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REVIEW

Children With Enthesitis-Related Arthritis and Possible Benefits From Treatments for Adults With Spondyloarthritis

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This review will summarize clinical, genetic, and pathophysiologic characteristics that are shared between children with enthesitis-related arthritis (ERA) with axial involvement and adults with nonradiographic (and in some cases radiographic) axial spondyloarthritis (SpA), as well as between children with ERA and primarily peripheral disease manifestations and adults with peripheral SpA. Due to the differences in classification criteria for children with ERA and adults with axial and peripheral SpA, the US Food and Drug Administration (FDA) granted automatic full waivers of studies in children for new medications for "axial spondyloarthropathies including ankylosing spondylitis" up until July 2020. Thus, although current juvenile idiopathic arthritis treatment guidelines recommend the use of biologic disease-modifying antirheumatic drugs as part of the early treatment for patients with ERA, none of the FDA-approved therapies for peripheral SpA or nonradiographic axial SpA (certolizumab pegol, ixekizumab, and secukinumab) have been studied or are labeled for use in children with ERA. Considering the similarities between adult SpA and ERA in terms of etiology, genetics, pathogenesis, and clinical manifestations summarized in this review, medications approved for axial SpA or peripheral SpA should also be studied in children with active ERA involving axial or peripheral joints, respectively, with the intent to achieve labeling for use in children. Considering the current lack of effective FDA-approved therapies for ERA, the FDA should also consider requiring pediatric studies for medications that have already been approved for the treatment of adults with SpA.

Introduction

Juvenile idiopathic arthritis (JIA) is a group of chronic pediatric rheumatic diseases of unknown etiology that present by the age of 16 years. JIA is classified into 6 mutually exclusive categories by the International League of Associations for Rheumatology (ILAR) criteria (1); a seventh category, "undifferentiated," is for children fulfilling criteria for more than 1 category. Patients categorized as having extended oligoarticular JIA or polyarticular JIA are accepted as the pediatric extensions of rheumatoid arthritis for US Food and Drug Administration (FDA) drug approval, and, likewise, those categorized as having juvenile psoriatic arthritis are the extensions of psoriatic arthritis in adults, respectively. Enthesitis-related arthritis (ERA) was the JIA category applied to children with spondyloarthritis (SpA), recognizing enthesitis as a

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defining characteristic. The prevalence of JIA is estimated at 20 to 45 per 100,000 children, of which 15–20% have ERA (2). The ILAR criteria for ERA are arthritis plus enthesitis, or arthritis or enthesitis plus at least 2 of the following: sacroiliac tenderness or inflammatory back pain, HLA–B27 positivity, first-degree relative with HLA–B27–associated disease, acute anterior uveitis, and arthritis in a male individual older than 6 years (1). The ERA criteria do not specifically account for inflammatory bowel disease arthropathy, ankylosing spondylitis, or reactive arthritis, which are clinical conditions included with adult SpA; children with these conditions may or may not meet the ERA criteria depending upon what disease features are present.

This review will summarize clinical, genetic, and pathophysiologic characteristics shared between children with ERA with axial involvement and adults with nonradiographic, and in some cases radiographic, axial SpA, as well as between children with ERA and peripheral disease manifestations and adults with peripheral SpA. Further, insights into validated outcome measures and therapy for ERA and adult SpA are provided.

Evidence that ERA and SpA are similar diseases based on biology

Much of our understanding of ERA pathogenesis is derived from studies of HLA–B27, a risk allele for adult and juvenile SpA. HLA–B27 is linked to activation of the interleukin 23 (IL-23/IL-17) axis through noncanonical mechanisms not involving antigen presentation to CD8+ T cells (3). A population of CD4/CD8-negative T cells in the entheses was shown to mediate IL-23–driven SpA (4,5). These cells were first identified in mice, and an equivalent type 3 innate-like lymphocyte has been described in human entheses (6). Juvenile SpA, like its adult counterpart, may also have an extra synovial basis of disease (7–9). The overlap in genetic susceptibility to ERA and SpA also includes endoplasmic reticulum aminopeptidase 1 (10), a peptidase specialized to produce peptides presented on class I major histocompatibility complex molecules, and a major risk gene for ankylosing spondylitis (11).

Subsets of adults with SpA and children with ERA have bowel inflammation (12). This has been studied more in adults (13), as access to intestinal tissue from children with subclinical inflammation is limited by ethical concerns. A number of different cell types have been implicated, and studies have emphasized the potential importance of bacterial dysbiosis, although cause and effect relationships remain unclear.

