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A Road Map of the Axial Spondyloarthritis Continuum

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Abstract

Axial spondyloarthritis (axSpA) is a chronic, immune-mediated inflammatory disease characterized by inflammatory low back pain, inflammation in peripheral joints and entheses, and other extra-articular or systemic manifestations. Although our understanding of the natural history of axSpA has been limited by incomplete knowledge of disease pathogenesis, axSpA is increasingly understood as a spectrum of axial, peripheral, and extra-articular inflammatory conditions that includes nonradiographic axSpA and radiographic axSpA, also known as ankylosing spondylitis. In this narrative review, we present a road map of this axSpA continuum, highlighting genetic risk factors for the development of axSpA, triggers of disease, and reasons for and implications of diagnostic delay. We present a detailed overview of the spectrum of axSpA clinical manifestations and highlight factors known to influence the risk of disease progression. Finally, we provide some expert commentary on the practical use of this road map to assist health care providers in the identification of axSpA in clinical practice.

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BACKGROUND

Axial spondyloarthritis (axSpA) is a chronic, immune-mediated inflammatory disease manifesting as a spectrum of inflammatory conditions, including inflammatory back pain, inflammation in peripheral joints and entheses, extra-articular involvement, and comorbidities.[1,2] The prevalence of axSpA in the US population is estimated to be 0.9% to 1.4%,[3,4] and it typically is manifested in patients younger than 45 years, most frequently in patients aged 20 to 30 years.[5]

The natural history of this disease has been obfuscated by an evolving but not yet well defined understanding of the etiology and pathophysiology of this condition, the pleiotropic co-manifestations and comorbidities associated with axSpA, the lack of information on the early manifestations of this entity, and the changing classification criteria.[6] Axial spondyloarthritis encompasses patients with radiographic (x-ray) sacroiliitis visible on imaging (radiographic axSpA [r-axSpA] or ankylosing spondylitis [AS]) and those without evidence of radiographic damage in the sacroiliac (SI) joints (nonradiographic [nr]-axSpA).[7] The terms AS and r-axSpA can be used interchangeably, and r-axSpA can be used in describing previous studies of patients with AS.[8] Throughout this narrative review, we use r-axSpA to refer to patients with AS. For regulatory purposes in the United States, nr-axSpA and r-axSpA are classified as distinct entities, although they are increasingly understood to represent 2 regions on a continuum of clinical symptoms and radiographic anomalies constituting axSpA.[9,10] Although nr-axSpA can occur in patients without SI changes on radiography but with evidence of inflammation on magnetic resonance imaging (MRI), nr-axSpA does not absolutely require MRI changes and can exist without any imaging abnormalities in patients who are HLA-B27 positive. The continuum of disease presentation does not necessarily reflect disease course, as not all patients with nr-axSpA will progress to r-axSpA (Figure).[11,12] Radiographic features of axial disease in r-axSpA are quantifiable on classic radiography and can more readily contribute to diagnoses than the less distinctive peripheral inflammation and extra-articular manifestations

that characterize nr-axSpA or early axSpA, resulting in differential diagnoses and diagnostic delay among patients with nr-axSpA.[13,14]

As knowledge of the axSpA continuum continues to grow along with the landscape of effective treatment options,[15] identification of axSpA by rheumatologists and other health care providers is critical to realize ideal patient outcomes. This review presents a road map of axSpA as a continuum of disease manifestations that can be classified as nr-axSpA or r-axSpA, discusses factors influencing the development and progression of axSpA, and provides some expert commentary to assist health care professionals in identification of the spectrum of axSpA manifestations in clinical practice.

ARTICLE HIGHLIGHTS

- Axial spondyloarthritis (axSpA) is a heterogeneous disease that can be represented by a continuum encompassing both nonradiographic and radiographic axSpA.
- The clinical course of axSpA may be nonlinear and unique to individual patients, and underrecognition of axSpA in patients with chronic back pain or extra-articular manifestations can result in misdiagnoses or delayed diagnosis.
- Advanced features of radiographic axSpA are the most easily recognizable, although more subtle manifestations can contribute to significant disease burden and respond to therapy.
- Effective therapies are available to treat the complete spectrum of axSpA manifestations.
- It is critical for health care providers to become familiar with the continuum of axSpA manifestations to ensure that all patients can receive appropriate and timely treatment.

