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Unmet Needs in Spondyloarthritis: Pathogenesis, Clinical Trial Design, and Nonpharmacologic Therapy

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ABSTRACT. A program focused on pathogenesis, clinical trial design, and nonpharmacologic mind-body therapy for spondyloarthritis (SpA) was presented at the Spondylitis Association of America Unmet Needs Conference IV. SpA pathogenesis is incompletely understood but involves a complex set of drivers, including genetics, biomechanical stress, and microbial factors. Affected tissues may include axial and peripheral joints, entheses, skin, uvea, and intestines. The specific role of key cytokines like interleukin (IL)-23, IL-17, and tumor necrosis factor in the phases of this inflammatory process remains unclear. New insights into pathogenesis will continue to generate targets for novel therapeutics. How to optimally evaluate those therapeutics in clinical trials, and for the various manifestations of SpA, remains less clear. Future trials need better generalizability, robust subgroup analyses to assess differential responses for distinct disease manifestations, a focus on comparative efficacy, and outcomes relevant to the clinician and the patient. Additionally, study designs need to leverage available technology to facilitate subject participation in trials. In view of the interplay between biologic, physical, and psychological aspects of disease, there is increasing attention to nonpharmacologic agents, with the aim of maximizing long-term health-related quality of life through the control of symptoms and inflammation. Recent studies provide encouraging evidence that mind-body interventions such as tai chi, qigong, yoga, and meditation have benefits for patients with SpA, particularly those with pain. The advances in our understanding of pathogenesis, novel therapeutics, and nonpharmacologic interventions have revolutionized the management of SpA, but numerous questions around optimal management remain.

Key Indexing Terms: ankylosing spondylitis, outcomes, spondyloarthropathy

Introduction

The advances in our understanding of pathogenesis, novel therapeutics, and nonpharmacologic interventions have revolutionized the management of axial spondyloarthritis (axSpA). However, there are still a number of unanswered questions around optimal ways to study and manage this condition.[1] At the Spondylitis Association of America (SAA)/National Institute of Arthritis, Musculoskeletal and Skin Diseases Unmet Needs Conference in Bethesda, Maryland in September 2023, Drs. Laura Coates, Georg Schett, and Chenchen Wang provided their perspectives on the critical unmet needs in axSpA regarding pathogenesis, clinical trial design, and nonpharmacologic therapy. The key aspects of each lecture are highlighted below.

Pathogenesis

The pathogenesis of SpA is incompletely understood but involves a complex set of drivers, including common genetic variants, biomechanical stress, and microbial factors, which facilitate an

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excessive and sustained inflammatory response in target tissues. Affected tissues include axial and peripheral joints and entheses, skin, uvea, and intestines. Key cytokines like interleukin (IL)-23, IL-17, and tumor necrosis factor (TNF) are involved, but their specific role in various phases of the disease process remain unclear.

Specific tissue features of SpA. Inflammation and damage of peripheral and axial entheseal structures are a hallmark of SpA and can include vascular growth, vasodilation, osteitis, and osteoblast differentiation, with the latter eventually leading to new bone formation. Multiple cytokines emanating from innate (ILC3-like) and adaptive (Th1 and Th17) immune cells, and likely mesenchymal stromal cells, are involved in initiating and sustaining the immune response in SpA. Prostaglandin E2, IL-17, and IL-22 can mediate the differentiation of mesenchymal cells into osteoblasts at entheses, whereas expression of receptor activator of nuclear factor-κB (RANK) ligand, macrophage colony-stimulating factor, TNF, and IL-17 in the synovium stimulate osteoclasts to resorb bone. Osteoclasts are also found in inflamed vertebral body bone marrow as well as in adjacent fat lesions.[2] TNF appears to be particularly important for driving uveitis, and TNF and IL-17 are major contributors to inflammation in the axial skeleton. TNF and IL-23 can be predominant cytokines in the gut when inflammatory bowel disease (IBD) is present, and TNF, IL-17, and IL-23 are involved in skin inflammation in psoriatic arthritis (PsA). Macrophage migration inhibitory factor (MIF) may connect innate and adaptive immune responses and can promote pathogenic Th17 responses. Inhibition of MIF has been shown to prevent SpA in a mouse model.[3]

