily axial spondyloarthritis with comorbid psoriasis/IBD or primarily psoriatic/IBD disease with concomitant axial inflammation.

Diagnosis

No diagnostic criteria are available for axial spondyloarthritis; classification criteria are intended for use in research studies. A rheumatologist should be consulted for patients with suspected axial spondyloarthritis to ensure timely diagnosis and management.

To diagnose axial spondyloarthritis, it is important to determine if patients have back pain symptoms with inflammatory features (**Box 2**) or symptoms of peripheral arthritis or enthesitis and

Box 2. Commonly Asked Questions

When should the diagnosis of axial spondyloarthritis be considered?

Axial spondyloarthritis should be considered for people presenting with chronic low back pain that started before age 45 years and that has any of the following features: inflammatory back pain (defined as gradual-onset pain that improves with activity but not with rest, is associated with prolonged morning stiffness, and typically improves with nonsteroidal anti-inflammatory drugs), peripheral arthritis, enthesitis, dactylitis, psoriasis, uveitis, or inflammatory bowel disease.

What are first-line treatments for axial spondyloarthritis?

First-line treatment for axial spondyloarthritis consists of nonsteroidal anti-inflammatory drugs such as selective and nonselective cyclooxygenase inhibitors. Physical therapy helps to maintain physical function, range of motion, and mobility. For patients who do not improve with nonsteroidal anti-inflammatory drugs, treatment options include biologic and targeted synthetic disease-modifying antirheumatic drugs such as tumor necrosis factor inhibitors, interleukin 17 inhibitors, and Janus kinase inhibitors.

What initial diagnostic testing should be performed for patients being evaluated for axial spondyloarthritis?

Patients being evaluated for axial spondyloarthritis should undergo laboratory testing for C-reactive protein level and human leukocyte antigen B27 and have sacroiliac joint radiographs. Patients should be referred to a rheumatologist for confirmation of the diagnosis and further management.

Table 2. Differential Diagnosis of Axial Spondyloarthritis and Differentiating Factors

Condition	Differentiating factors
Diffuse idiopathic skeletal hyperostosis	Commonly presents in patients older than 50 y with mechanical pain symptoms
Osteitis condensans ileii (ileal sclerosis)	Commonly observed in postpartum females on radiographs, usually asymptomatic
Degenerative spinal disease	Commonly presents in elderly patients with mechanical pain symptoms
Fibromyalgia	Widespread pain with no signs of inflammation
Sacroiliac joint infection or diskitis	Suggestive history such as fevers and risk factors (for example intravenous drug use)
Malignancy	Suggestive history such as fevers, unintentional weight loss, night sweats
Fractures	Suggestive history such as trauma or falls, accompanied by severe pain

to assess for family history of axial spondyloarthritis, which is present in 27% to 30% of patients who test positive for HLA-B27.[29]

A comprehensive history, physical examination, and targeted investigations such as laboratory tests and imaging should be performed to rule out conditions in the differential diagnosis such as diffuse idiopathic skeletal hyperostosis, osteitis condensans ileii, and degenerative spinal disease (**Table 2**).

