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UPDATE ON JUVENILE SPONDYLOARTHRITIS

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INTRODUCTION

Spondyloarthritis (SpA) encompasses a group of disorders linked by overlapping clinical manifestations and genetic predisposition. SpA typically includes ankylosing spondylitis (AS), psoriatic arthritis (PsA), reactive arthritis (ReA), arthritis associated with inflammatory bowel disease (IBD), and undifferentiated spondyloarthritis (USpA). Newer classification systems developed for adults with SpA focus on identifying individuals with axial or predominantly peripheral involvement. All forms of SpA can begin during childhood, and can be considered on a continuum with adult disease. Nevertheless, there are important differences in presentation and outcome that depend on age at onset. This article highlights these differences, what has been learned about genetics and pathogenesis of SpA, and important unmet needs for future studies.

CLASSIFICATION

Rosenberg & Petty emphasized the importance of enthesitis and peripheral arthritis in the absence of back pain, when they describe dsero negative enthesopathy and arthropathy (SEA) syndrome as a form of juvenile SpA distinct from other forms of chronic childhood arthritis¹. When the International League of Associations for Rheumatology (ILAR) formulated new classification criteria for chronic childhood arthritis, the term juvenile idiopathic arthritis (JIA) was adopted and divided into seven subtypes (Table 1)². Using the ILAR system, most forms of juvenile SpA are encompassed by enthesitis-related arthritis (ERA), (juvenile) psoriatic arthritis (PsA), and undifferentiated arthritis (Table 2). Exclusion criteria render ERA and PsA non-overlapping, while children with chronic arthritis who do

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not fit into any category, or meet criteria for more than one category, are considered to have undifferentiated arthritis.

The ILAR classification is generally accepted for systemic, oligoarticular, and polyarticular forms of JIA, while it can be confusing for the concept of SpA as a group of overlapping disorders. The pros and cons of the ILAR classification system for juvenile SpA have been the subject of much discussion³. For the purposes of this article we will use ERA, PsA, and undifferentiated arthritis as defined by ILAR when discussing specific studies where patients were classified using this system. In other places we will refer to juvenile SpA (jSpA?) as a term that broadly encompasses SpA in childhood. Juvenile ankylosing spondylitis (juvenile AS) will be used to describe children who fulfill the modified New York criteria (Table 3) before age 16, and juvenile *onset* AS for the 10–20% who have symptoms before age 16 but do not meet criteria for AS until later.

The recent development of criteria by the Assessment of Spondyloarthritis International Society (ASAS) classifying adults with SpA based on primarily axial (Box 1) or peripheral (Box 2) involvement has reinforced the concept of SpA as a disease continuum^{4, 5}. Prior to the emergence of the ASAS criteria, ‘undifferentiated SpA’ was most often classified based on the European Spondyloarthropathy Study Group (ESSG)⁶ or Amor⁷ criteria. Using the ASAS criteria, ‘axialSpA’ identifies individuals who have radiographic sacroiliitis but lack clinical criteria for AS, those who have MRI evidence of sacroiliitis (bone marrow edema adjacent to the sacroiliac joint), and subjects with no imaging evidence of sacroiliitis, but have HLA-B27 and SpA features that are highly predictive of eventual axial disease. It remains unknown what percentage of individuals with axial SpA will eventually meet full criteria for AS. Nevertheless, considering the 7–8 year lag between the onset of symptoms and a diagnosis of AS⁸, the identification of patients with axial SpA affords an opportunity to ask whether early aggressive treatment can change the course and outcome of disease. Whether this can be achieved with TNF inhibitors is an important unresolved question.

Many pediatric rheumatologists perceive the need to re-classify juvenile SpA in a way that harmonizes with the adult classification system, including criteria that identify children with axial involvement⁹. This group is at greatest risk for progression to AS, and may benefit the most from early intervention. While the ASAS criteria for axialSpA (Box 1) are both sensitive (83%) and specific (84%) when applied to adults, they require at least 3 months of back pain as a starting point, and thus have limited sensitivity in children with SpA.

CLINICAL FEATURES

Enthesitis

Inflammation at entheses where ligaments, tendons, fascia, and joint capsules attach to bones, is a defining characteristic of SpA, and can cause pain, swelling and tenderness (Figure 1). Enthesitis can be evaluated clinically by placing pressure on the enthesis with the dominant thumb until the nail bed blanches. If a dolorimeter is used, typically up to 40 lbs/in² is applied to determine whether the patient is tender. In our experience it is not uncommon to exert greater than 40 lbs/in² with thumb pressure, however this varies between examiners. Therefore, the use of a dolorimeter can improve both inter-rater and even intra-rater reliability.