TNF and IL-17 are master control cytokines in SpA. There is an enhanced IL-17 signature in SpA relative to other immune-mediated inflammatory diseases in the SpA family. One mechanism of increased IL-17 signaling may be through prostaglandin E2.[4] Prostaglandin E2 stimulates IL-17 production and can act independently from IL-23, increasing its effects.[5]

The IL-23 paradox. Interestingly, IL-17 blockade, but not IL-23 blockade, is efficacious in SpA. Further, there is emerging evidence that IL-23 blockade works well in PsA and IBD, but not SpA. Part of this differential response may be explained by the fact that epithelial surfaces like the gut and the skin contain a large number of mature dendritic cells resulting in a large IL-23 signal, whereas tissues such as the entheses and the bone marrow contain only a limited number of mature dendritic cells and therefore provide a weaker IL-23 signal. It is also unclear whether the predominant effect of IL-23 in the axial skeleton and entheses occurs earlier in the axSpA disease course, which would perhaps explain its limited efficacy when tested in therapeutic studies conducted later in the disease course.

Therapies targeting the aberrant immune response. IL-17 and TNF inhibitors control tissue responses and limit the remodeling phase of disease. The mechanisms by which Janus kinase (JAK) inhibitors work in SpA are not entirely clear; however, we know they block not only cytokines that trigger and polarize the adaptive immune response but also cytokines released from effector cells that sustain the immune response. In recent trials, JAK inhibition also demonstrated efficacy in patients with ankylosing spondylitis (AS) who failed TNF inhibitor therapy.

Autoimmunity-associated T cell receptors recognize HLA-B27–bound peptides. Recent studies suggest there may be a role for selective targeting of T cell clones in the treatment of axSpA. Isolation of T cells from the blood and synovial fluid of individuals with AS and from the eyes of patients with acute anterior uveitis demonstrated an enrichment of orphan T cell receptors (TCRs), expressing a disease-associated public β-chain variable region–complementary-determining region 3β (BV9-CDR3β) motif.[6] TCRs with the BV9-CDR3β motif can recognize potential self and microbial antigens with shared structural features, lending credence to the arthrogenic peptide hypothesis.

Clinical trial design

Inclusion criteria: limitations of generalizability and consideration of SpA, including axSpA and PsA, as a multisystem condition. Given concerns about safety and potential heterogeneous treatment effects, patients with multiple medical conditions are typically excluded from clinical trials, which limits generalizability of the data. Additionally, related conditions like uveitis or IBD can be an exclusion alongside other comorbidities, which limits the inclusion of more typical clinic patients into the trials. Given the multisystem nature of SpA, this is a particular concern for generalizability of results. There are multiple domains of disease to be considered, including peripheral arthritis, axial disease, enthesitis, dactylitis, and skin and nail disease, many of which may not be assessed by existing measures of disease activity or trial design. Nearly all clinical trials focus on axial or peripheral arthritis, with other domains considered only as secondary outcomes. Trials of peripheral disease require 3 or 5 active joints for inclusion, which excludes patients with monoarthritis or oligoarthritis, and those with predominant enthesitis or predominant axial involvement. This leaves an evidence gap that can limit access to therapies in the clinic.

Limited comparative efficacy trials. The majority of drug approvals are based on placebo-controlled trials, with very few studies designed to compare new treatments head-to-head against existing therapies. For example, to our knowledge, in AS, there are no head-to-head studies comparing biologics and there is just 1 study comparing a biologic with a conventional disease-modifying antirheumatic drug.[7] Thus, when writing treatment recommendations, or applying them in the clinic, there are very limited data helping clinicians to choose between the many therapies available.

Placebo: is this still ethical? The continuation of placebo-controlled trials for new medications in development raises 3 critical issues. First, patients selected for studies often have moderate to severe disease and some trials are even enriched for patients who are more likely to show progression of joint damage. Evidence from long-term extension studies shows that after active treatment in an open-label study period, patients initially randomized to placebo may never quite catch up with the patients treated with active drug therapy throughout.[8] Given the emphasis on rapid

effective treatment of SpA to control inflammation and prevent progression of disease, the extended use of placebo for 4 to 6 months raises ethical issues. Second, the use of placebo affects recruitment. Many trials recruit more slowly than anticipated because a period of placebo treatment is not attractive to participants who already have access to approved therapies known to be effective. Comparing new therapies to existing proven therapies in head-to-head studies is much more appealing to patients who want to receive more definitive treatment for their disease. Third, there is a significant risk to taking part in the study of a new therapy and often it requires an increased burden on participants, with regular study visits, blood tests, and questionnaires.

