NAVIGATING ADVANCEMENTS IN DIAGNOSIS & TREATMENT OF AXIAL SPONDYLOARTHRITIS

ANNENBERG CENTER FOR HEALTH SCIENCES AT EISENHOWER
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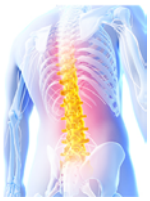

Overview

More than 80% of the population has significant back pain at some point in their life, with 30% of adults in the United States stating they have chronic low back pain at any given time; 5% of whom have inflammatory back pain. Axial spondyloarthritis (axSpA) affects almost 1.5% of patients with inflammatory back pain; however, the majority of individuals suffering with back pain are not being treated by a rheumatologist, which only exacerbates the challenge to diagnose those with axSpA.

Dr. Leonard Calabrese discusses both radiographic and nonradiographic ankylosing spondylitis in detail, differentiating their diagnostic properties and how to properly treat and manage patients with this inflammatory disease that affects daily function and quality of life. Dr. Calabrese emphasizes appropriate testing and imaging with use of ASAS guidelines to provide an accurate diagnosis, while sharing case examples through disease progression and treatment selection.

CE Information

Target Audience

This activity was developed for rheumatologists, primary care physicians, nurse practitioners, physician assistants and other healthcare providers who diagnose and manage patients with axial spondyloarthritis.

Learning Objectives

At the conclusion of this activity, participants should be better able to:

- Diagnose ankylosing spondylitis (AS) using ASAS guidelines
- Diagnose non-radiographic axial spondyloarthritis (nr-axSpA) using ASAS guidelines
- Utilize validated tools to assess AxSpA disease burden and response to treatment
- Summarize the safety and efficacy of biologic treatments for AxSpA
- Utilize a treat-to-target approach with individualized evidence-based therapy to reduce symptom burden and, when possible, achieve disease remission/low disease activity

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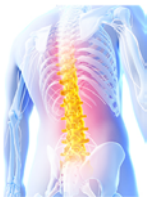

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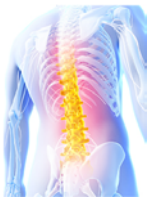

Abbreviations

- AP, anterior posterior
- AS, ankylosing spondylitis
- ASAS40, Assessment of Spondyloarthritis International Society 40
- ASAS, Assessment of Spondyloarthritis International Society Criteria
- axSpA, axial spondylarthritis
- CRP, C-reactive protein
- CZP, certolizumab pegol
- ESR, erythrocyte sedimentation rate
- HLA, human leukocyte antigen
- JAK, Janus kinase 1 inhibitor
- MI, major improvement
- NBBM, nonbiologic background medication
- Nr-axSpA, nonradiographic axial spondylarthritis
- NSAIDs, nonsteroidal anti-inflammatory drugs
- RAPID3, Routine Assessment of Patient Index Data
- TNFi, tumor necrosis factor inhibitors
- VAS, visual analog scale

Pathogenesis, Patient Burden

Axial spondyloarthritis (axSpA) is the overarching form of a family of disease, with the hallmark symptom of inflammatory back pain, as well as bone and cartilage loss, and subsequent remodeling with new bone formation taking place in the entheses, axial skeleton, and peripheral joints.[1] There are 2 known forms of axSpA: Radiographic ankylosing spondylitis (AS, also known as radiographic axSpA), which is the most common and the most severe form of axSpA; and nonradiographic axial spondylarthritis (nr-axSpA), which has the clinical signs and symptoms of SpA, but without characteristic radiographic changes on pelvic X-rays.[2] The latter is described as axial inflammatory arthritis; a diagnosis of nr-axSpA has not caused substantial erosive damage to the sacroiliac joints; however, caution must be taken, as it can evolve into the more severe form of AS.[3]

Testing and Imaging

B27 testing is helpful in making the diagnosis of axSpA, and should be done early in patients with inflammatory back pain. Magnetic resonance imaging (MRI) scans can assist in early diagnosis, and are the mainstay of diagnostic imaging in patients with nr-axSpA, providing identification of inflammatory abnormalities for these patients.[3,4] The use of MRI can detect typical active inflammatory lesions, such as bone marrow edema, when fluid builds up in the bone marrow, representing early stages of inflammation, or osteitis, as seen in patients with AS; however, the complex anatomy of the sacroiliac joint makes interpretation of these radiographs challenging.

Burden of Disease

Both nonradiographic and radiographic axSpA have similar burden of disease. The primary of which is the impact of the disease and the decrease in patients' quality of life, including day-to-day function, disability, missed time at work, and increased health care costs. Lower back pain is one of the leading causes of disability in the United States, contributing to the overall disease burden through the indirect costs of lost wages, lost work, and disability payments.[5] Assessment criteria, such as Spondyloarthritis Research Consortium of Canada (SPARCC) at week 52, Bath Ankylosing Spondylitis Metrology Index (BASMI), and Maastricht Ankylosing Spondylitis Enthesitis Score (MASES), help measure patient-reported quality of life outcomes.