THE STARTING POINT: GENETIC PREDISPOSITION TO AXSPA

Axial spondyloarthritis is a heritable disease with strong familial clustering. Among patients from the Icelandic genealogy database, risk ratios of first-, second-, and third-degree relatives of individuals with r-axSpA were 75.5, 20.2, and 3.5, respectively ($P<.0001$ for all comparisons).[16] In a study of all patients diagnosed with r-axSpA in Sweden during a 16-year period, the overall familial odds ratio (OR) for r-axSpA was 19.4 (95% CI, 18.1 to 20.8), and patients with more than 1 family member with r-axSpA had a higher risk for development of the disease (OR, 60.8; 95% CI, 51.3 to 90.1) compared with patients with no known family history.[17]

Several genetic risk factors have been associated with the development of axSpA. Among these, the presence of the genetic marker HLA-B27 is consistently and strongly associated with development of axSpA.[18-21] Approximately 80% to 95% of patients with criteria-defined r-axSpA are HLA-B27 positive compared with less than 10% of the general population.[22-24] Predominant hypotheses relating the presence of HLA-B27 to axSpA pathogenesis include potential arthritogenic activity of peptides presented by HLA-B27,[25] misfolding in the endoplasmic reticulum,[26] and homodimerization of HLA-B27[27,28] contributing to aberrant immune response, including signaling through the interleukin (IL) 23/17 pathway.[29] Bacterial dysbiosis in patients who are HLA-B27 positive may also play a role in the development of axSpA.[30] Other genetic markers have been associated with axSpA,[31] including polymorphisms in *ERAP1* (OR, 1.29; $P<.0001$), *RUNX3* (OR, 1.15; $P<.0001$), *PTGER4* (OR, 1.08; $P<.0001$), and *IL23R* (OR, 1.62; $P<.0001$).[32] Supporting the understanding of these as manifestations of the same disease process, nr-axSpA and r-axSpA have been found to have similar genetic features.[33]

BEGINNING THE JOURNEY: TRIGGERING EVENTS

Several hypotheses concerning initiation of axSpA have been proposed, although definitive causes have yet to be established. Mechanical stress on entheses has been proposed as a triggering event of axSpA.[34] An anatomic link between the enthesis and synovium is well established,[35,36] although it remains unclear whether aberrant response to mechanical stress alone is sufficient to initiate axSpA.[34] Direct evidence in humans is lacking, although a model of joint