Enteseal pain and tenderness can occur in other JIA subtypes, and is sometimes seen in otherwise healthy children¹⁰. Pain and tenderness at or near entheses is also common in children with overuse or traction injuries such as apophysitis (e.g. Sever’s and Osgood-Schlatter syndrome), and can be confused with tender points in fibromyalgia¹¹. As a presenting symptom, enthesitis is more common in juvenile than adult SpA. A cross-

sectional study using the Childhood Arthritis and Rheumatology Research Alliance (CARRA) registry revealed that patients with ERA had higher pain intensity and poorer health status compared to other subtypes of JIA, with enthesitis, sacroiliac tenderness and NSAID use independently associated with increased pain intensity¹². In addition, enthesitis early in disease was predictive of ongoing disease activity at 1 year and beyond¹³.

Several indices have been developed to assess enthesitis in adult SpA (Table 4). Sites that are common to 3 or more indices are shaded. There are currently no universally accepted enthesitis indices for jSpA, although involvement of the patellae and heel insertions or areas⁹ is common. Clinical evaluation alone tends to overestimate enthesitis, and thus ultrasound and whole-body (WB) MRI are being explored as research tools to study the specificity of clinical exam, and better understand the pathophysiology of this important clinical feature. Imaging studies to validate clinical findings may be beneficial when testing the efficacy of new biologics.

Ultrasound is non-invasive, relatively inexpensive, and can be performed in the clinic. Its use in rheumatology has become more widespread in recent years. Although heavily operator-dependent, it is emerging as a valid diagnostic tool in SpA^{14–16}, and can be used to visualize synovitis, tendonitis and enthesitis. Features of enthesitis that are captured by ultrasonography include thickening, calcification, bony erosions and tendon hypoechogenicity¹⁷. While there is increasing evidence to support the use of ultrasound in detecting and monitoring enthesitis in SpA, better consensus on abnormal findings that define enthesitis lesions and standardization of methods is needed¹⁴. In the pediatric population, studies comparing enthesitis in SpA, to apophysitis, overuse injury, and even fibromyalgia might be useful to help discriminate inflammatory enthesitis where tendon hypoechogenicity, vascularization on power Doppler, and erosions have been documented¹⁸.

Whole Body (WB) MRI is frequently used to determine the presence and extent of bone marrow edema in suspected AS (Figures 2¹⁹ & 3), to assess enthesitis in various forms of SpA²⁰, and to evaluate active inflammatory lesions and structural damage in patients with non-radiographic axial SpA²¹. Few studies to date have explored the utility of WB MRI in the pediatric population. Preliminary data suggest that arthritis may be underestimated by clinical exam compared to WB MRI, whereas enthesitis is overestimated²². We have made a similar observation, noting poor agreement between enthesitis by clinical exam and WB MRI²³.

Enthesitis is a key clinical and pathologic feature of jSpA, including ILAR classified ERA and PsA. A clinical enthesitis index supported by objective imaging evidence of abnormalities is needed. This is critical for development of therapeutic trials and would likely be a key component of any disease activity measure developed for jSpA.

Peripheral Arthritis

Peripheral arthritis in jSpA typically involves large joints of the lower extremities and tends to be asymmetric. Hip involvement is more frequent in jSpA than in adult onset disease, and in long-term outcome studies is associated with more frequent hip arthroplasty^{24, 25}. Hip arthritis is also a significant risk factor for sacroiliitis²⁶. Tarsitis is also more common in jSpA than other forms of JIA or adult SpA. In a recent study from Spain, it was present in nearly one-third of children with jSpA and was often misdiagnosed as soft tissue infection²⁷.