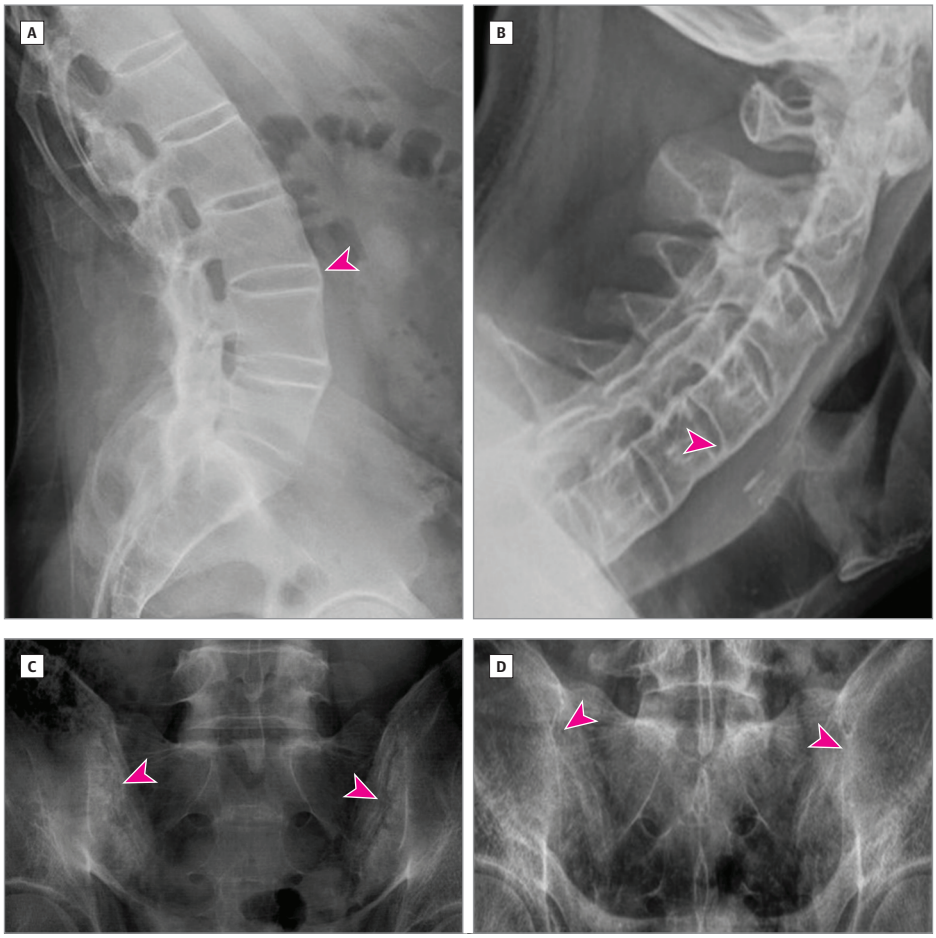
Physical examination should include an assessment of spinal tenderness and range of motion. Maneuvers to evaluate the flexibility and range of motion of the spine have a sensitivity of 68% to 79% and specificity of 36% to 45% for diagnosing axial spondyloarthritis.[30] Clinicians should examine the peripheral joints, entheses, and digits for signs of inflammation such as tenderness to palpation, redness, swelling, and warmth and be vigilant for extramusculoskeletal findings of well-circumscribed scaly skin rash (psoriasis) and ocular erythema, pain, and photophobia (uveitis). If acute anterior uveitis is suspected based on clinical history of pain and photophobia and on physical examination findings of ocular erythema, patients should be urgently referred to an ophthalmologist for a comprehensive eye examination including slit-lamp examination to decrease the risk of vision loss.

Laboratory tests such as HLA-B27 (sensitivity, 50%; specificity, 90%)[31,32] and C-reactive protein (CRP) level (elevated in ≈40% of patients with axial spondyloarthritis [sensitivity, 35%; specificity, 91%])[33] are not diagnostic of axial spondyloarthritis because 6% of the US general population is positive for HLA-B27,[2] and CRP level may be elevated in several conditions such as obesity, infections, and many immune-mediated inflammatory diseases such as rheumatoid arthritis and crystal arthritis (gout and calcium pyrophosphate deposition). In a study that enrolled 133 consecutive patients with back pain, 47 (35.3%) had a diagnosis of spondyloarthritis[31]; of these, 49% tested positive for HLA-B27 and 40% had elevated CRP levels.[31] Because the prevalence of axial spondyloarthritis in the general population is relatively low (1%), the specificities of HLA-B27 positivity and CRP level are not high enough to confirm a diagnosis in unselected patients. Approximately 6% of HLA-B27–positive individuals in the US general population have axial spondyloarthritis.[34]

Imaging plays an important role in the diagnosis of axial spondyloarthritis. The main feature that differentiates radiographic from nonradiographic disease is the presence of definite sacroiliitis on plain radiographs. Sacroiliitis on radiographs is defined by any combination of sclerosis, erosions, narrowing or widening, or fusion of the sacroiliac joints (**Figure 3**). Because it can take up to 10 years for sacroiliitis to appear on radiographs,[35] a negative radiograph does not rule out axial spondyloarthritis if the clinical history is suggestive of the disease. In addition, findings of sacroiliitis on plain radiography have poor reproducibility, with studies showing interreader agreement (κ value) ranging between 0.36 and 0.55.[36] Plain radiography has a sensitivity of 66% and a specificity of 68% for diagnosis of axial spondyloarthritis.[37]