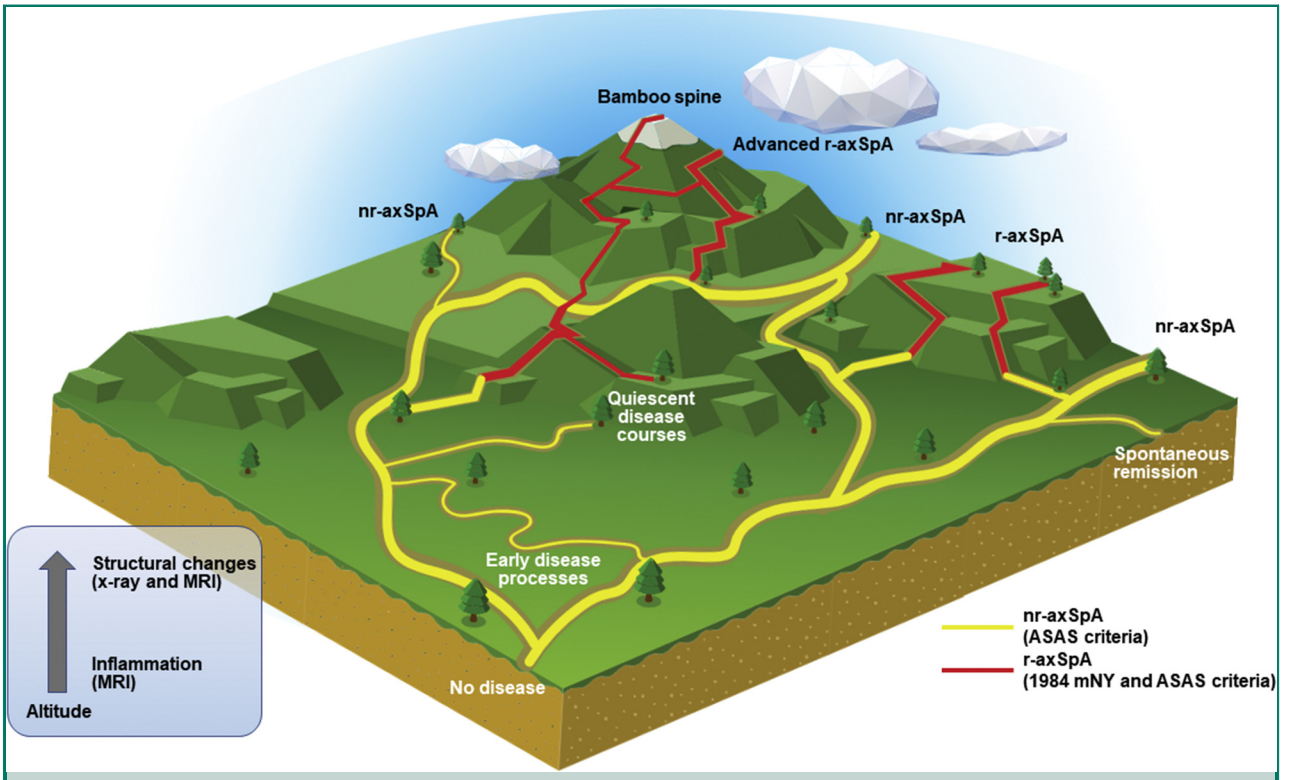

FIGURE. Road map of the continuum of nonradiographic axial spondyloarthritis (nr-axSpA) through radiographic axial spondyloarthritis (r-axSpA). ASAS, Assessment of SpondyloArthritis international Society; 1984 mNY, 1984 Modified New York Criteria for Ankylosing Spondylitis; MRI, magnetic resonance imaging.

loading in mice with increased tumor necrosis factor α (TNF-α) signaling supports a link between mechanical strain, entheseal inflammation, and new bone formation.[37] Increased disease activity and burden among patients with r-axSpA who have been exposed to manual labor or whole-body vibration in the workplace indirectly support this hypothesis.[38-40] In 1 cohort study, patients with axSpA who had physically demanding jobs had greater increases in the modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS) for every unit of Ankylosing Spondylitis Disease Activity Score compared with patients with sedentary job responsibilities (1.2 vs 0.2 mSASSS; P=.014).[40] Changes to the microbiome have been observed in patients with axSpA compared with healthy controls, and some potentially causal relationships between dysbiosis of the gut microbiota and the development of axSpA have been proposed.[41]

REALIZING WHEN THE JOURNEY HAS STARTED: DELAY IN DIAGNOSIS

Axial spondyloarthritis is a notoriously underreported disease. Delay in diagnosis has been attributed to the insidious onset and slow progression of signs and symptoms; the nonspecific nature of early symptoms, such as back pain or peripheral joint pain; the lack of specific biomarkers for axSpA; and the evaluation and management by health care providers not familiar with this disease entity.[13,42,43] If axSpA is not accurately identified and effectively treated early in the disease course, patients experience poorer clinical outcomes and quality of life and more substantial economic burden, and those with radiographic disease experience greater structural damage.[13,44-48] For example, a cross-sectional study of patients with r-axSpA found correlations between diagnostic delay and sacroiliitis grade (P=.042), chest expansion (P<.001),