Pathogenesis of AxSpA

The pathogenesis of AxSpA may be associated with environmental and genetic factors, including a link with the HLA-B*27 antigen (patients frequently carry the gene for HLA-B27), which has been found to play a pivotal role of the pro-inflammatory cytokine, interleukin 17A (IL-17A). Fatty lesions are also predictive of radiographic progression in axSpA. Radiographic progression is highly variable, with a study over 12 years showing up to 25% of axSpA patients without progression.[3]

Clinical Manifestation

Axial spondyloarthritis commonly affects individuals in their second or third decade of life. Radiographic AS affects the sacroiliac joints and the tip of the column, with a tendency to later ankylosis, in addition the peripheral joints, entheses. Related extra-articular spinal systemic manifestations are often involved, specifically psoriasis and inflammatory bowel disease (IBD). Interestingly, there is a strong association of IBD, with 15% of patients with AS developing overt IBD and up to 60% exhibiting evidence of underlying subclinical microscopic colitis.[6]

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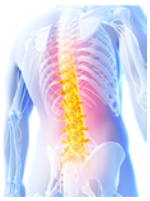


Part 1: Diagnosis of AS

When discussing axSpA, it is important to understand the data and prevalence surrounding back pain. The National Health and Nutrition Examination Survey (NHANES) from 2009–2010 shows more than 80% of the population has significant back pain at some point in their life. In 2016, 28.4% of adults [29.9% female; 26.7% male] in the United States stated they have chronic low back pain at any given time, and 5% have inflammatory back pain.[7,8] Most rheumatologist find axSpA affects at least 1.5% of their patients with inflammatory back pain.[5] It is also important to note that the majority of individuals suffering with back pain are not seeing a rheumatologist, but rather they turn to their primary care physician, chiropractor, osteopath, physiatrist, sports medicine provider, and other providers, which only exacerbates the challenge to diagnose those who have axSpA.

In a 2016 interview with renowned rheumatologist, John Reveille, MD, former director of the North American Spondylitis Consortium, only 14% of people with chronic back pain are ever seen by a rheumatologist, resulting in many patients with axSpA remaining undiagnosed due to low awareness of the condition among primary care practitioners. For AS, the gap between disease onset and diagnosis has been reported to range from 5 to 8 years. In addition, a startling 2017 statistic shows 55.1% of adults treated their own back pain, and of those, 49% treated using pain killers, while 32% self-treated with physical activity, and 30% used specific back exercises at home. As of 2018, 73% of adults with chronic back pain took nonsteroidal anti-inflammatory drugs (NSAIDs) for their pain.[7]

Inflammatory back pain

It is essential that providers and clinicians determine the specific cause of back pain afflicting patients in order to diagnose their symptoms properly, highlighting the patients with AS or nr-axSpA and referring them to a rheumatologist who can provide these patients with the necessary and appropriate treatment. The underlying symptom of these patients is inflammatory back pain. It cannot be stressed enough that the gateway symptom of inflammatory back pain is readily recognizable by a rheumatology specialist.

Clinical Features

Clinicians need to understand what SpA looks like and recognize inflammatory back pain in their patients. The primary features in AS include inflammatory back pain, with onset most often before the age of 45, as well as sacroiliitis on anterior-posterior (AP) plain radiograph, and at least 1 additional clinical feature that is equally important when diagnosing either AS or nr-axSpA. Additional extraspinal systemic manifestations may include inflammatory arthritis or the presence of enthesitis, synovitis, dactylitis, uveitis, psoriasis, Crohn's disease, or family history. Patients also tend to have a good response to NSAIDs.[4] These patients also have an elevated erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP), which are present in only 30% to 40% of patients, but it is important to remember a normal rate does not preclude inflammation.[2,3] Some clinicians use ESR or CRP to monitor disease flares or to predict a more favorable response to treatment. Through use of these essential tests, an alternative diagnosis is very unlikely.

Assessment of ASAS criteria for patients with inflammatory back pain

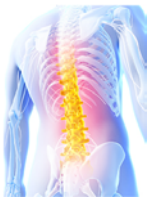
Diagnose inflammatory back pain, 4 out of the 5 parameters should be present

Back pain for >3 months
Age at onset <40 years
Insidious onset
Improvement with exercise
No improvement with rest
Pain at night (with improvement when getting up)

Adopted from Tsoi C, et al. *Quant Imaging Med Surg.* 2019.[9]

Distinguishing AS from RA

The clinical overview of axSpA is distinct with the musculoskeletal issues characterized by enthesitis, axial involvement, and the presence of characteristic extra-articular manifestations, as mentioned, including psoriasis, anterior uveitis flares, and inflammatory bowel disease (IBD), along with other SpA conditions. Enthesitis has been shown to be more common and more severe among female patients. Also, female patients experience more back, neck, knee, and hip pain, as well as IBD, compared to male patients, while male patients tend to



have acute anterior uveitis more frequently, and foot and joint pain.[10,11] Studies show that males fare worse with more severe radiological progression, including development of syndesmophytes.[10]

Part 2: Diagnosis of nr-axSpA

Nr-axSpA clinical features and diagnostic tools

The ACR/SAS 2015 recommendations state that nr-axSpA includes "patients who have chronic back pain and features suggestive of SpA but who do not meet the classification criteria for AS."[12,13] The main feature of nr-axSpA is that patients are negative for sacroiliitis, which requires evidence with X-rays or MRI. Advances in imaging have allowed for the identification of disease much earlier in the course of patient symptoms. The primary diagnosis process of nr-axSpA is determined, as noted, by negative evidence through X-ray of sacroiliitis, an HLA-B27 test, positive MRI (might be equivocal), or elevated CRP (might be borderline) to reveal inflammatory back pain.