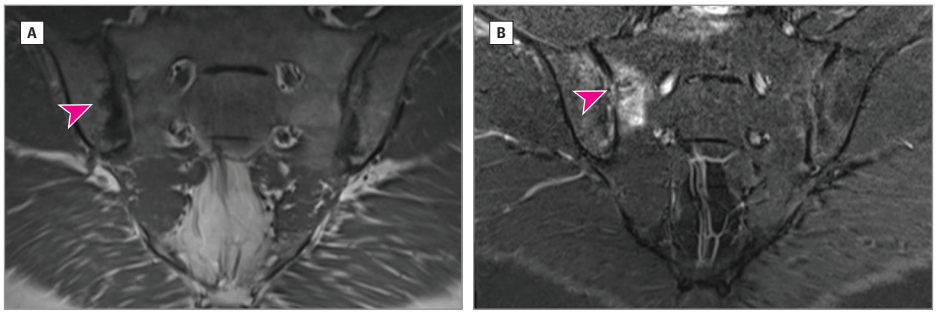
Magnetic resonance imaging of the sacroiliac joint should be obtained if the diagnosis is not established based on clinical features and plain radiography,[38] and contrast is not needed unless there is a concern for infection or malignancy. MRI semicoronal scans of the cartilaginous portion of the sacroiliac joints should include T1-weighted sequences that show structural lesions such as fatty replacement of the bone marrow (known as fat metaplasia), erosions, and ankylosis and short tau inversion recovery sequences that demonstrate active inflammatory lesions such as bone marrow edema, capsulitis, enthesitis, and joint fluid (**Figure 4**).[39] While bone marrow edema is suggestive of an inflammatory process, an isolated lesion is not sufficient to diagnose axial spondyloarthritis, because sacroiliac joint bone marrow edema can be observed in athletes such as healthy runners (up to 35%) and in individuals with nonspecific back pain (23%).[40] Similarly, bone marrow edema can be observed on MRI in up to 77% of postpartum individuals.[41] Because specific sequences on MRI of the sacroiliac joint have similar sensitivity to computed tomography to detect structural lesions (46% in nonradiographic and 95% in radiographic disease) and have the additional benefit of detecting active inflammatory lesions,[42] MRI

Figure 3. Classic Features of Axial Spondyloarthritis on Spinal and Sacroiliac Joint Radiographs



A, Syndesmophytes in the lumbar spine (arrowhead). B, Syndesmophytes in the cervical spine (arrowhead). C, Erosions, narrowing, and partial fusion in the sacroiliac joints (arrowheads) (bilateral grade 3 sacroiliitis). D, Complete ankylosis (fusion) of the sacroiliac joints (arrowheads) (bilateral grade 4 sacroiliitis).

Figure 4. Findings on Magnetic Resonance Imaging



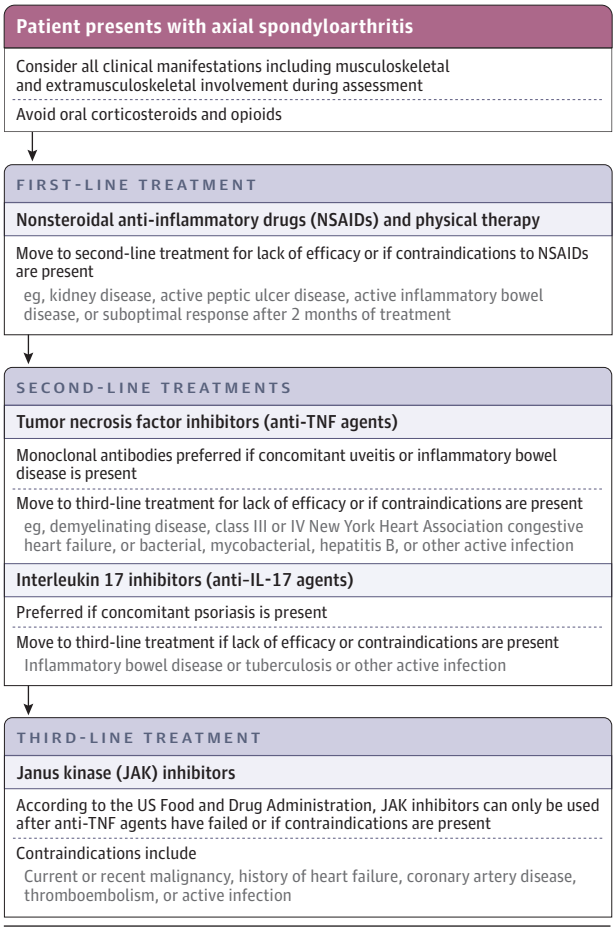
A, T1-weighted magnetic resonance imaging (MRI) sequence showing erosions in the sacroiliac joint (arrowhead). B, Short tau inversion recovery magnetic resonance imaging sequence showing bone marrow edema (arrowhead).

of the sacroiliac joints is currently the preferred imaging test for evaluating axial spondyloarthritis in patients whose radiographic images are not diagnostic. Low-dose computed tomography of the sacroiliac joints can detect bony erosions with a relatively low radiation exposure (<1 mSv)[43] and is used for patients with contraindications to MRI imaging or if there is concern about structural damage (eg, an erosion) that is not well identified on MRI.