Outcomes: are they relevant to patients and clinicians? Using outcomes that are relevant to both patients and their clinicians is critical. Typically, the primary outcome of trials is a composite measure that combines multiple single outcomes into a response criterion or score. For example, the Assessment of Spondylarthritis international Society 20% improvement (ASAS20) includes patient global assessment score and measures of back pain, function, and inflammation. Composite measures allow for a better estimate of overall disease activity and can help to influence treatment decisions given the overall disease burden. Considering the increasing focus on treat-to-target in rheumatology,[9] these measures are optimal to assess remission or low disease activity across a disease affecting multiple tissues. Individual measures, such as joint counts, can be used to focus on 1 particular element of response, but these are typically less responsive to change and are therefore less powerful as a primary outcome in a study. However, they might be crucial to inform treatment selection in practice, as there may be differential efficacy of different therapies seen in different tissues.

Thus, the optimal outcome measures for a trial should be considered carefully in light of the research question. Establishing overall disease efficacy can be well addressed with a composite measure that also provides an efficient primary outcome to minimize the sample size required. However, in studies aiming to establish efficacy in a particular domain, a single measure would be more suitable; for example, in the GO-DACT (Golimumab plus methotrexate [MTX] vs placebo plus MTX in improving dactylitis in MTX-naive patients with PsA) study of TNF inhibition for dactylitis, a single measure focused on dactylitis was the obvious choice.[10] Several studies have had different conclusions and interpretations based on different outcomes measured. For example, the Psoriasis Randomized Etanercept Study in Subjects With Psoriatic Arthritis (PRESTA) study enrolled patients with PsA with active skin and joint disease and tested 2 different dosing regimens of etanercept.[11] Measures focused on arthritis, such as the American College of Rheumatology 50% improvement (ACR50) or the Disease Activity Index for Psoriatic Arthritis score, showed no difference between the groups. However, composite measures looking at disease control in multiple domains, including skin disease, identified that the higher dosing regimen was significantly better at controlling psoriasis.[12]

Finally, within outcome measures, there is the issue of response levels and remission. A minimal response, such as a 20% improvement in signs/symptoms of disease, is highly effective at differentiating between drug and placebo. However, this is not as relevant to patients. A patient's impression of an acceptable symptom state, low disease activity, or remission is similar to that of clinicians', and is exemplified by low levels of symptoms and disease impact.[13,14] Interestingly, these higher measures of response, such as minimal disease activity criteria and ACR70 (a 70% improvement in measures rather than 20%) are much more effective at differentiating between 2 active treatment arms.

Trial approach: thinking outside the box. Participation in clinical trials is a burden for participants, contributing to slow recruitment and limited generalizability to the wider population. The advent of digital health technologies has the potential to change this but has not been fully harnessed in rheumatology. Digital health options that remain underused include remote study visits and digital solutions to collect patient-reported outcomes, which also enable measurement of fluctuating symptoms over time. For patients, the use of digital health technologies seems to improve their awareness of their condition and improve self-management and overall satisfaction. Studies have also started using passive data collection with smart watches and similar devices. These can measure geolocation, movement, and sleep using objective assessments.

Nonpharmacologic therapies

The role of integrated mind-body therapies. Current treatment for SpA encompasses both pharmacological and nonpharmacological therapies, with the aim of maximizing long-term health-related quality of life through the control of symptoms and inflammation, particularly musculoskeletal pain. In the past decade, the use of integrated mind-body therapies (MBTs)—including tai chi, qigong, yoga, and meditation—have been shown to be effective in reducing symptoms and inflammation, improving quality of life for patients who suffer from chronic rheumatic conditions like axSpA. Importantly, the mental components of the interventions uniquely promote integration of mind and body to reduce pain, improve self-efficacy, function, psychological well-being, life satisfaction, and slow disease progression and disability associated with arthritis.