Similarity of clinical features

SpA develops on a continuum with a major peak of onset in young adulthood (14). Although sacroiliitis is well documented in ERA (15), the ILAR classification criteria focus on the importance of extra-axial manifestations, i.e., peripheral arthritis and enthesitis. Conversely, SpA classification in adults considers the presence of axial disease and peripheral disease (1). For reasons that remain unclear, common presenting features of juvenile-onset disease localize more to hips and peripheral joints (16), while adults experience predominantly inflammatory back pain (17).

Table 1 highlights the similarities and differences between the ERA classification criteria, the Assessment of SpondyloArthritis international Society (ASAS) criteria for nonradiographic axial SpA, and the ASAS criteria for peripheral SpA (18). The principal commonalities of children with ERA and axial arthritis, and adults with nonradiographic axial SpA, include enthesitis, arthritis, inflammatory back pain, anterior uveitis, HLA–B27 positivity, and family history of HLA–B27–associated disease. Magnetic resonance imaging (MRI) is increasingly used to confirm the presence of subchondral bone marrow edema around the sacroiliac joints; many patients have elevated C-reactive protein (CRP) levels, and the majority of patients experience some response to nonsteroidal antiinflammatory drugs (NSAIDs). One study reported 62% of ERA patients had axial disease at the time of diagnosis, and 63% of patients with only peripheral arthritis at the time of diagnosis developed axial involvement within 5 years (19). Figure 1 demonstrates that the inflammatory changes in the sacroiliac joints are indistinguishable between adults and children. In children, maturational changes may be mistaken for inflammatory changes by those with less experience evaluating the pediatric sacroiliac joint (Figure 2) (20). Unlike nonradiographic axial SpA, ERA is exclusive of psoriasis, while inflammatory bowel disease and reactive arthritis are largely ignored. Taken together, despite common clinical, laboratory, and radiographic features, differences in the classification between ERA and adult SpA can unduly complicate communication between providers, insurance carriers, and regulatory agencies (including the FDA), the transition from pediatric to adult care, and access to medications.

Similar outcomes in imaging outcome measures between pediatric and adult disease

For children and adults, evaluation for axial disease often includes MRI. Pediatric studies (15,21) utilize the ASAS MRI lesion definitions (22). Further, there are validated tools for assessment of axial joint inflammation and damage in adults and children. The Spondyloarthritis Research Consortium of Canada (SPARCC) sacroiliac joint inflammation score (SIS; range 0–72) considers site, extent, and severity of sacroiliac joint inflammation and has been validated for use in adults and children to capture response to therapy (23,24). A change in SIS score of 2.5 is considered clinically relevant in both populations (23). Damage in the sacroiliac joint can be quantified by the SPARCC sacroiliac structural score (SSS), which features 4 domains, including erosion (0–40), fat metaplasia (0–40), backfill (0–20), and ankylosis (0–20); there is no total score. The SPARCC SSS is validated in children and adults (24,25).

Table 1. Comparison of classification criteria used in children and adults*

	ERA	Nonradiographic axial SpA	Peripheral SpA
Criteria set	ILAR	ASAS	ASAS
Inclusion or entry criteria	Arthritis and enthesitis OR arthritis or enthesitis plus ≥2 supporting features	≥3 months of back pain starting before age 45 years AND sacroiliitis on imaging plus ≥1 SpA feature OR ≥2 SpA features	Arthritis OR enthesitis OR dactylitis† OR plus ≥1 group A feature OR ≥2 group B features
Supporting features			
Enthesitis	X	X	X (group B)
Arthritis	X	X	X (group B)
Dactylitis		X	X (group B)
Sacroiliac tenderness or IBP	X	X‡	X (group B)‡
Anterior uveitis	X	X	X (group A)
Psoriasis		X	X (group A)
IBD		X	X (group A)
Preceding infection§			X (group A)
Imaging			X¶
HLA–B27 positivity	X		
Family history	HLA–B27–associated disease in 1st-degree relative	1st- or 2nd-degree relative with SpA	Group B: 1st- or 2nd-degree relative with SpA
Markers of inflammation/ elevated C-reactive protein		X	
Therapeutic response to NSAIDs		X	

* ASAS = Assessment of SpondyloArthritis international Society; ERA = enthesitis-related arthritis; IBD = inflammatory bowel disease; IBP = inflammatory back pain; ILAR = International League Against Rheumatism; NSAIDs = nonsteroidal antiiflammatory drugs; SpA = spondyloarthritis.
† Arthritis, enthesitis, or dactylitis must be present at the time of evaluation.
‡ Inflammatory back pain only.
§ Urethritis/cervicitis or diarrhea within 1 month prior to onset of symptoms.
¶ Sacroiliitis on imaging (bilateral grade 2 to 4 or unilateral grade 3 to 4 on radiographs or active sacroiliitis on magnetic resonance imaging).