Treatment

The ACR/SPARTAN/SAA published revised treatment guidelines in 2019,[8] and the Association of Spondyloarthritis International Society/EULAR revised guidelines were published in 2022.[9] According to the ACR/SPARTAN/SAA guidelines, when choosing a therapy for axial spondyloarthritis, it is important to consider all clinical manifestations, including musculoskeletal and extramusculoskeletal involvement (**Figure 5**). First-line treatment for axial spondyloarthritis (sacroiliac joints, spine, and peripheral joints) is nonsteroidal anti-inflammatory drugs (NSAIDs). However, a population-based survey of 842 patients with ankylosing spondylitis reported that only 19.1% achieved complete symptom control with NSAIDs alone.[44] While NSAIDs reduce the symptoms of axial spondyloarthritis, the data on radiographic progression are conflicting. An earlier trial reported that

Figure 5. Axial Spondyloarthritis Treatment Algorithm Based on the 2022 European Alliance of Associations for Rheumatology Guidelines



continuous celecoxib use slowed radiographic progression,[45] but a more recent trial showed that continuous diclofenac did not affect radiographic progression after 2 years of use.[46]

Per ACR and EULAR guidelines, physical therapy should be recommended to all patients with axial spondyloarthritis, except for those with advanced spinal fusion. Physical therapy is important for muscle strengthening, to maintain good range of motion and appropriate posture.[47] A multicenter randomized clinical trial of 100 patients with axial spondyloarthritis reported that high-intensity exercise supervised by a physical therapist led to improvements in disease activity scores (Ankylosing Spondylitis Disease Activity Score, −0.6 [95% CI, −0.8 to −0.3]; $P < .001$; minimal clinically important difference, 1.1) and functional status (Bath Ankylosing Spondylitis Functional Index, −0.9 [95% CI, −1.3 to 0.4]; $P < .001$; minimal clinically important difference, 0.7).[47]

Oral glucocorticoids and conventional synthetic disease-modifying antirheumatic drugs such as sulfasalazine and methotrexate are not recommended to treat axial (spinal and sacroiliac joint) inflammation.[48,49] Conventional synthetic disease-modifying antirheumatic drugs may be useful to treat concomitant peripheral arthritis, extramusculoskeletal manifestations such as uveitis, or inflammatory bowel disease, but these agents and oral glucocorticoids should be avoided for axial skeletal manifestations.

Most patients (≥75%) with axial spondyloarthritis require treatment with a biologic or targeted synthetic disease-modifying antirheumatic agents (biologic disease-modifying antirheumatic drugs, targeted synthetic disease-modifying antirheumatic drugs) such as anti-TNF agents, anti–IL-17 agents, or JAK inhibitors. In 2003, the first anti-TNF was approved by the US Food and Drug Administration (FDA) for the treatment of active ankylosing spondylitis.[50] Since some patients respond to NSAIDs, and because of possible adverse effects and high costs, biologics are not considered first-line treatment for axial spondyloarthritis.[8]

Biologic therapy with anti-TNF or anti–IL-17 agents is considered second-line treatment for axial spondyloarthritis, after a suboptimal response to 2 different NSAIDs at maximum doses for 2 months.[8] There are 5 original anti-TNF agents (**Table 3**) and currently multiple other anti-TNF biosimilars. All approved anti-TNF agents demonstrated similar efficacy for treating spinal and sacroiliac joint inflammatory arthritis in clinical trials (Table 3),[53-57] and there are currently no published trials comparing individual anti-TNF agents. Although the TNF receptor fusion protein inhibitor etanercept has not improved outcomes in patients with inflammatory bowel disease and uveitis, the 4 monoclonal antibodies against TNF (adalimumab, certolizumab, golimumab, and infliximab) are efficacious for treating inflammatory bowel disease and preventing recurrence of uveitis.[77]