Features of nr-axSpA in women

Although radiographic SpA is predominantly a disease among males, many studies show that females are equally and more prominently affected by nonradiographic axSpA. Features of nr-axSpA in women include more nonspinal pain and are often confused with fibromyalgia. It is noted that uveitis appears to be more prevalent among patients with AS than nr-axSpA, and subsequently more prevalent in male patients than female.[4,10] Meta-analysis studies indicate that female patients experience more IBD compared to male patients, as well as a higher prevalence of psoriasis compared to males with axSpA.[10]

Differential diagnosis

There are several conditions associated with chronic low back and spinal pain that may present similarly to axSpA. Some conditions that may be considered in the differential diagnosis include acute or chronic mechanical nonspecific back pain and inflammatory back pain without SpA, as well as fibromyalgia, diffuse idiopathic skeletal hyperostosis, vertebral compression fracture, sacroiliac joint infection, osteitis condensans ilii, insufficiency bone fractures, erosive osteochondrosis and Schmorl's nodes, and familial Mediterranean fever (FMF), in which patients may develop symptoms of back pain and imaging changes consistent with sacroiliitis.[14] In clinical practice, the diagnosis for SpA is often reached through the exclusion of other potential causes based on the presenting symptoms or findings.[3]

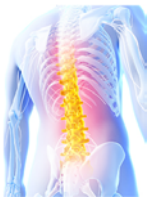
A high level of disease activity suggests, in the majority of patients with active disease, that nr-axSpA does not spontaneously remit and cannot be controlled with nonbiologic medications.[14] The study (n=317) demonstrated the limitations of nonbiologic treatments in patients with active disease, with objective signs of inflammation, in whom treatment with at least 2 NSAIDs was unsuccessful.[15] The *2019 Update of ACR Research and Treatment Recommendations* provides current recommendations for the treatment of adults with nonradiographic axial SpA.[16]

Case Diagnosis of a patient with nr-SpA

A 37-year-old male has a 12-year history of intermittent lower back pain that has gotten worse over the last 9 months. He recalls back pain in his 20s when he was playing soccer with a club and attributes his pain to recurrent injuries. Over the ensuing years, he has had several episodes of Achilles tendonitis, but attributed this to daily running, and treated with nonsteroidals. His mother has psoriasis.

He describes his pain as chronic, worse in the morning, and improves when he goes out for a light jog. Upon questioning, he tells you his back pain has increasingly been waking him in the middle of the night. Upon further questioning about what he does when he wakes with back pain, he states he paces around the house until it "loosens up." He has been using *PRN* over-the-counter nonsteroidals, but lately they are having no effect. He had seen his primary care doctor on several occasions and had gotten "back films," which were completely normal. He's frustrated and depressed that he is having difficulty conducting his activities of daily living and leisure time.

In review of the case, this patient has had chronic back pain, with insidious onset at a young age; it's worse in the morning, but better with exercise; diagnosis is inflammatory back pain; he's had back films.



Case Discussion

It is important to note that providers, when evaluating back pain, often obtain lumbosacral X-rays, and do not explicitly order anterior-posterior (AP) pelvis films to look at sacroiliac joints. In this case, the patient had both, and both were normal. This patient has normal X-rays and classic, chronic, inflammatory low-back pain. At this juncture, in the absence of X-ray abnormalities of the sacroiliac joints, the patient does not have axial spondyloarthropathy. **The next steps** would be to get a CRP test and an MRI of sacroiliac joints of his pelvis to explore the diagnosis of nr-SpA. A B27 test was obtained and was positive (HLA-B27 may be positive in up to 90% of most ethnic groups with axSpA; and 40%–70% with other SpA variants), which further supports the diagnosis. CRP is obtained and is elevated at 1.1mg%. The MRI was obtained and is normal. **In conclusion:** This patient with impressive inflammatory back pain and with an elevated CRP would meet criteria for nonradiographic axial spondyloarthropathy even in the absence of MRI changes. **End Case**

Part 3: Validated Tools

Assessing disease activity/burden

There are several validated and endorsed tools (ie, BASDAI, ASDAS, BASFI) used more often in clinical research and at specialized sites, to measure patients with axSpA, rather than by practicing rheumatologists. Clinicians use more readily available activity assessment measurements, such as Patient Global Pain, which is based on the question "How active was your spondyloarthritis last week?" with the answer noted on a NRS or a VAS, and score ranging from 0 (not active) to 10 (very active).[2] Clinicians also use the composite index Routine Assessment of Patient Index Data (RAPID3) as a useful, practical, and effective quantitative assessment tool to measure disease activity, as well as function in relation to quality of life.[17] RAPID3 has been found helpful in a busy clinical setting to facilitate quantitative measure of patients with active AS in routine care. Castrejón et al demonstrated in their DESIR study (n=461) over 6 months that the RAPID3 index in well-characterized patients with axSpA provides similar responsiveness to BASDAI and ASDAS-CRP.[18] The BASDAI is easy to administer and contains a global overall level of pain, and a reduction of 2 points, or greater than 50% of baseline, is a reasonable treatment response. It must be remembered that global pain responses can also be affected by psychosocial issues.

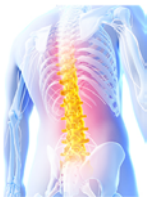
A minimum set of variables for axSpA is reviewed to understand the extent of the disease. These include questions pertaining to physical function, spinal stiffness to provide insight into inflammatory symptoms, patient global assessment, spinal mobility, fatigue, and pain.[2] Peripheral joint involvement is frequent and can be assessed using the 44-joint count, which measures the presence of swelling, with a total score varying from 0 to 44.[2]

Core domains and questions for clinical assessment of axSpA

Physical function	How long does your morning stiffness last from the time you wake up?
Patient global assessment	How active was your spondyloarthritis last week?
Spinal mobility and fatigue	How would you describe the overall level of fatigue/tiredness you have experienced?
Pain	How much pain of your spine due to AS do you have?
	How much pain of your spine due to AS do you have at night?

