Ankylosing Spondylitis and Nonradiographic Axial Spondyloarthritis: Emerging Treatment Recommendations

**BACKGROUND**

With the advent of biologics for the treatment of immune-mediated arthritis in the 21st century, clinicians and people with autoimmune arthritis now have numerous therapeutic options. Axial spondyloarthritis (axSpA) is a term describing conditions including radiographic axial spondyloarthritis, ankylosing spondylitis (AS), and non-radiographic axial spondyloarthritis (nr-axSpA.)1 The disease presents as inflammatory back pain and stiffness involving the spine and the sacroiliac joints with varying peripheral joint and extra-articular manifestations.2

The disease typically manifests in people in their third decade of life, with a 3:1 ratio of males to females in AS and a 1:1 ratio in nr-axSpA, and has a probable genetic component based upon inheritance of the *human leukocyte antigen-B27* (*HLA-B27*) gene.3 The prevalence of axSpA ranges from 0.32% to 1.4% of the global population and depends upon ethnicity and geography.2,4 Most studies have focused on AS, so the true prevalence and incidence of nr-axSpA is unknown.2

There is a strong association between *HLA-B27* and axSpA, but the role of *HLA-B27* in the disease still is not clear.1 People in far north cultures (eg, Scandinavian Lapps, Alaskan and Siberian Eskimos) have a higher frequency of the *HLA-B27* gene and have a higher frequency of occurrence of axSpA.3 Western Canada and US Native American tribes also have a more frequent occurrence of spondyloarthrits.3

Therapy for axSpA is targeted to reduce inflammation and prevent new bone formation, which in turn, decreases disease burden and improves quality of life for people with axSpA.5 Exercise and non-steroidal anti-inflammatory drugs (NSAIDs) are the mainstays of treatment for axSpA, and, for up to 40% of affected individuals, this is enough to maintain disease control.7,8 People with AS have seen a substantial change in treatment protocol with the use of biologic disease-modifying antirheumatic drugs (bDMARDs), which is a viable treatment strategy for those who do not obtain relief with traditional treatment regimens.8

Clinical trials have shown that interleukin (IL)-17 and tumor necrosis factor (TNF) are both involved in disease pathogenesis, and therapies have been directed towards these cytokines.1 Tumor necrosis factor alpha inhibitors (TNFi) are used to treat axSpA if NSAIDs do not work. TNFis include adalimumab, etanercept, certolizumab pegol, and golimumab.7 For people with ankylosing spondylitis (AS), infliximab is also an option.7

Recent approval of secukinumab, an IL-17A inhibitor, has ushered in a new alternative in disease management.8 According to Rademacher and Poddubnyy,there remains “an unmet need for further emerging therapeutic options” and “an emerging need for trials aiming at identification of optional treatment strategies” in axial spondyloarthritis.6 In addition to secukinumab, ixekizumab is “the second emergent IL-17A antagonist”option for those people with axSpA who do not respond to or tolerate TNFi.9

**EDUCATIONAL ANALYSIS**

**Gap #1: Clinicians may be unaware of the 2019 update of the American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network recommendations for the treatment of AS and nr-axSpA**

**Learning Objective #1: Review the updated treatment recommendations for AS and nr-axSpA**

The 2015 guidelines of the American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network set forth recommendations for the treatment of people with AS and nr-axSpA.2,5 The use of NSAIDs and physical therapy was strongly supported along with hip arthroplasty if warranted. If NSAIDs did not decrease disease activity, the use of TNFi was then recommended. The use of systemic glucocorticoids was not recommended, and no particular TNFi preference was given, with the exception of TNFi monoclonal antibody use in people with Inflammatory Bowel Disease IBD.5

Because of the introduction of new medications to treat axSpA, the 2019 update of the American College of Rheumatology/Spondylitis Association/Spondyloarthritis Research and Treatment Network recommendations for the treatment of AS and nrSpA was released.10 The 2019 update added to the 2015 guidelines with recommendations on how to fit these new medications into treatment regimens.10 Also included is the use of imaging to diagnose and to track disease progress.10

In January 2016, the IL-17 A inhibitor secukinumab was approved for the treatment for AS and psoriatic arthritis.11 This followed three phase 3 studies (MEASURE1, MEASURE2, and MEASURE3), which demonstrated substantial and rapid improvement in the patients’ signs and symptoms.12 In the MEASURE3 study, the positive response rate was significant with both a 300-mg treatment (P < 0.01) and 150-mg treatment (P < 0.05).12

Ixekizumab gained FDA approval in late 2017 for the treatment of adults with active psoriatic arthritis.13 On August 26, 2019, it was announced that the drug was approved for use in adults with active AS.13 In a multicenter phase 3 study, ixekizumab significantly reduced disease signs and symptoms and improved quality of life in AS patients with both twice-a-month treatment (*P* = 0.003) and monthly treatment (*P* = 0.017).14 Improvements were noted early in the trial.13  Adverse effects to ixekizumab included mild infections (upper respiratory tract infections and nasopharyngitis) and injection site reactions, with only 2 serious infections encountered.14

**Gap #2: Clinicians may be unaware of new medication clinical trials for the management of AS and nr-axSpA**

**Learning Objective #2: Review information on new medication clinical trials for future management of AS and nr-axSpA**

New treatments for spondyloarthritis are currently in various stages of development. While many of the currently used medications have been studied and labeled for AS, current research strategies are aimed at both AS and nr-axSpA.7 Researchers are pursing varying immunological avenues to develop treatments aimed at the IL-17 and IL-23 receptors and to inhibit Janus kinase (JAK).6 The cytokines in the IL-17 pathway contribute to inflammatory disease by overproduction of the cytokines which lead to inflammation, bone destruction, and, in the case of AS, new bone formation.15,16

The IL-17 receptor blocker brodalumab,previously approved by the FDA for the treatment of plaque psoriasis, is in the process of being studied as a treatment for axSpA.6,8 This monoclonal antibody binds to IL-17 receptor A to inhibit production of the cytokine.16 It was found during the trials for plaque psoriasis to cause suicide ideation and behavior prompting the FDA to require a warning label. This warning will likely be the same if approval is given for brodalumab for axSpA treatment.17

Bimekizumab targets two IL receptors: IL-17A and IL-17F to inhibit production of these cytokines.6,8 This dual inhibitor is being studied for its effect on AS along with psoriasis and psoriatic arthritis with good results in this early stage.18 It is currently in phase 3 clinical trials and has been shown to improve clinical symptoms rapidly.19 As with most IL inhibitors, adverse effects primarily are an increased susceptibility to infections.19

Research is also ongoing for other pathways involved in the pathogenesis of AS and nr-axSpA. The IL-23 inhibitors risankizumab and guselkumab along with JAK inhibitors upadacitinib, baricitinib, and filgotinib are all potential future treatments to add to the arsenal of medications used to treat these and other inflammatory diseases.6,8

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**CONCLUSION**

Axial spondyloarthritis is a potentially debilitating disease that had limited treatment options in the past. With the advent of biological therapeutics, inflammation, bone destruction, and new bone formation can be limited earlier in the disease, increasing quality of life for people with axial spondyloarthritis. Physicians need to keep up-to-date on the new treatment options, which are expanding rapidly, so they can chose the most effective options for their patients. In addition, multiple drugs targeting different pathways in the disease process are being developed, which can aid the physician in future treatment protocols.

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