In a trial of adalimumab that included 208 patients, 121 (58%) achieved the primary end point of Assessment in Ankylosing Spondylitis Response Criteria 20 (ASAS20) at week 12, compared with 22 (21%) receiving placebo ($P < .001$).[54] ASAS20 is a composite score that includes 4 domains: patient global assessment, pain, function, and inflammation; ASAS20 is achieved when 3 of 4 domains improve by at least 20% and there is no worsening in the remaining domain. In a randomized clinical trial (RCT) of 277 patients, 82 (59%) who received etanercept achieved the ASAS20 responses at week 12, compared with 39 (28%) in the placebo group ($P < .001$).[53] For golimumab, in an RCT of 356 patients, 82 (59%) achieved the ASAS20 outcome at week 14, compared with 22% in the placebo group ($P < .001$).[55] In an RCT of 325 patients, 68 (64%) who received certolizumab pegol at a dose of 400 mg every 4 weeks achieved the ASAS20 response at 12 weeks, compared with 41 (38%) receiving placebo ($P < .001$).[56] For infliximab, in an RCT of 279 patients, 123 (61%) achieved ASAS20 responses at 24 weeks, compared with 19% in the placebo group ($P < .001$).[57] In retrospective cohort studies, anti-TNF agents were associated with a reduced rate of radiographic progression of spinal damage (lower rates of new bone formation, erosions, and fusion). A North American study (Prospective Study of Ankylosing Spondylitis) followed up a cohort of 334 patients with axial spondyloarthritis (133 anti-TNF agent–naive, 201 receiving anti-TNF agents) over a mean of 2.87 years (range, 1.5-9 years) and obtained radiographs of the spine at different time points at least 1.5 years apart.[78] This study reported that the use of anti-TNF agents was associated with a 50% reduction in the odds of radiographic progression (odds ratio, 0.52 [95% CI, 0.30-0.88]; absolute data not available).[78]

Despite the efficacy of anti-TNF treatments in treating axial spondyloarthritis, 13% to 68% of patients either do not respond or have a decreased response over time due to either antidrug antibody formation or for unclear reasons.[79] Treatment guidelines recommend that patients who have a reduced clinical response over time might benefit from a different anti-TNF agent, while patients who did not

Table 3. Major Clinical Trials of NSAIDs, TNF Inhibitors, IL-17 Inhibitors, and JAK Inhibitors in Axial Spondyloarthritis

Medication	Route and dose	Efficacy outcome	Comments	Adverse effects
NSAIDs (level of evidence: low)				
			Avoid in patients with history of cardiac disease, kidney disease, uncontrolled hypertension, active peptic ulcer	Cardiovascular Gastrointestinal Kidney
Celecoxib	Oral: 100 mg or 200 mg twice per d	Mean improvement in pain intensity on a scale of 1-100: −30 celecoxib vs −10 placebo, $P < .001$ (N = 611)[51]		
Naproxen	Oral: 500 mg twice per d	Mean improvement in pain intensity on a scale of 1-100: −35 naproxen vs −10 placebo, $P < .001$ (N = 611)[51]		
Etoricoxib[a]	Oral: 90 mg daily	Mean improvement in pain intensity on a scale of 1-100: −41 etoricoxib vs −12 placebo, $P < .001$ (N = 387)[52]		
Anti-TNF agents (level of evidence: high)				
				Injection site or infusion reactions: 7%-30%[53-57] Infections: 20%-45%[53-57]
Adalimumab	Subcutaneous: 40 mg every 2 wk	ASAS20 at wk 12: 58.2% adalimumab vs 20.6% placebo, $P < .001$ (ATLAS[54] [N = 315][b])[c] ASAS40 at wk 12: 36% adalimumab vs 15% placebo, $P < .001$ (ABILITY-1[58] [N = 192][b])[c]	Screen for tuberculosis, hepatitis B Avoid in demyelinating disease and advanced congestive heart failure Efficacy in uveitis, inflammatory bowel disease, and psoriasis	
Etanercept	Subcutaneous: 50 mg every wk	ASAS20 at wk 12[c]: 59% Etanercept vs 28% placebo, $P < .0001$ (Davis et al[53] [N = 277][b]) 60% Etanercept vs 23.1% placebo, $P < .001$ (Calin et al[59] [N = 84][b]) ASAS40 at wk 12[c]: 32% Etanercept vs 16% placebo, $P = .006$ (EMBARK[60] [N = 215][b])	Screen for tuberculosis, hepatitis B Avoid in demyelinating disease and advanced congestive heart failure Efficacy in psoriasis but suboptimal for uveitis and inflammatory bowel disease	
Golimumab	Subcutaneous (50 mg every 4 wk) or intravenous (2 mg/kg at weeks 0 and 4 then every 8 wk thereafter)	ASAS20 at wk 14[c]: 59.4% Golimumab vs 21.8% placebo, $P < .001$ (GO-RAISE[55] [N = 356][b]) ASAS20 at wk 16[c]: 71.1% Golimumab vs 40% placebo; $P < .0001$ (GO-AHEAD[61] [N = 198][b]) 73.3% Golimumab vs 26.2% placebo; $P < .001$ (GO-ALIVE[62] [N = 208][b])	Screen for tuberculosis, hepatitis B Avoid in demyelinating disease and advanced congestive heart failure Efficacy in uveitis, ulcerative colitis, and psoriasis Intravenous form has the advantage of being dosed based on weight	
Certolizumab pegol	Subcutaneous: 400 mg at 0, 2, and 4 wk then 200 mg every 2 wk or 400 mg every 4 wk	ASAS20 at wk 12[c]: 57.7% Certolizumab every 2 wk vs 63.6% certolizumab every 4 wk vs 38.3% placebo, $P \leq .004$ (RAPID-axSpA[56] [N = 325][b])	Screen for tuberculosis, hepatitis B Avoid in demyelinating disease and advanced congestive heart failure Efficacy in uveitis, Crohn disease, and psoriasis Since it lacks the Fc portion, it is less likely to cross placenta and has minimal excretion in breast milk Anti-TNF agent of choice in pregnancy and peripartum period	
Infliximab	Intravenous: 5mg/kg at 0, 2, and 6 wk then every 6 wk thereafter	ASAS20 at wk 24[c]: 61.2% Inflixmab vs 19.2% placebo, $P < .001$ (ASSERT[57] [N = 279][b])	Screen for tuberculosis, hepatitis B Avoid in demyelinating disease and advanced congestive heart failure Efficacy in uveitis, inflammatory bowel disease, and psoriasis Weight-based therapy	