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Bath Ankylosing Spondylitis Metrology Index score ($P<.001$), Bath Ankylosing Spondylitis Functional Index score ($P=.003$), Bath Ankylosing Spondylitis Disease Activity Index score ($P=.026$), and AS quality of life ($P=.008$).[47] In a separate study analyzing the economic impact of treatment and specialized testing before diagnosis of spondyloarthritis (SpA) among patients in the Italian Health Search Database, patients had a health care expense of roughly €153,000 ($203,000 [2013]) in the 3 years before a diagnosis of SpA.[44]

Diagnostic delay is a major barrier to proper treatment of axSpA, and ranges of 5 to 14 years from onset of symptoms to diagnosis are typically cited.[46,49-52] This delay in diagnosis does not appear to be improving over time. One retrospective analysis found that diagnostic delay was similar between patients diagnosed with axSpA between 1996 and 2005 and those diagnosed between 2006 and 2016.[53] A retrospective chart review found median diagnostic delay to be stable at 5.0 years among patients diagnosed at different periods of time: 1999 to 2003, 2004 to 2008, and 2009 to 2013.[54] Finally, a recent systematic literature review and meta-analysis of 64 studies found the diagnostic delay to be 6.7 years (95% CI, 6.2 to 7.2); this delay did not change when results were stratified by publication year.[55] Many patients see multiple practitioners, including primary care physicians, rheumatologists, orthopedists, chiropractors, urgent care/emergency department physicians, sports medicine specialists, dermatologists, physiatrists, obstetricians and gynecologists, physical therapists, and podiatrists, and receive different diagnoses on their path to correct diagnosis of axSpA.[43,45,46] There is room for education to mitigate delay in diagnosis through improved identification of axSpA and early referral of patients to rheumatologists. Screening of patients with inflammatory back pain or extra-articular manifestations of axSpA could shorten this delay.[13,56]

TRIANGULATION OF LOCATION: DIAGNOSIS

No diagnostic criteria currently exist for axSpA, and the current classification criteria can lead to confusion if misused in the diagnostic process. The 1984 modified New York criteria proposed that patients must have definitive sacroiliitis by classic radiography, defined as bilateral grade 2 or higher or unilateral grade 3 or higher sacroiliitis, to be classified as having r-axSpA.[57] In real-world practice, 50% or more of patients with axSpA do not fulfill the classification criteria for r-axSpA[52]; many of these patients satisfy the Assessment of SpondyloArthritis international Society (ASAS) criteria for axSpA and may be classified as having nr-axSpA.[7] These terms are useful in classifying patients for inclusion in clinical trials and for use in epidemiologic studies, but they are not diagnostic criteria.[9]

Diagnostic criteria for axSpA have not been formalized, largely for the same reasons such criteria have not been developed for other syndromes and diseases.[58] In particular, there is concern for potential misapplication of such criteria, leading to overdiagnosis and the resulting unnecessary, costly, and potentially harmful treatment of inappropriately diagnosed patients.[59] Diagnosis should be made at the exclusion of other possible conditions and not by simply determining whether a patient has a sufficient number of axSpA features, which may be present as a result of other causes. For example, mechanical back pain is a differential diagnosis of particular concern because of some overlapping signs and symptoms, and patients with mechanical back pain would not benefit from axSpA treatment.[56] Instead, the standard for axSpA diagnosis remains clinician judgment when radiographic findings, physical examination findings, HLA-B27 status, C-reactive protein level, and presence of other SpA features are evaluated in totality.[56]