Similarity of response to therapy in children and adults

Algorithms to treat ERA with axial arthritis and nonradiographic axial SpA are similar, as is evidenced by published American College of Rheumatology (ACR) treatment recommendations for both conditions (26,27). The recommended initial treatment of both is NSAIDs, followed by tumor necrosis factor (TNF) inhibitors if NSAIDs are not tolerated or ineffective. Numerous trials in adults have shown that conventional disease-modifying antirheumatic drugs (cDMARDs) do not improve axial disease (28). Although similar trials have not been conducted in ERA, ACR pediatric treatment recommendations strongly advise against methotrexate monotherapy and moving directly to anti-TNF therapy, based on extrapolation from the adult studies and clinical experience (26).

Treatment algorithms for children with ERA and adults with SpA and peripheral disease depend upon the number of affected joints and risk factors present. For peripheral disease affecting fewer than 5 joints, intraarticular joint injections with or without NSAIDs are considered first-line therapy (26). For peripheral disease affecting 5 or more joints, cDMARDs including methotrexate are first-line therapy and may be used with TNF inhibitors, if joint damage is present or if there is involvement of high-risk joints (cervical spine, wrist, hip) (26). While there are no formal guidelines for treatment of adults with peripheral SpA, treatment algorithms are analogous to those used in children with ERA and inflammation of peripheral joints.

Response to therapies is also similar in ERA and adults with SpA. Randomized placebo-controlled clinical trials in adults (29–31) and data from children (32,33) show the efficacy of TNF inhibitors for peripheral arthritis, enthesitis, and axial arthritis. However, as many as half of adults with axial disease are unable to achieve remission with TNF inhibitors, with 15% of adults with axial SpA failing to show any improvement with TNF inhibitors (34). Similarly, 33% of children with ERA treated with TNF inhibitors and NSAIDs lack response to therapy (19). In 1 study, only 24% of children with ERA achieved inactive disease during the initial 12 months of treatment (35), and fewer than 20% achieved remission within 5 years (36). Additionally, physical function limitations and moderate chronic pain are more prevalent with ERA than with other JIA