(continued)

respond initially to an anti-TNF agent should be treated with a different class of medications such as an anti–IL-17 agent or JAK inhibitor (level of evidence very low).[8] Absolute contraindications to anti-TNF therapy include a history of demyelinating disease, such as multiple sclerosis, class III or IV New York Heart Association congestive heart failure, active bacterial or mycobacterial infection, and hepatitis B infection.

The 2019 ACR/SPARTAN/SAA treatment guidelines consider anti–IL-17 agents such as secukinumab and ixekizumab to be third-line treatment for axial spondyloarthritis.[63,66,71,72,80] A recent randomized trial of 859 patients with radiographic axial spondyloarthritis compared the anti–IL-17A secukinumab doses of 150 mg and 300 mg vs an adalimumab biosimilar (anti-TNF agent).[81] At 2 years, the proportion of patients without radiographic progression was 66.1% in the secukinumab (150 mg) group, 66.9% in the secukinumab (300 mg) group, and 65.6% in the adalimumab biosimilar group (P = not significant). The safety profiles of both anti–IL-17A medications (secukinumab and ixekizumab) are similar,

Table 3. Major Clinical Trials of NSAIDs, TNF Inhibitors, IL-17 Inhibitors, and JAK Inhibitors in Axial Spondyloarthritis (continued)