Ongoing research on axSpA manifestations is being conducted to assist clinicians in making reasoned diagnostic decisions. A recent latent class analysis of patients from

the SpondyloArthritis Caught Early (SPACE) and DEvenir des Spondylarthropathies Indifférenciées Récentes (DESIR) cohorts identified 3 recognizable clinical entities of axSpA.[60] These include pure axial SpA, which reflects the traditional clinical manifestations of axSpA captured by the ASAS criteria; axial SpA with peripheral signs, which consists of patients who mostly fulfill the ASAS peripheral SpA criteria and may represent a substantial clinical overlap between peripheral SpA and axSpA; and axial SpA at risk, which consists of patients with risk factors for axSpA who may not have and may never develop axSpA.[60] Because up to 60% of the patients in the axial SpA at risk group fulfilled ASAS criteria for axSpA despite that only 11% progressed to axial SpA with peripheral signs after 5 years of follow-up,[60] this group may be at risk of overdiagnosis and overtreatment by clinicians who improperly rely on the ASAS criteria for diagnosis.

THE TERRAIN: CLINICAL PRESENTATION OF THE AXSPA CONTINUUM

A defining manifestation of axSpA is chronic inflammatory back pain lasting more than 3 months in patients younger than 45 years, the onset of which is frequently insidious.[61-63] Inflammatory back pain usually is manifested in the lower back but may affect any region of the spine; patients also may notice alternating buttock pain that is not radicular in character.[61,64] Up to 50% of patients may report neck pain as an early symptom of axSpA,[65] and cervical spinal involvement is more common in women than in men.[66,67] Patients with inflammatory back pain often experience worse pain at night, which may cause awakening in the second half of the night; morning stiffness persisting for more than 30 minutes is common.[61,68] Inflammatory back pain generally improves with activity and responds well to nonsteroidal anti-inflammatory drugs (NSAIDs).[62,68,69]

Axial spondyloarthritis is a systemic disease that can result in manifestations and complications that are remote from the axial skeleton. Signs and symptoms can also be manifested in the peripheral skeleton, with some patients experiencing enthesitis, dactylitis, and peripheral inflammatory arthritis.[70-73] Patients with axSpA also frequently experience extra-articular manifestations of this systemic inflammatory disease.[2,70,74,75] Between 4% and 6% of patients with axSpA have been found to have a history of inflammatory bowel disease,[70,75] although up to 50% may have asymptomatic inflammation of the ileal and colonic mucosa.[76,77] Anterior uveitis is a relatively common extra-articular manifestation, affecting approximately 25% to 35% of patients with axSpA and presenting as unilateral eye pain and redness, photophobia, and blurred vision.[78,79] Approximately 10% of patients with axSpA also experience psoriasis[80]; psoriatic disease has been associated with HLA-B27,[81] potentially representing an overlap among axSpA and psoriatic arthritis classification criteria. In addition, HLA-B*0801 has been identified in patients with sacroiliitis as a manifestation of psoriatic arthritis.[82] A number of comorbidities are associated with axSpA, including osteoporosis, cardiovascular disease, dyslipidemia, depression, fatigue, and obstructive sleep apnea.[83-87]

The ASAS developed classification criteria for the identification of axSpA, including nr-axSpA and r-axSpA, dividing patients into 2 arms based on imaging and clinical criteria. To be classified as having nr-axSpA, patients must have 3 months or more of back pain, have an age at onset before 45 years, and meet the criteria for either the imaging or clinical arm.[7] To be classified under the imaging arm as having nr-axSpA, patients must have evidence of sacroiliitis by MRI along with 1 or more SpA features; patients in the clinical arm must be HLA-B27 positive and have 2 or more SpA features and need not have any imaging abnormalities.[7] Features of SpA include inflammatory back pain, arthritis, enthesitis, uveitis, dactylitis, psoriasis, Crohn disease or ulcerative colitis, good response to NSAIDs, HLA-B27 positivity, and elevated C-reactive protein level. Classification of patients with r-axSpA requires definitive x-ray evidence of sacroiliitis.

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The earliest manifestation of the disease involving inflammation before permanent radiographic damage is classified as nr-axSpA.[75] Patients with nr-axSpA frequently experience SpA features despite having limited or no discernible radiographic changes in the SI joints or spine.[7,75,88] Many of these patients will never develop such radiographic changes.