Axial Arthritis

Inflammatory back pain (IBP) has various definitions. ASAS has defined it as beginning before 40 years of age, insidious in onset, occurring at night, and improving with exercise but not with rest²⁸. It often awakens patients at night, is typically associated with morning

stiffness, and improves initially with NSAIDs. It sometimes results in buttock pain, which can alternate from side to side. Persistent IBP for at least 3 months is common in adults with axial arthritis, and thus is a major criterion required to classify an individual with axial SpA (Box 1). In contrast, IBP is not a common clinical feature of jSpA. While this has generally been interpreted to indicate lack of axial and in particular sacroiliac involvement in jSpA, this may not always be the case. Stoll and colleagues demonstrated that while sacroiliitis was present in 37% of their juvenile SpA patients, 21% had ‘silent’ sacroiliitis detected only by imaging and were lacking suggestive symptoms or physical examination findings²⁶. In this study, hip arthritis was a major risk factor for sacroiliitis, whereas dactylitis was negatively associated. In another study by Pagnini et al., 30% of children with ERA developed sacroiliitis documented clinically or by imaging, which was detectable by MRI as early as one year after disease onset. The main predictors of sacroiliitis in this cohort were active joint and enthesitis counts at onset²⁹.

Detecting Sacroiliitis—Spinal involvement in AS is first detected in the sacroiliac joints in the vast majority of patients. Given the insensitivity of plain radiography for early sacroiliitis, criteria for defining active sacroiliitis by MRI have been developed³⁰ and are used in the ASAS classification scheme for axial SpA. The presence of either subchondral or periarticular bone marrow edema (BME) on STIR (short τ inversion recovery) imaging, or osteitis on T1 post-gadolinium images, are considered highly suggestive of active sacroiliitis. Importantly, the presence of enthesitis, synovitis, or capsulitis on MRI without concomitant bone marrow edema, while consistent with sacroiliitis, is not considered evidence of active sacroiliitis³⁰. While gadolinium is helpful to detect active synovitis, STIR sequences are sufficient to detect active BME³¹. Therefore, it is frequently preferable to obtain STIR MRI alone when evaluating children for sacroiliitis, considering the risks associated with gadolinium administration and the discomfort associated with placement of an intravenous catheter.

In the absence of inflammatory back pain or stiffness, alternating buttock pain, or hip pain, it can be difficult to judge when to pursue further sacroiliac imaging in children with SpA. This is an important question as the presence of sacroiliitis may have implications for treatment and long-term prognosis. The sensitivity of tenderness along the sacroiliac joint margin, reduced lumbosacral flexion (Schober test), or a positive Patrick’s test (or FABER test, for pain elicited by flexion, abduction and external rotation of the leg) for predicting sacroiliac joint inflammation is not known, but in our experience is low. If sacroiliitis is suspected, radiographs are often obtained. Although they are low yield in early disease as previously discussed, they provide an important baseline and can be helpful for future comparison considering the subtle changes that can sometimes indicate ongoing sacroiliitis (Table 3). STIR MRI of the pelvis can be obtained without the need for sedation in most school-age children suspected of having axial SpA. In rare cases where imaging is necessary in younger children, it may be necessary to provide sedation to obtain high quality images.

Extra-Articular Manifestations

Uveitis—Acute anterior uveitis (AAU) is the most common extra-articular manifestation of jSpA, and is also more frequent in HLA-B27 positive individuals even in the absence of arthritis or other features of SpA. AAU generally presents as unilateral, acute onset ocular inflammation resulting in redness, pain, and photophobia. Up to one-third of AS patients will develop AAU sometime during the course of their disease, with the highest risk being associated with HLA-B27, and about 50% experience at least one recurrence³². While HLA-B27 positive AAU is frequently considered in the SpA category even in the absence of articular features, a new diagnosis of AAU can also lead to the recognition of pre-existing non-specific symptoms that are in fact due to other SpA features³³. More than 50% of

patients with HLA-B27 positive AAU will eventually be diagnosed with another form of SpA including AS³³.

AAU should be contrasted with the chronic uveitis associated with other forms of JIA (including early onset PsA) that is most often asymptomatic. The risk of chronic uveitis is increased in ANA positive patients, and ophthalmologic screening with a slit-lamp examination can detect early asymptomatic disease, enabling prompt treatment and reducing the risk of vision loss. Guidelines for screening children classified with juvenile rheumatoid arthritis (prior to the adoption of JIA criteria) have been published³⁴ but do not address juvenile spondyloarthritis or ERA. For children with jSpA who are ANA negative but at risk for AAU, we provide education and counseling about obtaining prompt evaluation for ocular symptoms, and recommend yearly ophthalmologic examination. Children with early onset PsA should be tested for ANA and screened according to current guidelines for oligo or polyarticular arthritis³⁴.