Previous work demonstrates mixed results regarding the association of MBTs on circulating, cellular, and genomic markers of inflammation, including reduction of C-reactive protein and IL-6. More consistent findings have been observed for gene expression, with trials showing decreased expression of inflammation-related genes and reduced signaling through the proinflammatory transcription factor nuclear factor–κB.[15] These immunomodulatory effects warrant further methodologically rigorous studies to determine the clinical implications of these findings for inflammatory disease outcomes in SpA.

Tai chi and yoga. There have been several recent randomized, controlled studies of tai chi and yoga interventions in patients with SpA. Practicing regular tai chi or yoga (20-60 minutes, 2-3 times/week for 8-12 weeks) significantly improved function, psychological well-being, and overall quality of life in patients with SpA. However, definitive conclusions across these studies are

limited due to variation in trial design, comparators, outcomes, and inadequate controls. High-quality, well-controlled, and longer randomized trials of these interventions are needed to better inform clinical decisions.

Acupuncture. Acupuncture, originating in China more than 3000 years ago, is one of the most popular sensory stimulation therapies. A previous metaanalysis including 10 randomized trials demonstrated that when compared to the control groups, acupuncture showed significant short-term improvements in pain, function, and symptom score in patients with SpA.[16] Further work is needed to understand the mechanisms by which acupuncture can improve clinical symptoms and immune function.

What challenges remain in the study of MBTs? First, disease heterogeneity may influence the accuracy of treatment responses. MBTs are multifaceted and the various factors that may influence treatment response must be considered in the design of studies to facilitate achievement of rigorous, yet clinically useful and generalizable, results for patients with axSpA. An adequate understanding of the heterogeneity of treatment effects or lack thereof will generate critical insights into comparative clinical effectiveness research to provide optimal treatments for patients, especially for improving long-term outcomes. Second, a lack of appropriate control groups can hinder drawing meaningful conclusions. There is a need for valid and well-defined comparison groups in every study to enhance the validity and reliability of testing the MBTs, given their complexity. Third, the exploration of plausible scientific mechanisms is essential to understand the holistic role of integrative and whole person approaches within the context of modern medicine. Finally, dissemination of the potential high value of integrative and whole person approaches in the care of patients with axSpA is greatly needed to better provide the best patient-centered care.

Despite these challenges, we are poised at a paradigm shift in health care that leverages personalized medicine to optimize health, including individualized therapy and self-management to combat disease. Targeted or individualized treatment that includes integrative and whole person approaches offers the undeniable potential to positively affect the progression of SpA while simultaneously diminishing pain and morbidity. The demand for effective whole person healthcare options will continue to grow beyond the already enormous demand today.

Unmet needs in therapeutics in SpA

In summary, there remain many gaps in our understanding of SpA and axSpA, including the specific and differential role(s) the cytokines play in triggering and sustaining the inflammatory response at the various target tissues in this heterogeneous disease (Box).

As we continue to elucidate the pathogenesis of the disease, we will continue to generate targets for novel therapeutics. How to best study those therapeutics in clinical trials remains uncertain. It is clear that future trials need to be more inclusive for better generalizability, have robust subgroup analyses to assess differential responses for distinct disease manifestations, focus on comparative efficacy and rely less on placebo comparisons, and include outcomes that are relevant to both the clinician and the patient. Patient engagement in the design of studies is critical. Additionally, future study designs need to leverage new available technologies to facilitate subject participation in trials. Finally, pain and morbidity from SpA is nontrivial; therefore, individualized treatment strategies that include integrative and whole person approaches offer the potential to positively affect the progression of SpA synergistically with more traditional therapeutics.

Box. Unmet needs and future directions for research in SpA.

- Understand the differential role(s) cytokines play in triggering and sustaining the inflammatory response at target tissues
- Identify novel targets for therapeutics
- Enhance study design and methodology to evaluate differential therapeutic response(s) at target tissues
- Design studies to focus on comparative efficacy over placebo-controlled studies
- Increase use of patient-reported and patient-prioritized outcomes in trials
- Test integrative and whole person management options in axSpA and elucidate their role in a comprehensive and individualized management plan

axSpA: axial SpA; SpA: spondyloarthritis.

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