The terms r-axSpA and AS are interchangeable, as more than 90% of patients with definitive sacroiliitis fulfill both the ASAS criteria for r-axSpA and the modified New York criteria for AS.[8] Patients with r-axSpA can experience bone erosion in the SI joints and spine as well as syndesmophyte and new bone formation; these structural changes are detectible by classic radiography.[89] These patients can experience decreased spinal mobility and chest wall expansion related to both inflammatory disease and structural changes as disease progresses.[90]

The most advanced form of axSpA is known as bamboo spine, in which widespread syndesmophyte formation leads to vertebral body fusion known as ankylosis.[91] Patients with bamboo spine experience severely diminished spinal mobility and rib cage expansion.[92] One retrospective chart review study of patients with r-axSpA found bamboo spine present in 34% of men and 12% of women with AS.[93]

Although manifestations and extent of radiographic damage differ between nr-axSpA and r-axSpA, disease burden and response to treatment are similar. In a systematic literature review and meta-analysis of randomized controlled trials of patents with either nr-axSpA or r-axSpA, patients with nr-axSpA more frequently had peripheral involvement and patients with r-axSpA had more impaired mobility, although disease burden, response to treatment, and other aspects of clinical presentation were similar.[71] For example, patients with nr-axSpA had more peripheral arthritis, dactylitis, and enthesitis than those with r-axSpA ($P<.01$ for all comparisons), and patients with r-axSpA had higher mSASSS ($P<.001$) and were more likely to have MRI SI joint erosions ($P=.032$) and MRI SI joint fatty lesions ($P<.001$) than those with nr-axSpA.[71] However, disease burden was similar as measured by Bath Ankylosing Spondylitis Disease Activity Index, patient global assessment, Health Assessment Questionnaire for Spondyloarthropathies, EuroQol 5-Dimension questionnaire, and the 36-Item Short Form Health Survey mental and physical component summaries ($P>.05$ for all comparisons).[71] No differences in response to treatment with NSAIDs, conventional synthetic disease-modifying antirheumatic drugs, biologics, or systemic glucocorticoids were identified between groups ($P>.05$ for all comparisons).[71]

MULTIPLE ROUTES OF TRAVEL: PROGRESSION OF AXSPA

The clinical course of axSpA may be nonlinear and unique to individual patients (Figure).[11] Only a subset of patients with nr-axSpA may eventually have radiographic damage.[11,12] Overall, an estimated 5% to 10% of patients with nr-axSpA will develop structural changes in the SI joints indicative of r-axSpA during 2 years, increasing to 5% to 40% within 10 years of disease onset.[12,94,95] The lifetime chances of progression from nr-axSpA to r-axSpA have been estimated to be 50%.[12]

Predictors of the progression from nr-axSpA to r-axSpA have been identified,[12] including HLA-B27 positivity,[96] smoking,[97] and baseline SI joint inflammation on MRI.[98] Findings on MRI generally precede permanent radiographic structural damage and are a risk factor for future radiographic progression.[98,99] In patients with r-axSpA and existing radiographic damage to the spine, the presence of existing syndesmophytes is the strongest risk factor for the development of new syndesmophytes.[100]

Some differential risk factors have been identified between sexes. Multiple studies have shown that men have a higher risk for development of radiographic damage to the SI joints or spine.[101-103] Elevated C-reactive protein levels and smoking are risk factors for radiographic progression in men but not in women.[104] High Bath Ankylosing

Spondylitis Metrology Index scores and bisphosphonate use have been found to be risk factors for progression among women.[104]