Gastrointestinal inflammation

There is a strong link between gut inflammation and arthritis, particularly in SpA. Peripheral and axial arthritis occur in up to 30% of patients with IBD. Conversely, 6.5% of AS patients eventually develop IBD, but nearly 60% have subclinical gastrointestinal inflammation^{35, 36}. The prevalence of gut inflammation in jSpA is not known. IBD-associated arthritis is not specifically addressed by the ILAR classification system, except as an exclusion for psoriatic arthritis, and consequently children would mostly be classified as ERA or undifferentiated arthritis. Interestingly, elevated levels of fecal calprotectin, a marker of intestinal inflammation, were seen in a small series of ERA patients compared to healthy, other JIA, and other connective tissue disease controls³⁷. In a follow-up study, MR enterography performed on 5 patients with JIA and elevated fecal calprotectin, including 4 with jSpA, showed evidence of intestinal inflammation³⁸.

Other extra-articular manifestations

Long-standing AS is associated with atherosclerotic and non-atherosclerotic cardiac manifestations¹⁷. Atherosclerotic consequences include an increased risk for myocardial infarction, with a two-fold increased risk for ischemic heart disease noted in a Swedish population³⁹. Non-atherosclerotic complications including aortitis, aortic regurgitation, and aortic and mitral valve thickening without regurgitation have been reported, even in relatively early AS⁴⁰. Although cardiac manifestations of jSpA are relatively mild⁴¹, they can occur, making cardiac risk factor and functional assessment important for long-term care.

PSORIATIC ARTHRITIS

Juvenile psoriatic arthritis appears to be comprised of two distinct clinical subgroups⁴². One is characterized by early onset (peak age of 1–2 years) with features similar to oligoarticular and polyarticular JIA, including a predilection for females with a positive ANA, chronic uveitis, and an HLA-DR5 association. The second subgroup reflects later onset (peak age between 8 and 12 years), association with HLA-B27 but not ANA, equal sex ratio, and more frequent dactylitis, enthesitis, nail pitting, and axial involvement^{42, 43}. Clinical and genetic characteristics of the latter group are more representative of the SpA continuum. Re-classification of jSpA in a manner that recognizes these sub-groups may be helpful for future studies and in communicating the different implications for outcome. Recent studies by McGonagle and colleagues suggest that nail involvement in PsA may have an anatomical basis reflecting the presence of a bone-enthesitis-nail complex^{44, 45}. In this context, distal

interphalangeal joint involvement along with onycholysis and nail pitting in PsA are considered components of extensor tendon enthesopathy rather than synovitis^{46, 47}.

GENETIC SUSCEPTIBILITY AND PATHOGENESIS

Significant advances in understanding genetic susceptibility to SpA have been made in the last several years⁴⁸. The majority of these discoveries pertain to AS and PsA, as well as underlying conditions psoriasis and IBD. Several concepts have begun to emerge from this work. First, there are significant overlaps between genes that predispose to AS and risk genes for psoriasis and PsA, and between AS and IBD including both Crohn's disease and ulcerative colitis. Some degree of shared genetic predisposition might be expected because of the clinical features common to various forms of spondyloarthritis. In contrast, there is currently no overlap between AS and autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematosus. Second, genes in pathways relevant to the IL-23/IL-17 axis⁴⁹ are involved in susceptibility to AS, most notably the IL-23 receptor (*IL23R*) and the p40 subunit of IL-12 (*IL12B*) (which combines with IL-23p19 to produce the active IL-23 cytokine). These genes are also implicated in susceptibility to IBD and psoriasis. *STAT3*, another gene involved in transmitting cellular cytokine signals including the response to IL-23, is also implicated in susceptibility to AS and IBD. A third important lesson from genome-wide association studies (GWAS) in AS that is also true for other complex genetic diseases, is that the majority of heritability remains to be explained. For example, in AS only about 25% of overall heritability has been accounted for⁴⁸ despite large-scale studies involving several thousand affected individuals and even greater numbers of controls in the several GWAS performed to date. HLA-B27 accounts for the vast majority (23.3 of the 25.4%) of the known heritability, with newly discovered genes or gene regions accounting for the remaining 2.1%. The unidentified heritability may be related to rare variants and/or copy number differences not detected by commonly used high throughput methods of SNP detection, and/or gene-gene interactions that remain to be thoroughly assessed. While there have been no GWAS performed in ERA or juvenile PsA, it is interesting that a small pediatric study confirmed associations between *IL23R* variants and PsA in 93 individuals, and *ERAPI* SNPs and ERA in 74 subjects⁵⁰. Although HLA-B27 is clearly associated with jSpA, its true prevalence in ERA and juvenile PsA cannot be determined because it is used for classification in the ILAR criteria.