Classification for both AS and nr-axSpA

There are a myriad of endorsed classification scoring and indices that assess the burden of disease, which are used primarily in clinical research. The use of scoring helps determine progression of AS and nr-axSpA; the response criteria are also intended to measure a response to treatment.



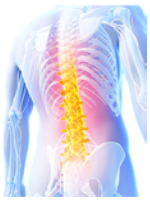
Classification and Scoring Disease Activity Indices	Criteria Assessment
Ankylosing Spondylitis Disease Activity Score (**ASDAS**)	Algorithm combining BASDAI elements, patient global assessment with lab measures to assess back pain, patient global assessment, duration of morning stiffness and peripheral pain/swelling from a score 0 to 10.
Ankylosing Spondylitis Quality of Life (**ASQoL**)	Patient-reported outcome (PRO) questionnaire to assess quality of life
Assessment of Spondyloarthritis International Society* (**ASAS**)	Assesses individuals <45 years of age and >3 months of chronic back pain; classification criteria performed in patients presenting with peripheral arthritis, enthesitis and/or dactylitis to measure function, pain, spinal mobility, and patient's global pain.
Bath Ankylosing Spondylitis Disease Activity Index (**BASDAI**)	Diagnostic test (patient-self report measures) to determine effectiveness of a current drug therapy or the need of a new drug therapy for treatment; Based on **6 questions** scored on an NRS or on a 10 cm VAS: fatigue, spinal pain, peripheral joints, entheses, intensity of morning stiffness, and duration of morning stiffness
Bath Ankylosing Spondylitis Functional Index (**BASFI**)	**10 questions** [8 refer to aspects of functional anatomy, 2 on ability to cope with everyday life], answered on a VAS; final score is avg of questions, from 0 (no limitation) to 10 (max limitation in function) to **assesses degree of functional limitation**
Bath Ankylosing Spondylitis Metrology Index (**BASMI**)	Provides baseline measurement to monitor change in spinal mobility over time; combines **5 measures**: TWD, modified Schober's test, cervical rotation, lateral spinal flexion, and intermalleolar distance
Berlin Enthesitis Index (**BEI**)	Validated enthesitis index includes 12 sites
Maastricht Ankylosing Spondylitis Enthesitis Score (**MASES**)	Assesses enthesitis in certain locations, such as the rib cage, lower back, and Achilles tendons; Includes 13 sites and only takes values per site of 0 (absent) or 1 (present)
Modified New York criteria (**mNY**)	Limitation of motion of the lumbar spine in all 3 planes; pain at the thoracolumbar junction or in the lumbar spine and stiffness >3 mo, improving with exercise but not relieved by rest
Modified Stoke Ankylosing Spondylitis Severity Score (**mSASSS**)	Modified SASSS by adding a score for the cervical spine and defining squaring; sum of the lumbar and cervical spine score (range 0– 72)
Routine Assessment of Patient Index Data (**RAPID3**)	Scoring method useful in most of rheumatic diseases in a clinical setting; facilitates implementation of quantitative measures in routine care
Spondyloarthritis Research Consortium of Canada (**SPARCC**)	Validated enthesitis index includes 16 sites
Leeds Enthesitis Index (**LEI**)	Validated enthesitis index includes 6 sites

*European based. NRS, numerical rating scale, TWD, tragus-to-wall distance; VAS, Visual analogue scale

Part 1: Treatments

Initial treatment

The good news is that axSpA responds well to treatment, with both nonsteroidals and biologic agents, which work best earlier in the disease course.[5] That said, initial treatment should always by a physical therapy program early, upon diagnosis.[12,16] According to ACR guidelines and recent updated recommendations, physical therapy along with NSAIDs are the mainstay of initial therapy for patients with symptomatic disease,[12,16,19] while biologics have transformed the treatment paradigm of patients



with severe and active disease axSpA.[3,20] Targeted therapies approved for nr-axSpA include TNF inhibitors and IL-17 inhibitors; however, promising early phase results of JAK inhibitors in active AS suggest these are likely to join the armamentarium for nr-axSpA in the future. A combination of the 4 domains of inflammation (defined by morning stiffness), patient's global assessment, back pain, and function, should be used to differentiate and assess treatment.[2]

NSAIDs efficacy for pain management

Nonsteroidal anti-inflammatory drugs have been considered the cornerstone of first-line treatment up to the maximum dose, taking risks and benefits into account, with patients suffering from active axSpA, to relieve pain and stiffness rapidly.[19] In placebo-controlled trials, 70% to 80% of patients taking NSAIDs reported good or very good improvement of their symptoms.[20] Data show NSAIDs can be effective but may not be effective in all patients.[19,20] According to the Assessment in Ankylosing Spondylitis (ASAS) International Working Group, up to 15% of patients with active AS, treated with a full dose of an NSAID, fulfill the criteria for partial remission.[20] In studies from 2010, greater than 50% of patients who started with an NSAID in early disease received an Assessment of Spondyloarthritis International Society 40 (ASAS40) response or 35% of patients in ASAS, partial remission.[19] The ASAS40 is a criteria measure defined as improvement of 40% or more from baseline of 2 units or more (range 0–10) in at least 3 of the 4 symptom domains, including patient global pain, spinal pain, inflammation, and function.[21] A good response to NSAIDs is also characteristic of inflammatory back pain, and may be useful to differentiate patients with AS and those with other causes of back pain. It is important to take the risks and benefits into account when considering long-term treatment of NSAIDs.