Sex-specific differences in disease manifestation have been observed, and sex may influence the progression or course of the disease.[51,67] The prevalence of r-axSpA is approximately 2:1 to 3:1 in men vs women,[66,105] and increased understanding of the axSpA continuum suggests an approximate 1:1 distribution of nr-axSpA across the sexes.[67,88] Women have shown less spinal radiographic damage, as assessed by the Bath Ankylosing Spondylitis Radiology Index, than men, yet more functional impairment at the same level of radiographic damage.[106] In general, men may be more likely than women to progress to r-axSpA or to develop structural changes earlier in the disease course.[88] In a real-world study of patients with axSpA, women were found to have higher disease burden, including poorer patient global assessment scores, worse patient-reported outcomes, greater disease activity, and greater peripheral arthritis, despite having greater spinal mobility than men.[107] These observed sex-specific differences in disease presentation and course may be founded on pathophysiologic differences between men and women; gene expression profiles differ between men and women with AS, which may have a role in driving the direction and extent of the disease course.[108] Women experience an increased diagnostic delay compared with men,[67,109] possibly as a result of these sex-specific differences in axSpA manifestations, particularly the greater risk of radiographic damage in male patients and overall lack of knowledge of nr-axSpA and its approximately equal distribution across sexes. Fibromyalgia and chronic, widespread pain, which may accompany axSpA, can contribute to diagnostic delay among women with axSpA.[43,110,111] In a real-world study of patients' diagnostic journeys, women were more likely than men to be misdiagnosed with fibromyalgia (20.7% vs 6.6%; $P<.05$) or psychosomatic disorders (40.8% vs 23.0%; $P<.05$) before diagnosis with axSpA.[43]

Axial spondyloarthritis does not progress similarly in all patients; some may exhibit a quiescent disease course.[11] Spontaneous remission of r-axSpA is uncommon but has been observed in a limited number of patients.[11,112] Results from the C-AxSpAnd study of patients with nr-axSpA suggested that spontaneous remission is unlikely in patients without biologic treatment; only 7.0% of patients randomized to receive placebo and nonbiologic background medication achieved Ankylosing Spondylitis Disease Activity Score major improvement (decrease of $\geq$2.0 units or achievement of the lowest possible score of 0.6) at week 52 compared with 47.2% of patients randomized to receive certolizumab pegol and nonbiologic background medication ($P<.0001$).[113] With regard to progression, there are data to suggest that at times a discordance exists between peripheral and axial disease. In a study of Brazilian patients with axSpA, with increasing age at onset, the proportion of patients with purely axial symptoms decreased while the proportion of patients with purely peripheral symptoms increased ($P<.001$).[114]

Treatment guidelines recently updated by the American College of Rheumatology, in partnership with the Spondylitis Association of America and the Spondyloarthritis Research and Treatment Network, provide similar recommendations regardless of radiographic progression.[15] First-line treatment with NSAIDs remains the cornerstone of axSpA management. For many patients, NSAID treatment is sufficient to manage signs and symptoms. Systemic glucocorticoids are not recommended for the treatment of axSpA. Biologics are recommended for patients with inadequate response to or who are intolerant of NSAIDs, with conditional recommendations for treatment with TNF-α inhibitors over treatment with secukinumab or ixekizumab. The TNF-α inhibitor certolizumab pegol and the IL-17A inhibitors secukinumab and ixekizumab are the only biologics to be approved by the

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Food and Drug Administration for both nr-axSpA and r-axSpA. The TNF-α inhibitors adalimumab, etanercept, golimumab, and infliximab are currently Food and Drug Administration approved for r-axSpA only. Treatment with systemic biologics can result in sustained clinical remission.[112,115,116] The TNF-α inhibitors adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab have been proven effective in the management of axSpA and have demonstrated improvement in inflammation detectable by MRI.[117] Although inhibition of TNF-α or IL-17A can result in lower objective measures of inflammation in patients with axSpA,[112,118,119] the impact of these treatments on radiographic progression remains an area of investigation. Recent work suggests that these therapies potentially limit structural progression; for example, a meta-analysis of 24 studies, including 18 studies in which patients received TNF-α inhibitors, found a protective effect of TNF-α inhibition on radiographic progression after 4 years of treatment.[120]