Considerable evidence implicating the IL-23/IL-17 axis in SpA pathogenesis has accumulated over the last several years. Studies have documented IL-23 and IL-17 overexpression and expansion of Th17 T cells in both IBD and arthritis in HLA-B27 transgenic rats^{51, 52}, as well as in synovial fluid and peripheral blood from SpA patients^{53, 54}. In rats IL-23 overproduction has been linked to HLA-B27 misfolding and endoplasmic reticulum (ER) stress through activation of the unfolded protein response⁵¹, while loss of tolerizing dendritic cells may be important as well⁵⁵. Human macrophages from subjects with HLA-B27-positive SpA produce more IL-23 without evidence of ongoing ER stress through a mechanism that remains to be defined⁵⁶. Interestingly, dimers of HLA-B27 heavy chains expressed on the cell surface of antigen-processing-deficient cells can trigger leukocyte immunoglobulin-like receptors in the killer immunoglobulin receptor (KIR) family, particularly KIR3DL2⁵⁷. When present on CD4+ Th17 T cells, KIR3DL2 activation can promote survival and increase IL-17 production, providing another possible link between HLA-B27 and Th17 cytokines in pathogenesis. The discovery of *ERAPI* (formerly *ARTS1*) as a risk gene⁵⁸, and subsequently a gene-gene interaction with HLA-B27 in AS⁵⁹, suggests that qualitative and/or quantitative differences in peptides that affect HLA-B27 folding and assembly, peptide presentation, and/or cell surface dimerization are important in disease susceptibility and pathogenesis.

Further support for the important role of IL-23 in SpA comes from a recent paper showing that systemic delivery of this cytokine in mice can result in peripheral and axial enthesitis (without synovitis), aortic root inflammation, and osteoproliferation⁶⁰. The location of IL-23-driven inflammation in this model was found to be a consequence of a newly discovered population of enthesal-resident T cells expressing the IL-23 receptor. These cells also express other transcription factors that direct the production of Th17 cytokines including IL-17A, TNF α , and IL-22 but differ from classical Th17 T cells in that they are CD4 negative. IL-22 was particularly important for induction of bone remodeling.

TREATMENT

The approach to managing juvenile SpA is guided in large part by evidence from studies in adults with SpA and children with other forms of JIA. Non-steroidal anti-inflammatory drugs (NSAIDs) are often the first line of therapy recommended in both axial and peripheral SpA⁶¹ as they improve symptoms and can reduce inflammation⁶². Traditional disease-modifying anti-rheumatic drugs (DMARDs) such as methotrexate and sulfasalazine are of limited utility for axial disease, despite their efficacy in other forms of inflammatory arthritis such as polyarticular JIA and rheumatoid arthritis. There is some evidence supporting the use of sulfasalazine in juvenile AS and SEA syndrome, but improvement was limited to patient and physician global assessment of disease activity and not in primary outcome measures⁶³. Other open label studies of sulfasalazine in juvenile AS, ERA and PsA have shown improvement in clinical symptoms, inflammatory markers and remission rates^{64, 65}. These DMARDs have not been effective for axial disease or enthesopathy, though they are still utilized for peripheral arthritis and some extra-articular manifestations⁶⁶. TNF inhibitors (TNFi) consistently reduce inflammation and signs and symptoms of AS/SpA in adults, and not surprisingly have also shown benefit for jSpA. Infliximab improved arthritis, enthesitis, inflammatory markers, pain and physical function in a three-month double-blind placebo controlled trial in jSpA SpA⁶⁷. Open-label trials in juvenile AS and ERA have shown improvement in all clinical outcomes with the use of both infliximab^{68, 69} and etanercept^{70–73}, and more recently a double-blind placebo controlled trial of adalimumab demonstrated efficacy in juvenile onset AS⁷⁴.