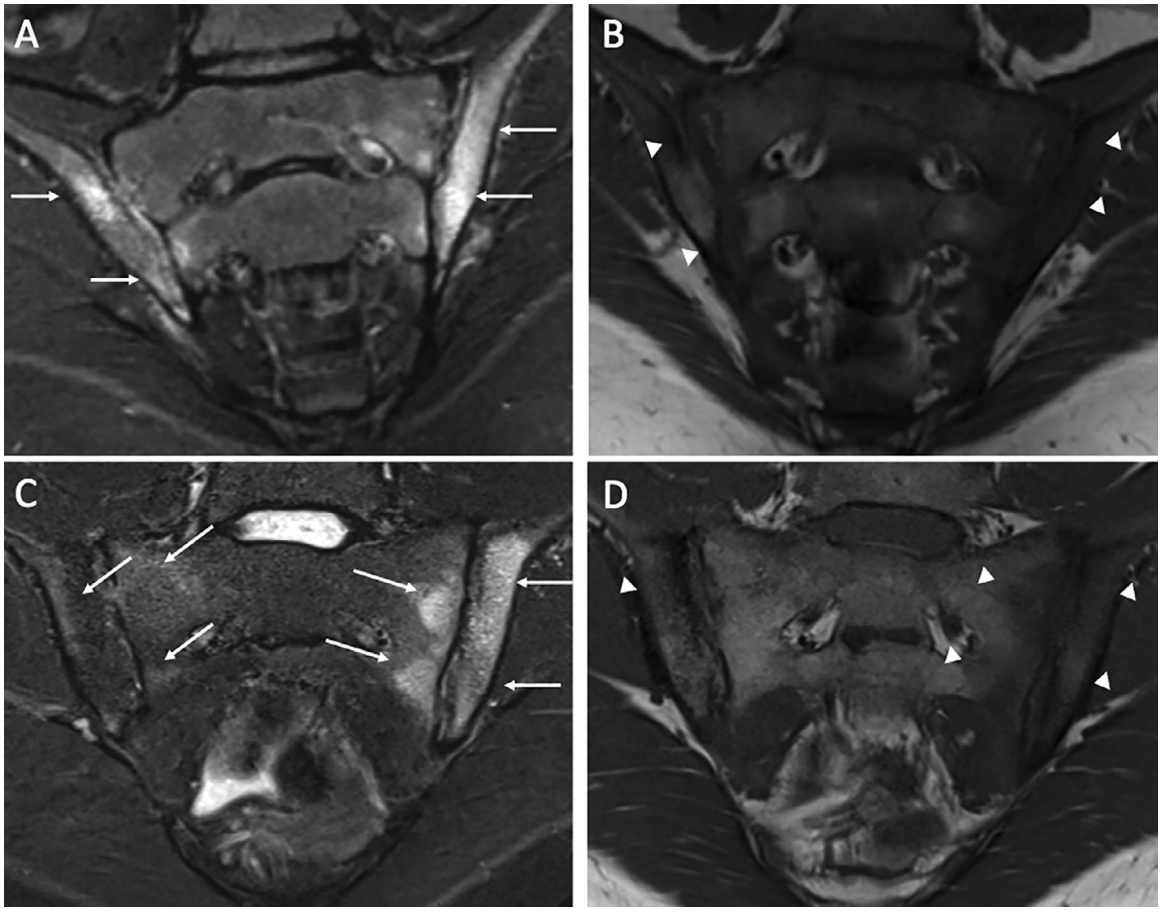

Figure 1. Coronal oblique STIR (**A** and **C**) and coronal oblique T1-weighted (**B** and **D**) images of the sacroiliac joints of a 7-year-old, HLA–B27–positive female patient (**A** and **B**) and a 20-year-old HLA–B27–positive male patient (**C** and **D**). There is active sacroiliitis with periarticular bone marrow edema within the iliac aspect of both joints as demonstrated by increased signal intensity on STIR imaging (**A**; arrows) and decreased signal intensity on T1-weighted imaging (**B**; arrowhead). There is active sacroiliitis with periarticular bone marrow edema within the sacral and iliac bones, much more intensely on the left than the right, as demonstrated by increased signal intensity on STIR imaging (**C**; arrows) and decreased signal intensity on T1-weighted imaging (**D**; arrowheads).

categories (37). Thus, achieving inactive disease status or clinical remission is difficult for children with ERA, and many continue to have disease activity despite off-label use of existing therapies.

Regulatory environment for medication approval

In the US, the FDA is the federal agency charged with overseeing drug manufacturing, labeling, advertisement, and safety of medications and biological products. The Best Pharmaceuticals for Children Act (BPCA) (38,39) and the Pediatric Research Equity Act (PREA) (40) govern medication approval for children in the US. While the BPCA encourages drug companies to test their products in children, the PREA necessitates the study of new drugs and biologic DMARDs (bDMARDs) in children if there is a pediatric disease similar to the non-orphan adult disease, and if it is likely that the new agent will be used in children (41).

The FDA gives automatic full waivers from conducting studies in children under the PREA if the pediatric equivalent of the adult disease "rarely or never occurs in pediatrics." This is because studies in children would be highly impractical. ERA is common, comprising 15–20% of JIA cases in the US. Indeed, ERA is at least as common as systemic JIA, for which clinical trials have been successfully completed (42). However, due to the differences in classification criteria outlined above, the FDA has granted automatic full waivers of studies in children for new medications for "axial spondyloarthropathies including ankylosing spondylitis" up until July 2020. Thus, although current JIA treatment guidelines recommend the use of bDMARDs as part of the early treatment for patients with ERA (43), none of the FDA-approved therapies for peripheral SpA or nonradiographic axial SpA (certolizumab pegol [2019], ixekizumab [2020], and secukinumab [2020]) have been studied or are labeled for use in children with ERA.

Recommendations to improve treatment options for children with ERA

Evidence of uncontrolled disease despite a trial of NSAIDs could identify children with ERA who require advanced therapies