Risk factors to consider when prescribing NSAIDs

There is a large cohort of patients who are unable to take NSAIDs, so it is important to be aware of which patients are eligible and those who are at risk, which include individuals with cardiovascular issues, renal conditions or hypertension, and some gastrointestinal (GI) issues. Dyspepsia has been found to increase with use, but risk of more serious GI adverse events includes bleeding, perforation, or gastric outlet obstruction. The following tests should be performed before prescribing NSAIDs, including urinalysis and checking liver enzymes, serum creatinine levels, and blood pressure the first month after starting treatment.[20]

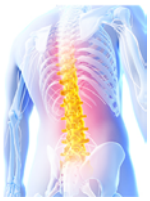
There is conflicting evidence that taking NSAIDs for a long period of time effects the natural history of the disease. There is also discussion on whether NSAIDs should be used "on demand" or in a fixed doses. An adequate trial of nonsteroidals is in the 6- to 12-week range. Most insurance companies indicate the patient will need to have failed 2 NSAID treatments, which is a common standard of care. According to the 2016 update of the ASAS-EULAR management recommendations for axial spondyloarthritis, the decision for continuous use of NSAIDs should be based on the symptoms of the patient rather than on a possible protective effect regarding structural progression.[19]

Case scenario: Treatment with NSAIDs

Based on our case in Module 2: On follow-up, our patient complains of continuing and increased low back pain that is interfering with his activities of daily living and his job. He said he has failed nonsteroidals, but upon closer questioning, he has only used them on a PRN basis a few times a week. Standard of care would be to give him a trial fixed-dose of naproxen at full dose (500 mg per day) for 6 to 12 weeks. You then assess the patient to see if he has had significant improvement in his disease activity measured by global pain, RAPID3 or other scales utilized.

Consider Risk factors

A major consideration for prescribing NSAIDs is their off-targets effects. It is important to ask if the patient has any co-morbidities to be considered, such as cardiovascular disease, hypertension, chronic renal disease, peptic ulcer disease, etc. that would make them ineligible for taking NSAIDs. In this case, our patient takes a full dose of naproxen (500mg per day) for 4 weeks with no benefit. He is switched to meloxicam (15mg per day) for 5 more weeks with only minimal improvement. His disease activity global pain scores are unchanged. RAPID3 is unchanged. He now returns for re-evaluation and to discuss his options to get his disease under control. **End case**



Part 2: Treatment Progression

Treatment Progression

As discussed, for a person with active disease, treatment usually begins with nonsteroidal anti-inflammatory agents. Data show that almost 50% of patients with active AS are controlled with use of NSAIDs alone in their full anti-inflammatory dose.[19] Conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) have not shown efficacy in axSpA; therefore, drugs used in RA, such as methotrexate or sulfasalazine, are not generally recommended in patients with active axSpA. The ACR/SPARTAN guidelines state, however, that patients with axSpA, who have a contraindication to biologic treatment, may be treated with the csDMARDs sulfasalazine.[12,19]

For individuals who do not have an adequate response of their inflammatory back pain after 3 months on 2 different nonsteroidals, a biologic agent should be considered.[12,16] The use of TNF inhibitors has improved our ability to achieve remission or low-disease activity in AS. In addition, large observational clinical trials of TNF inhibitors, with the primary endpoint measuring disease activity, physical function, and pain, have been shown to alter radiographic progression.[16]

Criteria for starting a biologic

In the case of patients with high-disease activity, when activity persists despite NSAID treatment (or intolerance/contraindication), tumor necrosis factor (TNF) inhibitors and recently approved IL-17 inhibitors, secukinumab or ixekizumab, may be considered, as they are currently the only approved biologic alternatives. In the case of patients with documented nr-axSpA or documented AS with high-disease activity, when prescribing biologics, it is important to take into consideration concomitant conditions, such as inflammatory bowel disease, psoriasis, uveitis, or other manifestations.

TNF inhibitors

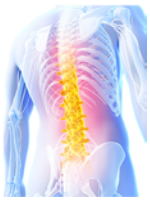
Tumor necrosis factor inhibitors (TNFi) are recommended as the first biologics to be used per the guidelines.[16,19] Infliximab, etanercept, adalimumab, certolizumab, golimumab are all approved TNFi for adults with active AS; however, the guidelines do not recommend any one TNFi as the preferred choice.[16]

Certolizumab pegol (CZP) is the most recently (March 2019) FDA-approved treatment of AS and nr-axSpA, based on a 52-week study (n=317) with data indicating that adding CZP to background medication was superior (47%) to adding placebo (7%).[15] The study was unique, in that it provided the ability to change background medication and switch to biologic treatment, with optimization of nonbiologic background medication (NBBM). In addition, the RAPID-axSpA trial assessed the long-term safety and efficacy of certolizumab pegol over 4 years of continuous treatment in patients with no new safety signals.[19]