Specific recommendations for the treatment of JIA were recently published⁷⁵. Treatment groups for non-systemic JIA were established based on the cumulative number of peripheral joints involved (4 or 5 joints), and whether or not active sacroiliitis was present. Following these recommendations, active sacroiliitis lowers the threshold for the initiation of a TNFi. Active sacroiliitis was not defined, although the need for both clinical and imaging evidence was noted. Since active disease cannot be determined by plain radiography, a positive sacroiliac MRI as defined by the ASAS criteria would seem appropriate. Parameters used to determine how quickly one should advance from NSAIDs, methotrexate or sulfasalazine to a TNFi include clinical presentation prognosis and disease activity measures. Poor prognosis is defined as radiographic damage (erosions or joint space narrowing) of any joint. However, in someone with jSpA who may have little peripheral or only sacroiliac arthritis, erosions may be a late finding and joint space widening may occur rather than narrowing⁷⁶. Given the lack of efficacy of methotrexate and sulfasalazine for axial disease in adult trials, it may be prudent to move more rapidly from NSAIDs to a TNFi when active sacroiliitis is present. Treatment recommendations for adults with axial SpA include the initiation of a TNFi when disease activity persists despite at least two 4-week courses of NSAIDs at optimal doses, with no requirement for DMARD failure⁷⁷. Peripheral disease is considered refractory when it remains active despite current or past intake of sulfasalazine or local corticosteroids⁷⁷. Predictors of a positive response to TNFi therapy in adults include short disease duration, younger age, better functional status, elevated inflammatory markers, HLA-B27 positivity, and higher spinal MRI scores^{78–81}. Many of

these predictors suggest that early active disease in younger patients will be more responsive to TNFi. Exercise and physical therapy for jSpA are also important adjuncts to therapy that should not be ignored.

The question of whether TNFi can slow syndesmophyte growth and axial progression in AS remains a subject of great debate⁸². While continuous use of NSAIDs has been shown to slow radiographic progression, the effect is small⁸³. This is measured with the mSASSS (Modified Stoke AS Spine Score), with increases 1 unit per year considered progression. Initial studies comparing patients on TNFi in large clinical trials to historical controls in the OASIS (Outcome in AS International Study) cohort suggested that despite having a marked effect on controlling disease activity and inflammation, TNFi were unable to slow the growth of syndesmophytes measured with the mSASSS^{84–86}. However, newer data are emerging that may challenge this concept. Gensler and colleagues analyzed 334 AS patients from several centers in North America who had been followed prospectively. Patients receiving TNFi at least 50% of the time with axial symptoms had a significantly lower rate of mSASSS progression than those not receiving TNFi⁸⁷. Predictors of progression included baseline inflammatory markers, smoking status, and the mSASSS. These results are encouraging and suggest that TNFi can modify axial progression. It will be important to confirm these results in additional studies. TNFi currently approved for use in AS are etanercept, infliximab, and adalimumab. Golimumab is approved for active AS and PsA in adults and several adult trials with certolizumabpegol are underway with preliminary efficacy and similar safety profiles as other TNFi^{88, 89}.

We are not aware of any studies on the efficacy of other biologic therapies in juvenile SpA. In adults with SpA, rituximab, anakinra and abatacept have been evaluated primarily in small open label pilot studies. Rituximab and anakinra have shown modest benefit in TNFi-naïve patients^{90, 91}. Multiple studies have failed to find any major improvement with abatacept in AS or SpA^{92, 93}, and the IL-6 inhibitor tocilizumab was not efficacious in axial SpA⁹⁴. Newer and more promising therapies include the anti-IL-17A antibody, secukinumab, which provided favorable results in a proof of concept trial in AS, including the open label extension phase up to 24 months^{95, 96}. The oral phosphodiesterase-4 inhibitor, apremilast, has also shown evidence of efficacy in AS⁹⁷. The recently elucidated role of IL-23 in SpA with its relationship to HLA-B27 and as a driver of enthesitis⁶⁰ (see below), may provide another therapeutic target for juvenile SpA in the coming years.

CONCLUSION

Juvenile spondyloarthritis occurs on a continuum with adult disease, although there are differences in presentation and outcome that pediatric and adult rheumatologists need to be familiar with. Major unmet needs include criteria to readily identify children with early axial involvement, and validated measures of disease activity. Significant advances in our understanding of genetic susceptibility and pathogenesis have identified new targets target genes? for enthesal inflammation in SpA and may explain unique aspects of the phenotype previously thought to be a consequence of auto reactive CD8+ T cells. TNF blockade continues to be a key treatment strategy, suppressing inflammation and providing symptom relief for a large number of patients suffering from SpA. New research suggests that IL-23, IL-17, and IL-22 could be equally important disease mediators. The ongoing development and clinical testing of antibodies that target these cytokines and/or their receptors hold considerable promise for improving the outcome for patients including children with spondyloarthritis.

