Juvenile Spondyloarthritis: The Latest in Treatment and Research

by Pamela Weiss, MD, MSCE

As doctors, we're sometimes asked, "Aren't children just little adults?" In the case of spondyloarthritis (SpA), the answer is, "Kind of, but not really."

In many ways, juvenile-onset SpA, or JSpA, is similar to adult-onset SpA—namely in the types of joints that can be affected, more frequent enthesitis (tender tendon attachments), gastrointestinal symptoms, and psoriasis. Like adults, children can also have related eye inflammation (called iritis or uveitis), though it's relatively rare.

However, there are also important differences between juvenile-onset and adult-onset SpA that make paying particular attention to children and adolescents important in both the clinical and research domains.

At diagnosis, children and adolescents tend to have more peripheral joint (knees, ankles, elbows, etc.) and hip joint involvement. Most children have less than five involved joints throughout the course of the disease, and only about 60% are HLA-B27 positive. Additionally, even though up to 20% have arthritis in joints of the lower back (sacroiliitis), children often don't complain of back pain.

The evaluation of JSpA also carries unique challenges—particularly the need to account for the different appearance of maturing joints on imaging. In children, MRI of the sacroiliac joint in particular can be difficult due to normal maturational marrow and cartilage changes that can be confused for JSpA-related inflammation by individuals who aren't familiar with pediatric musculoskeletal imaging. Lots of exciting work is underway, supported in part by SAA, to address these unique challenges with juvenile-onset disease.

What's new in juvenile spondyloarthritis treatment?

This year is an exciting year for JSpA treatment advances. Results of the JUNIPERA trial, which studied the dosing and safety of the biologic secukinumab (Cosentyx), an IL-17A inhibitor, led to FDA approval of this therapy for juveniles in January. Although many therapies used in everyday practice have been around for a long time, including the TNF inhibitors (TNFi), this is actually the first medication specifically labeled for use in children with enthesitis-related arthritis (a.k.a. JSpA) and psoriatic arthritis. Several TNFi therapies (adalimumab, etanercept, golimumab) are FDA-labeled for use in juvenile arthritis with a polyarticular course—meaning children who have five or more joints affected. However, only about 40% of children with SpA have five or more joints affected, making access to these medications oftentimes

difficult. However, work is being done to address shortfalls in TNFi labeling, too. Adalimumab (Humira) is being studied in children with enthesitis-related arthritis who had arthritis in at least three joints and were intolerant or non-responsive to methotrexate or sulfasalazine. Hopefully the results of that study will help with the labeling and subsequent availability of adalimumab for the JSpA population.

Several other targeted medications with promising results in adults with SpA are currently under evaluation in trials in the juvenile population, including ixekizumab (Taltz, an IL-17A blocker), baricitinib (Olumiant, a JAK-STAT inhibitor), and certolizumab (Cimzia, a TNFi). The ixekizumab trial is also comparing the response of children on this drug to adalimumab (Humira), so it will likely provide some guidance as to the comparative effectiveness of these drugs.

In 2019, updated American College of Rheumatology guidelines for the treatment of children and adolescents with sacroiliitis were announced. The take-home messages from these guidelines were that non-steroidal anti-inflammatory medications are helpful for many, but if sacroiliitis remains active, a TNFi therapy is recommended to help calm inflammation and help prevent damage. The guidelines also state that methotrexate is not an effective medication for the sacroiliac joint, though it continues to work quite well for arthritis elsewhere in the body. Steroids (by mouth or by joint injection) and/or physical therapy may be helpful in certain circumstances. As always, talk to your child's rheumatologist to figure out what the best treatment is for your child.

What's new in juvenile spondyloarthritis research?

2022 is also an exciting year for JSpA research. My own team from Children's Hospital of Philadelphia recently launched a trial called BACK-OFF JSpA, or *Biologic Abatement and Capturing Kids' Outcomes in Juvenile SpA*, at 21 sites across the U.S. This trial evaluates strategies to taper TNFi therapy in children with sustained inactive or quiet disease. If we can successfully decrease or stop TNFi use, we may save children and adolescents from unnecessary injections/infusions, side effects, and/or medication expenses. However, this trial may also show that it's not a good idea to decrease or stop medications. Either way, these are important questions to ask. One unique aspect of this study is that we have a group of parents, patients, and foundation stakeholders (including SAA) who helped plan the study, designed materials to be handed out to families, and will provide input throughout the course of the study. The National Institutes of Health (NIH) and SAA are sponsoring other studies related to this trial to evaluate whether there are markers in the blood or on imaging that can help us determine which kids are likely to do well off of medication, and whether there is a risk of developing antibodies to medications once they are decreased. More information on this study is available at: **BackoffJSpA.com**.

My team is also working with an international group of JSpA clinical and imaging experts to establish classification criteria for axial (spinal) arthritis in JSpA. Currently, there are no juvenile criteria for axial disease. Classification criteria will enable identification of children with axial SpA for entry into observational or clinical trials. These criteria are not diagnostic criteria—which is what physicians use in the clinic to determine treatment decisions—and are not intended to capture all possible subjects, but rather to describe most patients with key shared features of axial disease. The criteria are critical to develop for juvenile-onset disease so that emerging medical therapies can be tested and, if beneficial, made available to our children. We hope that establishing these criteria will allow for studies in this population of newer drugs that are showing benefit in adults with axial SpA. Although the NIH was the primary funder of this endeavor, SAA also helped fund a critical part of this project.

Other innovative, ongoing research includes studying the role of the microbiome in juvenile-onset disease. One theory regarding the association of the HLA-B27 gene with SpA is that HLA-B27 acts on the contents of the fecal microbiome to make it more pro-inflammatory. In a study funded by SAA, a research team led by Matt Stoll, MD, PhD from University of Alabama tested this possibility by studying the fecal microbiome of children of HLA-B27-positive ankylosing spondylitis (AS) patients. His team found that while the microbiome of HLA-B27-positive offspring differed from that of HLA-B27-negative offspring, the differences were the opposite of what was anticipated. Specifically, the HLA-B27-positive children had a substantially increased abundance of *Faecalibacterium prausnitzii*, an anti-inflammatory organism that is reduced in children and adults with SpA and inflammatory bowel disease. In another study that is about to launch in France, investigators will be exploring whether the imbalance of intestinal microbiota alter the efficacy of medications like methotrexate and sulfasalazine, and impact responses to treatment.

Last, researchers at the NIH, led by Robert Colbert, MD, PhD, are studying children and adolescents with SpA and their relatives to determine who may be more likely to develop severe forms of the disease.

Overall, this is an exciting time with many advancements on the way for JSpA. New treatments are on the horizon, which are greatly needed since not all children and adolescents respond to currently available therapies. Ongoing research will help us better understand the unique aspects of juvenile-onset disease and hopefully bring us closer to a personalized medicine approach for these very precious patients.

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