IL-17 antagonists

In 2016 the fully human IgG1 monoclonal antibody directed against IL-17A, **secukinumab,** was the first IL-17A approved for treatment of AS in the United States,[22] and most recently approved in 2020 for nr-axSpA based on the PREVENT phase 3 study.[23,24] The PREVENT study evaluated the efficacy of secukinumab in patients (n=555) with active nr-axSpA who had taken at least 2 NSAIDs but were biologic-naive. The trial met its primary endpoint of 40% improvement (ASAS40) at week 16 (41.5%) at 150 mg vs placebo (29.2%; *P <.05*), showing a significant reduction in disease in these patients.[23]

The initial approval for AS was based on 2 AS placebo-controlled phase 3 studies (MEASURE 1 and MEASURE 2) in which secukinumab met the primary endpoints achieving statistically significant improvements vs placebo, as measured by at least a 20% improvement in the ASAS20 at week 16.[22] Secukinumab at 150 mg subcutaneous proved effective in both studies, showing ASAS40 response rates of 42% and 32% (NNT: 3.4 and 4) in MEASURE 1 and MEASURE 2, respectively.[22,25] Secukinumab gave better results in TNFi-naïve patients compared to TNFi-experienced patients, but positive effects were also seen for these latter patients: ASAS40 43.2% vs 25%, respectively. Secukinumab has also shown to reduce MRI spinal inflammation early after its first administration in patients with AS, with a sustained resolution of inflammation by regression of spinal inflammation up to 2 years with its continuous



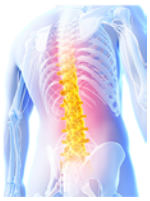
administration, showing a favorable safety profile over long-term treatment.[26,27]

The IL-17A inhibitor, **ixekizumab,** was recently approved at 80 mg/mL based on the double-blind COAST-X phase 3 clinical trial in patients (n=303) with active nonradiographic axial SpA (nr-axSpA) and previous inadequate response to or intolerance of NSAIDs. Data show patients treated with 80 mg of ixekizumab every 4 weeks (QW4) or every 2 weeks (Q2W) achieved ASAS40 response criteria at 52 weeks: Q4W 30% (*P* = .0045), Q2W 31% (*P* = .0037) vs 13% placebo, demonstrating statistically significant improvements in disease activity, function, quality of life, and spinal MRI-evident inflammation. Significant improvement was also observed in 35% (*P* <.01) of patients treated with ixekizumab at QW4, 40% at QW2 (*P* =.0016) vs 19% of those treated with placebo after 16 weeks of treatment. The most common side effects were nasopharyngitis and infection-site reaction. Frequency of serious adverse events was low (1%), but may include serious infections, such as tuberculosis or IBD.[21,28]

The approval of these IL-17A inhibitors provides alternative cytokine targets beyond TNF and therapeutic options for significant improvement in symptoms for those suffering with nr-axSpA, which is estimated to be half of those diagnosed with axSpA.[21,28]

FDA-approved Treatments

Agent	FDA approval	Dosing	Administration Frequency	Serious Adverse Events (SAEs)
TNFa inhibitors				
Adalimumab[29,30]	2006	40 mg by subc injection every other week	Every other week	**Common AEs:** Nasopharyngitis, injection-site reactions, headache **SAEs:** TB, invasive fungal, and other opportunistic infections
Etanercept[31,32]	2003	50 mg once weekly	Weekly	**SAEs:** Increased risk of serious infection, including TB, bacterial sepsis, and invasive fungal infections
Certolizumab pegol (CZP)[33] for nr-axSpA	2019	400 mg (given as 2 subc injections of 200 mg) initially, and at weeks 2 and 4; **maintenance** regimen 200 mg every other week or 400 mg every 4 weeks	Every 2 or 4 weeks, depending on dose	**SAEs:** Increased risk of serious infection, including TB, bacterial sepsis, and invasive fungal infections
Golimumab[34]	2017	50 mg by subc injection once a month	Monthly	**SAEs:** Increased risk of serious infection, including TB, bacterial sepsis, and invasive fungal infections
Infliximab[35]	2004	5 mg/kg at 0, 2 and 6 weeks, then every 6 weeks	Every 6 weeks	**Common AEs:** Fever, extreme tiredness, flu-like symptoms, skin rashes, cough, stomach pain **SAEs:** Increased risk of serious infection, including TB, bacterial sepsis, and invasive fungal infections



Agent	FDA approval	Dosing	Administration Frequency	Serious Adverse Events (SAEs)
Interleukin-17A				
Ixekizumab[36] for nr-axSpA	2019	80 mg/mL by subc injection every 4 weeks	Every 4 weeks	**Common AEs:** Injection site reactions, upper respiratory infections, nausea, fungal skin infections **SAEs**: increased risk for infection, including TB, IBD, hypersensitivity
Secukinumab[23] for nr-axSpA	2020	150 mg without loading dose every 4 weeks	Every 4 weeks	**SAEs**: Serious infections have occurred, including TB, IBD, hypersensitivity

IBD, inflammatory bowel disease; Subc, subcutaneous; TB, tuberculosis

Case summary with biologic, more complex treatment options

Continued from Module 3, our patient is a candidate for a TNF inhibitor, certolizumab pegol, the TNFi specifically approved for nr-axSpA, or an IL-17 antagonist—ixekizumab or secukinumab. He has spondyloarthritis of nonradiographic form, a disease known to respond similarly to radiographic disease. At the present time, these are the approved drugs for this condition.