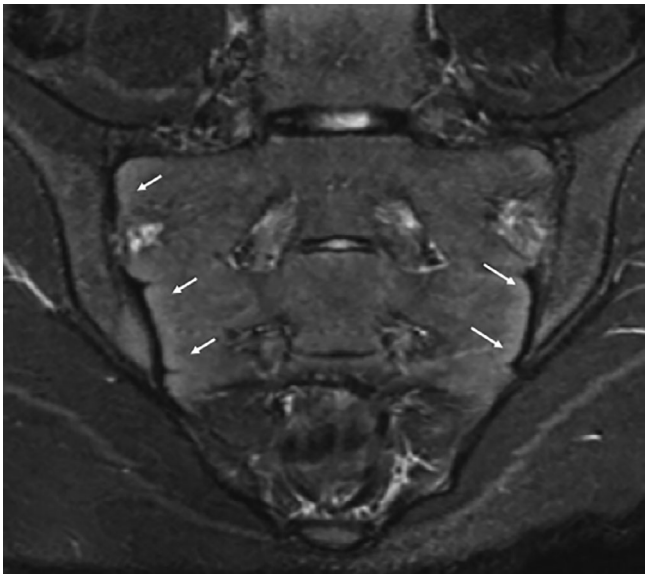

Figure 2. Coronal oblique STIR image of the sacroiliac joints of a 15-year-old female patient, demonstrating metaphyseal-equivalent hyperintense signal (arrows), a normal variant, that could be mistaken for subchondral inflammation by less experienced reviewers.

and may participate in clinical trials, irrespective of the presence of axial or peripheral involvement. Clinical trials in ERA should capture and evaluate response of axial and peripheral disease separately. This may be done via subanalysis of axial and peripheral disease response. Similar to trials of nonradiographic axial SpA (44), eligibility criteria for children with ERA and axial features could include the presence of some of the following disease features: active inflammatory sacroiliitis based on typical MRI changes according to ASA/Outcome Measures in Rheumatology criteria; elevated CRP level; and inadequate response or intolerance to NSAIDs. Because axial disease does not respond to treatment with cDMARDs and ~40% of children are HLA–B27 negative (45), absence of these features should not be exclusionary. Presence of acute uveitis should also not be exclusionary, as this is generally treatable with topical medications. The FDA grants partial waivers for study conduct in certain pediatric age groups. With respect to ERA, a partial waiver for studies of children younger than age 6 years seems sensible as disease onset prior to this age is unusual.

Similar to trials of adults with peripheral SpA (46), active disease in children with ERA and peripheral disease can be defined by a combination of the following: persistence of active arthritis in 1 or more joints, active enthesitis, and/or dactylitis despite NSAID exposure; evidence of systemic inflammation; physician global assessment of disease activity reflective of active disease; and patient global assessment of pain indicating ongoing ERA-related pain. Efficacy could be assessed using clinically meaningful change in validated composite disease activity scores or patient-reported outcomes. Given the challenges of entheseal assessment in children (47) and the lack of a validated pediatric enthesitis index, we caution against the use of enthesitis as a primary outcome.

The FDA encourages extrapolation of effectiveness from adult to pediatric populations when appropriate. With regard to ERA, extrapolation of effectiveness of a medication to control signs and symptoms should assume that an appropriate pediatric dose can be established either through achieving a similar exposure in children as the proven therapeutic exposure in adults, or by using an appropriate pharmacodynamic or clinical end point to achieve the targeted effect (48). Conversely, the ability to extrapolate safety from adults with SpA to children with ERA is limited, and special consideration should be made to utilize trial designs that allow for the assessment of unique pediatric toxicities, including the potential impact of the drug on growth and development (48).

To ensure the most appropriate dosing and confirm anticipated efficacy of a medication to be used in children with ERA, sufficient data need to be available. As is detailed in the Center for Drug Evaluation and Research document (49), the types of studies needed will depend on what is already known about pediatric dosing (pharmacokinetics) and whether there are differences between pediatric and adult pharmacodynamics, and therefore potential differences in efficacy. Study needs will have to be determined on a case-by-case basis. Depending on the available knowledge base, no additional studies may be required, or a randomized double-blinded study might be needed.

In summary, despite FDA-approved treatments for adult axial and peripheral SpA, there remains an unmet need for effective medications for children with spondyloarthropathies. Considering the similarities between adult SpA and ERA in terms of etiology, genetics, pathogenesis, and clinical manifestations (50), it is evident that medications approved for axial or peripheral SpA should be studied in children with ERA involving axial or peripheral joints, respectively, with the intent to achieve labeling for use in children. Considering the current lack of effective therapies for ERA, the FDA should consider requiring pediatric studies for medications that have already been approved for the treatment of adults with SpA. The design of trials in ERA will depend on the amount of prior knowledge about a given drug and could entail full and partial extrapolation strategies in support of achieving an indication for the treatment of ERA.

AUTHOR CONTRIBUTIONS

All authors drafted the article or revised it critically for important intellectual content, and approved the final version to be published.

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