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KEY POINTS

- Juvenile spondyloarthritis can be viewed on a continuum with adult onset disease
- Spondyloarthritis in children presents with peripheral arthritis and enthesitis more frequently than inflammatory back pain
- Sacroiliitis may be more common in children with juvenile spondyloarthritis than expected based on symptoms
- Validated measures of clinical disease activity, imaging, and biomarkers are needed to identify children with axial spondyloarthritis
- New therapeutic targets in the IL-23/IL-17 axis hold great promise for improving treatment options and outcomes in spondyloarthritis

Box 1. ASAS classification criteria for axial SpA

Sacroilitis on imaging* + 1 SpA feature**

HLA-B27 plus 2 other SpA features**

* - Active (acute) inflammation on MRI highly suggestive of sacroiliitis associated with SpA or Definite radiographic sacroiliitis according to modified New York criteria

** SpA features:

- - Inflammatory back pain
- - Arthritis
- - Enthesitis (heel)
- - Uveitis
- - Dactylitis
- - Psoriasis
- - Crohn's disease/ulcerative colitis
- - Good inflammatory response to NSAIDs
- - Family history for SpA
- - HLA-B27
- - Elevated CRP

From Rudwaleit M, et al., The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part II): validation and final selection. *Ann Rheum Dis* 2009; 68:777–783.

Box 2. ASAS classification criteria for Peripheral SpA

Arthritis* or **enthesitis** or **dactylitis**, PLUS either

One or more of the following:

- - Uveitis (anterior)
- - Psoriasis
- - Crohn's disease or ulcerative colitis
- - Preceding infection (within 1 month)
- - HLA-B27
- - Sacroiliitis on imaging

Two or more of the following:

- - Arthritis
- - Enthesitis
- - Dactylitis
- - Inflammatory back pain (ever)
- - Family history of SpA

*Peripheral arthritis; predominantly lower limb and/or asymmetric

Adapted from Rudwaleit M, et al., The Assessment of SpondyloArthritis International Society classification criteria for peripheral spondyloarthritis and for spondyloarthritis in general. *Ann Rheum Dis* 2011; 70:25–31.

Figure 1. Achilles tendon enthesitis. Heels of a nineteen year old HLA-B27-positive male with enthesitis and peripheral arthritis. Area of right Achilles tendon insertion on calcaneus is swollen, slightly erythematous, and tender to palpation, despite ongoing treatment with a TNF inhibitor.

Figure 2.

Whole body MRI in suspected early AS. Twenty-eight year old HLA-B27-positive male with inflammatory back pain for 7 months was evaluated. STIR images show (left) bone marrow edema adjacent to the lower portions of SI joints (open arrows), and (right) in anterior corners (closed arrows) of thoracic vertebral bodies. Image reproduced from reference¹⁹ with permission from author.

Figure 3. Whole body MRI of sixteen-year old HLA-B27-positive male with a one-year history of knee and hip pain, and six months of inflammatory back pain. Patient was on indomethacin at the time of imaging. STIR images of (A) thoracic region showing enhanced signal at cost over tebral junction (arrow), and (B) pelvis showing bone marrow edema on both the iliac and sacral sides of the sacroiliac joints bilaterally.

Figure 4.

Radiographic images of sacroiliac joints of 19-year old HLA-B27-positive male with two-year history of intermittent lower back pain and one episode of acute anterior uveitis. Plain radiographs (**A, B**) and CT scan (**C**) of sacroiliac joints. (**A, B**) reveal minimal sclerosis bilaterally with joint space widening (grade II). (**C**) Erosions and sclerosis.

Figure 5.

STIR image from whole body MRI of 19-year old male with two-year history of intermittent hip and alternating buttock pain, but lacking inflammatory back pain. Bone marrow edema is apparent on sacral and iliac sides of left sacroiliac joint. Patient had previous MRI showing bone marrow edema adjacent to the right sacroiliac joint correlating with right-sided symptoms.

Table 1**ILAR Classification of Juvenile Idiopathic Arthritis**

1	Systemic
2	Oligoarthritis
	a. Persistent
	b. Extended
3	Polyarthritis (rheumatoid factor negative)
4	Polyarthritis (rheumatoid factor positive)
5	Psoriatic arthritis
6	Enthesitis-related arthritis
7	Undifferentiated arthritis
	a. Fits no other category
	b. Fits more than one category

Data from Petty RE, et al. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. *J Rheum* 2004; 31:390–392.