TNFi vs IL-17i: How to select between approved biologics

The guidelines for AS suggest starting with a TNF inhibitor, however, the guidelines were published in 2015.[12] With the experience now of biologics overall, there are now 2 approved IL-17a inhibitors, approved for AS and nr-axSpA, based on phase 3 trials (**see Table**). They appear to be of comparable efficacy. Much of the decision may be based on toxicity and patient preference for dosing intervals (**see Table**). Some rheumatologists feel IL-17 have an enhanced margin of safety, although there are no head-to-head trials. The serious adverse events (SAEs) for TNF inhibitors include an increased risk of serious infection, including TB, bacterial sepsis, and invasive fungal infections. Major adverse events for IL-17a inhibitors also include an increased risk for infection, including TB, in addition to contributing to flare or preexisting nuance of IBD and hypersensitivity.[23,29-36]

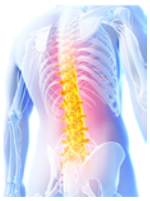
Case scenario for axSpA patient treated with IL-17 antagonist

Case continued, the patient is prescribed certolizumab pegol, 400 mg every 4 weeks. He responds well for 6 months. There is improvement in pain and mobility, and fatigue has also improved, but over the ensuing 6 months, he feels the medication has lost its effectiveness. He feels like he's back at ground zero with this disease and is again frustrated and looking for answers. While there are other TNF inhibitors available, and switching strategies is endorsed for radiographic AS, there is no current guidance for this in nonradiographic disease, as no others are currently approved for this indication. Thus, the option of starting an IL-17 inhibitor is discussed with the patient.

He begins ixekizumab, prescribed at 80 mg/mL every 4 weeks. His provider discusses the potential adverse events associated with this IL-17 inhibitor, including watching for candida, serious infections, signs or symptoms of inflammatory bowel disease. Over the next 4 months, he begins to feel better. **End case**

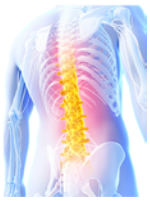
Emerging Therapies

Current treatments agents do not provide clinical benefit for about 40% of patients, therefore additional therapeutic options are necessary.[37] It is important to keep abreast of emerging treatments and results in recent clinical trials (see **Emerging Treatments Table**). The table below reviews the most prominent agents now in clinical trials, including dual Il-17A/F (bimekizumab), JAK1 (filgotinib) and JAK1/3 inhibitors (Tofacitinib), and IL-23 p19 (Tildrakizumab).[1,38-41]



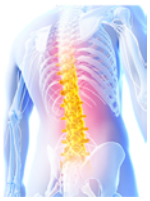
Emerging Treatments Trial Data

Agent (class)	Trial	N= AxSpA type	Dosing	Primary endpoint/ Secondary endpoint	Results	AEs
Bimekizumab[38,42] (dual IL-17A/F)	Phase 2b: NCT02963506 (Completed)	N=303 active AS	AS patients treated with 1 of 4 doses (16, 64, 160, or 320 mg) or a PBO every 4 wks for 12 wks; those on lower doses assigned to higher dose for additional 36 wks	ASAS40: improvement/ reduction of ≤40% in a min. of 3 of 4 domains: patient global assessment of disease, pain, function, and inflammation	87.5% completed the 48-wk treatment period; Improvements at 12 wks sustained up to 48 wks; 35.5%–64.0% achieved ASAS40; % achieving ASAS partial remission 20.6%–34.4%	77.6% experienced at least one AE **Common AEs:** inflammation in the nose and throat, or nasopharyngitis
Brodalumab[1] (IL-17RA)	Phase 3: NCT02985983 (Completed)	n=80 nr-axSpA	210 mg		70% achieved ASAS20 by Week 16, compared to 48% in placebo group	**Common AEs:** Nasopharyingitis ; potential to reduce patients' ability to combat infection
Filgotinib (JAK1 inhibitor)[39]	Phase 2b TORTUGA study NCT03117270 (Completed)	N=116 active AS	Nonresponsive to NSAIDs, randomized to 200 mg q.d. oral tablet or PBO for 12 wks	Change from baseline in ASDAS at week 12	Mean ASDAS change from baseline to wk 12 -1·47 (SD 1·04) and -0.57 (0·82) in the PBO grp; **Secondary outcome:** mean 2.41-point reduction from baseline on BASDAI, compared with a 1.44- decrease in controls, difference significant from wk 8 onward	**Common AEs:** nasopharyngitis



Agent (class)	Trial	N= AxSpA type	Dosing	Primary endpoint/ Secondary endpoint	Results	AEs
Tildrakizumab[1] (IL-23 p19)	Phase 3 NCT03552276 (Active, not recruiting)	n=540 AS and nr-axSpA	Randomized 100 mg (one 1-mL injection of 100 mg/mL + 1 mL PBO)	Incidence and intensity of adverse events will be assessed; Secondary: subjects achieving a 20% reduction from baseline in tender and swollen joints	Ongoing study in AS and PSA	**Common AEs:** upper respiratory infections, injection site reactions, and diarrhea
Tofacitinib[40] (JAK1/3 inhibitor)	Phase 2, NCT03738956 (recruiting)	N=207 active AS	Randomized (N=51, 52, 52, 52, respectively) to PBO or tofacitinib 2, 5, or 10 mg BID over 16-wk (12-wk treatment, 4-wk washout)	ASAS20 response rate at wk 12/objective measures of disease activity, patient-reported outcomes and MRI of sacroiliac joints and spine	@ 12 wks, 5 mg BID ASAS20/40 response rates 81%/46%; PBO responses also high (41%/20%)	**Common AEs:** bronchitis, diarrhea, dyspepsia, headache, nasopharyingitis, nausea **SAEs risks:** serious infections
Upadacitinib[43] (JAK1 inhibitor)	Phase 3 NCT04169373 (recruiting)	N=187 active AS	15 mg (oral tablet) daily	Study 1: ASAS40 response at wk 14 Study 2: ASAS40 response at wk 14/ wk 52	95.7% of participants completed study wk 14; 51.6% achieved ASAS40 at wk 14 vs 25.5% in the PBO group ($P < .001$)	Upper respiratory tract infections, nausea, cough, Fever **SAE risks:** increased risk for infection, including TB, bacterial, invasive fungal, viral

ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; JAK1, Janus kinase 1 inhibitor



Treatment Strategies

Treat to target

Remission in spondylarthritis is a work in progress. The current guidelines, ACR/SPARTAN and EULAR, identify treatment goals as low-disease activity or remission (defined by ASDAS), yet, in real-life practice this instrument is unwieldly and not normally employed in clinical practice. That said, it is important to have some assessment measurement, such as global pain assessment or the RAPID3.

Alternative real-life targets

The 2015 ACR guidelines reiterate that quantifying disease activity is important to help guide treatment decisions. The Tight Control in Spondyloarthritis **(TICOSPA) study** may provide evidence for whether this treatment paradigm is appropriate for management of AxSpA. The TICOSPA study (n=163) is a 1-year international clinical trial in Europe reviewing the treat-to-target strategy to manage patients with active AS.[44] Although it failed to meet its primary efficacy endpoint of getting patients to an ASDAS of less than 2.1, a 30% improvement in the ASAS Health Index, it showed suggestive beneficial indications compared with routine treatment or usual care. The tight control means that as soon as a treatment is initiated, the time to evaluate its potential efficacy/safety has to be determined (at least every 4 weeks). For example, in terms of efficacy it is recommended to evaluate an NSAID after 2 to 4 weeks of treatment intake, and the TNF blockers after 12 to 16 weeks.[44,45] The treat-to-target strategy means there is an *a priori* decision to intensify treatment in case the target is not achieved and is not generally utilized or recommended at the present time.

Switching treatments

Switching treatments occur primarily for 2 reasons: toxicity or due to lack of efficacy. For patients with radiographic axSpA, if they fail 1 TNF, they are candidates for another TNFi before moving on.[15] With the proliferation of the new class of agents, such as the IL-17 inhibitors, this is being reconsidered in the minds of many clinicians. Similar to rheumatoid arthritis, there is an impetus to change mechanism of action earlier rather than later. If there is an obvious failure of TNFi, then move on to another TNFi agent immediately. It is important to note, you can fail for several reasons. Primary failure is that there was never a good response to treatment. Secondary failure is the patient had a response, but it wore off. In the secondary failure, the reason is not always well understood. Another possible reason is that the patient developed antidrug antibodies, and in this case switching to another TNFi is possible. With the proliferation of options today, clinicians have more choices.

Nonpharmacologic measures

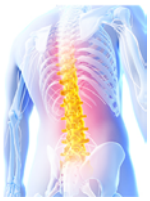
Per the guidelines, the optimal management of patients with axSpA requires a combination of nonpharmacological and pharmacological treatment.[19] Patient education in the area of nonpharmacological measures needs to stress the importance of physical exercise, which can include aquatic-based therapies, as well as physical therapy, and if applicable, smoking cessation. Additional nonmedical treatment can include massage therapy, acupuncture, and chiropractic treatment, along with a combination of biological treatments may provide enhanced patient outcomes.[46]

Shared decision making

An overarching principle for optimal care is based on a shared decision-making between the patient and the rheumatologist, which requires effective and sufficient education about the disease, appropriate information about risks and benefits of treatment options, as well as a management plan and strategies to monitor treatment success. This sentiment is reflected in the fourth principle of the 2016 update of the ASAS-EULAR management recommendations for axial spondyloarthritis in order to "to maximize health-related quality of life."[19] This includes an operative formal and informal relationship between patient and rheumatologist, and ultimately partnering in collective decision-making for the best possible clinical outcome, while promoting patient self-management as well as adherence.

Strategies to improve patient communication

The most important piece of patient communication is to make patients aware that axSpA exists, in both its forms AS and nr-axSpA. It is also important to stress the importance of getting patients involved in physical therapy and exercise early in their disease, and to clarify



any misconceptions about the disease, and assure them that effective treatments are available. Equally important is to get patients involved in the shared decision-making regarding preferred administration and frequency of treatment based on the various therapeutic options.

Conclusion

Pain and stiffness as a result of axSpA are often difficult to distinguish from other common causes of back pain, and therefore, patients who do see a rheumatologist may go undiagnosed for years from the onset of their symptoms. It is essential that clinicians recognize inflammatory back pain, and test patients early, to confirm a proper diagnosis. An early diagnosis can greatly influence what happens ultimately to the patient prognostically. Early intervention with NSAIDs, and with signs of high-disease activity, with biologics, can prevent the disability and deformity often associated with this disease. It is essential that clinicians are able to identify inflammatory back pain, and are able to assess function, pain, spinal mobility and global pain assessment of their patients with chronic lower back pain, to apply appropriate treatment.

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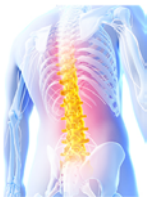

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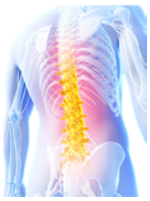

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