Medication	Route and dose	Efficacy outcome	Comments	Adverse effects
Anti-IL-17 agents (level of evidence: high)				
				Injection site or infusion reactions: 13%-16%[63-65] Infections: 16%-30%[63-67] Inflammatory bowel disease (exposure-adjusted incidence rate, 0.4-0.8 per 100 patient-years)[68,69]
Secukinumab (anti-IL17A)	Subcutaneous: 150 mg at 0, 1, 2, 3, and 4 wk then every 4 wk Intravenous: 6 mg/kg at wk 0 then 1.75 mg/kg every 4 wk	ASAS20 at wk 16[c]: 61% Secukinumab vs 29% placebo, $P < .001$ (MEASURE 1[70] [N = 590][b]) 61% Secukinumab vs 28% placebo, $P < .001$ (MEASURE 2[71] [N = 219][b]) 58.1% Secukinumab vs 36.8% placebo, $P < .05$ (MEASURE 3[66] [N = 226][b]) ASAS40 at wk 16[c]: 42.2% Secukinumab vs 29.2% placebo, $P = .0197$ (PREVENT[67] [N = 555][b])	Screen for tuberculosis, hepatitis B Avoid in active inflammatory bowel disease Efficacy in psoriasis Subcutaneous form suboptimal for uveitis; intravenous form may be helpful Intravenous form is dosed based on weight	
Ixekizumab (anti-IL-17A)	Subcutaneous: 160 mg at wk 0 then 80 mg every 4 wk	ASAS40 at wk 16[c]: 48% Ixekizumab vs 18% placebo, $P < .0001$ (COAST-V[63] [N = 341][b]) 25.4% Ixekizumab vs 12.5% placebo, $P = .017$ (COAST-W[65] [N = 316][b]) 35% Ixekizumab vs 19% placebo, $P = .0094$ (COAST-X[72] [N = 303][b])	Infection risk Screen for tuberculosis, hepatitis B Avoid in active inflammatory bowel disease Efficacy in psoriasis Suboptimal for uveitis	
Bimekizumab (anti-IL-17A/F)	Subcutaneous: 160 mg every 4 wk	ASAS40 at wk 16[c]: 47.7% Bimekizumab vs 21.4% placebo, $P < .001$ (BE-MOBILE1[64] [N = 254][b]) 44.8% Bimekizumab vs 22.5% placebo, $P < .001$ (BE-MOBILE2[64] [N = 332][b])	Infection risk Screen for tuberculosis, hepatitis B Avoid in active inflammatory bowel disease Efficacy in psoriasis Efficacy in uveitis unclear	
JAK inhibitors (level of evidence: high)				
				Cytopenias: 1%-4%[73-75] Hepatotoxicity: 3%-6%[73-75] Infections: 20%-24%[73-75] Shingles: 1%-2%[73,74] Thromboembolic disease: 0.23/100 patient-years[76] Black box warning for serious infections, mortality, malignancy, major adverse cardiovascular events, and thrombosis
Tofacitinib	Oral: immediate-release 5 mg twice daily or extended-release 11 mg once daily	ASAS20 at wk 16[c]: 56.4% Tofacitinib vs 29.4% placebo, $P < .0001$[73] (N = 269)	Bacterial and herpes zoster infection, cardiovascular, malignancy risk Screen for tuberculosis, hepatitis B/C Avoid in patients with increased cardiovascular risk Efficacy in ulcerative colitis and psoriasis; unclear efficacy in uveitis	
Upadacitinib	Oral: 15 mg once daily	ASAS40 at wk 14[c]: 52% Upadacitinib vs 26% placebo, $P = .0003$ (SELECT-AXIS1[75] [N = 187][b]) 45% Upadacitinib vs 23% placebo, $P < .0001$ (SELECT-AXIS2[74] [N = 313][b])	Bacterial and herpes zoster infection, cardiovascular, malignancy risk Screen for tuberculosis, hepatitis B/C Avoid in patients with increased cardiovascular risk Efficacy in inflammatory bowel disease and psoriasis Unclear efficacy in uveitis	

Abbreviations: ASAS, Assessment of Spondyloarthritis International Society; IL-17, interleukin 17; JAK, Janus kinase; NSAID, nonsteroidal anti-inflammatory drug; TNF, tumor necrosis factor.

[a] Not approved in the United States.

[b] Trial name/author not approved in the United States.

[c] ASAS20 is a composite score that includes 4 domains: patient global assessment, pain, function, and inflammation (ASAS20 is achieved when 3 of 4 domains improve by at least 20%, with no worsening in the remaining domain). ASAS40 has identical definition but with 40% improvement instead of 20%.

with the exposure-adjusted incidence rates of inflammatory bowel disease in patients with axial spondyloarthritis ranging between 0.4 and 0.8 per 100 patient-years.[68,69] Bimekizumab, a new agent that blocks IL-17A and IL-17F, has shown efficacy and safety similar to that of other anti–IL-17A agents.[64] While patients with axial spondyloarthritis can have concomitant inflammatory bowel disease, rare cases of incident inflammatory bowel disease associated with anti–IL-17 agents have been reported. Similarly, pooled data from anti–IL-17 phase 3 studies showed that the exposure-adjusted incidence rate of uveitis was 1.4 per 100 patient-years.[82] Absolute contraindications to use of anti–IL-17 agents include active inflammatory bowel disease, tuberculosis, bacterial infection, and hepatitis B infection.

Two JAK inhibitors (tofacitinib and upadacitinib) were approved by the FDA for the treatment of ankylosing spondylitis in 2022. While tofacitinib is approved for radiographic disease alone, upadacitinib is approved for both radiographic and nonradiographic axial spondyloarthritis (Table 3).[73-75,83,84] In an open-label extension of the SELECT-AXIS-1 trial of upadacitinib, 92 patients were followed up for 2 years and had follow-up sacroiliac joint radiographs; 89.7% had no radiographic progression.[85] JAK inhibitors can also be used for treatment of inflammatory bowel disease; tofacitinib is FDA approved for treatment of ulcerative colitis, and upadacitinib is approved for treatment of Crohn disease and ulcerative colitis. Based on safety data from a rheumatoid arthritis study (ORAL Surveillance), the FDA issued a black box warning for JAK inhibitors to indicate a potential increased risk of cardiovascular disease, thromboembolic events, and malignancy.[86] Therefore, JAK inhibitors should be avoided in patients with a current or recent malignancy and in those with a history of heart failure, coronary artery disease, or thromboembolism.