Table 2**ILAR Categories Encompassing Juvenile Spondyloarthritis**

Enthesitis-related arthritis	
Arthritis and enthesitis	
<i>or</i>	
Arthritis or enthesitis with at least 2 of the following:	
<ul style="list-style-type: none"> • Sacroiliac joint tenderness and/or inflammatory spinal pain • Presence of HLA-B27 • Onset of arthritis in a male over 6 years of age • Family history in at least one first-degree relative of ankylosing spondylitis, enthesitis related arthritis, sacroiliitis with inflammatory bowel disease, reactive arthritis, or acute anterior uveitis • Acute (symptomatic) anterior uveitis 	
<i>Exclusions</i>	
1	Psoriasis or a history of psoriasis in the patient or a first-degree relative
2	Presence of IgM RF on at least two occasions at least 3 months apart
3	Systemic JIA in the patient
Psoriatic arthritis	
Arthritis and psoriasis	
<i>or</i>	
Arthritis plus at least two of the following:	
<ul style="list-style-type: none"> • Dactylitis • Nail pitting or onycholysis • Psoriasis in a first-degree relative 	
<i>Exclusions</i>	
1	Arthritis in an HLA-B27-positive male beginning after the sixth birthday
2	AS, ERA, sacroiliitis with IBD, reactive arthritis or acute anterior uveitis, or a history of one of these disorders in a first-degree relative
3	Presence of IgM RF on at least two occasions at least 3 months apart
4	Systemic JIA in the patient
Undifferentiated arthritis	
Arthritis that fulfills none of the ILAR categories, or fulfills criteria in two or more categories	

Data adapted from From Petty RE, et al. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. *J Rheum* 2004; 31:390–392.

Table 3**Modified New York criteria for ankylosing spondylitis (AS)**

<i>Clinical criteria</i>	
1	Low back pain for at least 3 mos. improved by exercise and not relieved by rest
2	Limitation of lumbar spine motion in sagittal and frontal planes
3	Chest expansion decreased relative to normal values for age and sex
<i>Radiological criterion</i>	
Unilateral sacroiliitis grade 3–4, or	
Bilateral sacroiliitis grade 2–4	
<i>Definite AS</i>	
Radiological criterion and at least one clinical criterion	
<hr/>	
<i>Radiographic grading of sacroiliac changes:</i>	
Grade 0 = Normal	
Grade 1 = Suspicious	
Grade 2 = Sclerosis, some erosions	
Grade 3 = Severe erosions, widening of the joint space, some ankylosis	
Grade 4 = Complete ankylosis	

Data adapted from Van der Linden S, et al., Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. *Arthritis Rheum* 1984; 27:361–368.

Table 4

Enthesal Sites in Enthesitis Indices

Site	Leeds ^a	Gladman ^b	MASES ^c	Mander ^d	Major ^e	SPARCC ^f
Nuchal crests				X		
Manubriosternal				X		
Costochondral			X*	X		
Rotator cuff insertion at shoulder		X				
Greater tuberosity of humerus				X		X
Medial humeral epicondyle				X	X	X
Lateral humeral epicondyle	X			X	X	X
Iliac crest			X	X	X	
Anterior superior iliac spine			X	X		
Greater trochanter of femur				X	X	X
Medial femoral condyle	X			X		
Lateral femoral condyle				X		
Superior pole of patella						X
Inferior pole of patella						X [^]
Tibial tuberosity		X				
Insertion of Achilles tendons	X	X	X	X	X	X
Plantar fascia to calcaneus		X		X	X	X
Cervical spinous process				X		
Thoracic spinous process				X		
Lumbar spinous process			X [#]	X		
Ischial tuberosity				X		
Posterior superior iliac spine			X	X		
Total number of enthesal sites	6	8	13	66	12	16

^aLeeds Enthesitis Index⁹⁸,^bEnthesitis index developed by Gladman et al. for PsA⁹⁹;^cMaastricht Ankylosing Spondylitis Enthesitis Score¹⁰⁰,

- ^d Enthesitis index developed by Mander et al. for ankylosing spondylitis^{100, 101};
- ^e Major Enthesitis Index developed for ankylosing spondylitis¹⁰²;
- ^f Spondyloarthritis Research Consortium of Canada (SPARCC) Enthesitis Index¹⁰³.
- Shading indicates where a particular anatomical site is listed in 3 or more indices.
- * Includes 1st and 7th costochondral junctions.
- # Fifth lumbar spinous process.
- ^ Patellar ligament insertion into inferior pole of patella or tibial tubercle.