USING THE ROAD MAP: EXPERT COMMENTARY

The road map of axSpA continues to evolve as we learn more about the genetics, immunology, pathophysiology, and phenotype of this disease process. Some in the health care community may view the axSpA continuum as a progressive disease leading to irreversible damage, with nr-axSpA as a precursor to r-axSpA. However, not all patients progress along this continuum; nr-axSpA and r-axSpA refer to classifications of 2 regions along a continuous spectrum of disease, although these 2 phenotypes can result in similar disease burden and should therefore be treated similarly. From a regulatory or payer perspective in the United States, nr-axSpA and r-axSpA are viewed as 2 separate entities, complicating treatment decisions. Data demonstrating the effectiveness of treatments among patients with or without radiographic sacroiliitis may help inform formulary decisions among payers and regulators.

A straightforward and effective screening strategy is necessary to ensure timely referral of patients with suspected axSpA to rheumatologists. Early referral of patients with signs of chronic inflammatory back pain (≥3 months) to rheumatologists is likely to reduce diagnostic delay and to improve patient outcomes. To reduce diagnostic delay for all manifestations of axSpA, all health care providers likely to encounter patients with inflammatory back pain and the comanifestations of axSpA should be aware of this important concept and familiar with other key axSpA features, including peripheral arthritis, uveitis, inflammatory bowel disease, psoriasis, and fatigue. These presentations and manifestations can occur without discernible imaging changes. The occurrence of an atypical presentation in women should be carefully considered as potential signs of axSpA because definitive radiographic damage to the SI joints or spine occurs less frequently in women than in men.[101,103,104,121]

Diagnostic imaging tools, including classic radiography and MRI, have complementary roles in identifying disease in patients across the axSpA spectrum.[89,99,122,123] Clinicians should be aware of the utility of MRI for identifying active inflammation characteristic of axSpA, particularly of the SI joints,[124] before permanent radiographic damage occurs.[99,123] Magnetic resonance imaging of the spine is not recommended for axSpA diagnosis,[122,125] although it may have some value in monitoring disease course and response to treatment.

Patients who have received a diagnosis of axSpA should be aware that there is no monolithic prognosis; patients experience axSpA burden and progression differently (Figure). Not all cases of axSpA progress to radiographic disease, although patients with nr-axSpA can still experience substantial disease burden.[71] Currently, management of axSpA is recommended to be similar regardless of radiographic progression.[15] Many patients can adequately manage their disease with NSAIDs and exercise, and biologic agents have shown promise at improving clinical signs of axSpA and slowing

radiographic progression in patients who are not adequately treated with nonbiologic therapies.[15]

CONCLUSION

Axial spondyloarthritis is a heterogeneous disease with multiple manifestations and can be represented by a continuum encompassing both nr-axSpA and r-axSpA, which are associated with a similar disease burden and need for aggressive therapy. Underrecognition of axSpA symptoms in patients with chronic back pain or extra-articular manifestations may result in misdiagnoses or delayed diagnosis of axSpA. The most advanced features, such as imaging changes in the SI joints and spine, are also the most easily recognizable, although not all patients with axSpA who could benefit from therapy will ever display these radiographic changes despite having considerable disease burden. Keen awareness of axSpA features among health care providers is likely to improve diagnostic accuracy, resulting in reduced diagnostic delay and improved patient outcomes. The availability of effective therapies approved for the spectrum of axSpA manifestations from nr-axSpA to r-axSpA highlights the importance of awareness of the complete continuum of axSpA.

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Abbreviations and Acronyms: **AS**, ankylosing spondylitis; **ASAS**, Assessment of SpondyloArthritis international Society; **axSpA**, axial spondyloarthritis; **IL**, interleukin; **MRI**, magnetic resonance imaging; **mSASSS**, modified Stoke Ankylosing Spondylitis Spinal Score; **nr-axSpA**, nonradiographic axial spondyloarthritis; **NSAID**, nonsteroidal anti-inflammatory drug; **OR**, odds ratio; **r-axSpA**, radiographic axial spondyloarthritis; **SI**, sacroiliac; **SpA**, spondyloarthritis; **TNF-α**, tumor necrosis factor α

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