Local corticosteroid injection (eg, methylprednisolone [40 mg]) in the sacroiliac joints, peripheral joints, and upper extremity entheses can provide symptomatic relief, and injections may be repeated after at least 3 months. Corticosteroid injections in lower extremity weight-bearing entheses such as the Achilles tendon should be avoided because of the risk of tendon rupture. Opioids are not recommended to treat axial spondyloarthritis because they do not have anti-inflammatory properties, studies have not documented efficacy, and they are associated with risk of opioid addiction.[87]

Several studies have examined tapering or discontinuing biologics in patients with axial spondyloarthritis who are in an inactive disease state, defined by either disease activity scores (eg, Axial Spondyloarthritis Disease Activity Score [ASDAS] <1.3 [ASDAS is a disease activity score that assesses pain, stiffness, swelling, patient global assessment, and CRP level]) or by resolution of clinical symptoms. In a recent study, 736 patients with axial spondyloarthritis received the anti-TNF agent certolizumab pegol. At week 48, 313 patients who had achieved sustained remission were randomized to full-dose certolizumab pegol (200-mg subcutaneous injection every 2 weeks) (n = 104), lower-dose certolizumab pegol (200 mg subcutaneous injection every 1 month) (n = 105), or discontinuation of certolizumab pegol (n = 104).[88] During weeks 48 to 96, 83.7% of patients receiving the full maintenance dose, 79.0% receiving the reduced maintenance dose, and 20.2% receiving placebo were flare-free ($P < .001$ vs placebo in both groups). Disease flare was defined based on disease activity scores as either ASDAS 2.1 or greater at 2 consecutive visits or ASDAS greater than 3.5 at any point during the study. Additionally, in 12 clinical trials, 53% to 100% of patients had a flare within 12 months after discontinuing a biologic.[88-97] These data support lowering the dose of biologics, but not discontinuing them, in patients with axial spondyloarthritis who reach and maintain an inactive disease state for 6 months or longer.

Comorbidities and Prognosis

A 2020 systematic review and meta-analysis of 36 studies and 119 427 patients[98] reported that the most prevalent comorbidities in patients with axial spondyloarthritis were hypertension (23%), cardiovascular disease (12%), and depression (11%).[98] Rates of these comorbidities were higher than in age- and sex-matched controls without axial spondyloarthritis.[98] A nationwide population-based study from Taiwan that included 2331 patients with axial spondyloarthritis reported that depression was more prevalent compared with controls (3.1% vs 1.9%), with an adjusted hazard ratio of 1.71 (95% CI, 1.30-2.26).[99] Low bone density is also common in patients with axial spondyloarthritis due to chronic inflammation.[100] A study of 204 patients in Sweden with ankylosing spondylitis reported osteopenia in 44%, and osteoporosis in 21%, of patients older than 50 years.[101] A Danish Health registry reported an increased risk of spinal fractures (0.11% of the fracture cases were among patients with axial spondyloarthritis, compared with 0.07% in controls; odds ratio, 5.42 [95% CI, 2.50-11.70]).[102] Patients with axial spondyloarthritis should be counseled about fall risk to avoid fractures.

The goals of managing axial spondyloarthritis are to control symptoms, improve function, reduce or halt radiographic progression, and prevent complications such as osteoporosis and fractures. Currently available therapeutic agents, including biologic and targeted synthetic disease-modifying antirheumatic drugs (anti-TNF agents, anti–IL-17 agents, and JAK inhibitors), alleviate symptoms and slow disease progression. No longitudinal data of treatment effect for any medication on disease-related mortality are currently available.

Limitations

This review has several limitations. First, some relevant articles may have been missed in the literature search. Second, the quality of the included articles was not formally evaluated. Third, some topics related to axial spondyloarthritis, such as treatment options for extra-articular disease (uveitis, psoriasis, and inflammatory bowel disease), are not discussed.

Conclusions

Axial spondyloarthritis is an immune-mediated condition that primarily affects the sacroiliac joints and spine but is also associated with extra-articular manifestations such as uveitis, psoriasis, and inflammatory bowel disease. First-line treatment for axial spondyloarthritis is NSAIDS such as selective and nonselective cyclooxygenase inhibitors and physical therapy to reduce symptoms and improve functional status. Individuals who do not improve with initial therapy should be treated with more advanced targeted therapeutics such as biologics (anti-TNF agents, anti–IL-17 agents) and JAK inhibitors.

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Submissions: We encourage authors to submit papers for consideration as a Review. Please contact Kristin Walter, MD, at kristin.walter@jamanetwork.org.

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