Curr Treat Options in Rheum (2015) 1:350–364
DOI 10.1007/s40674-015-0027-2

Pediatric Rheumatology (A Stevens and S Ringold, Section Editors)

Evaluation and Treatment of Childhood Enthesitis-Related Arthritis

Sabrina Gmuca, MD[1,*]
Pamela F. Weiss, MD, MSCE[1,2]

Address
[*,1]Division of Rheumatology, The Children's Hospital of Philadelphia, 34th and Civic Center Blvd. 4 Wood, St. 4314, Philadelphia, PA, 19104, USA
Email: gmucas@email.chop.edu
[2]Department of Pediatrics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

Published online: 29 September 2015

This article is part of the Topical Collection on *Pediatric Rheumatology*

Keywords Enthesitis-related arthritis · Spondyloarthritis · Sacroiliitis · Juvenile idiopathic arthritis

Opinion statement

Enthesitis-related arthritis (ERA) is phenotypically distinct from the other categories of juvenile idiopathic arthritis (JIA). Therefore, patients with ERA warrant distinct pharmacological treatments tailored to their disease process. The advent of biologic disease-modifying agents (biologics) has revolutionized the treatment of ERA. Biologics are drugs that are genetically engineered from a living organism (such as a virus, gene, or protein) to modify signaling along the inflammatory pathway and thereby modulate the immune system. There has been movement over the last decade to categorize and treat patients with spondyloarthritis on the basis of axial disease since axial involvement warrants treatment with a biologic, in particular, a tumor necrosis factor alpha (TNF-α) blocker. To help identify ERA patients correctly for research purposes, the use of ultrasound with Doppler (USD) and/or whole-body magnetic resonance imaging (MRI) is being increasingly used; their role in clinical practice, however, is still undetermined. We strongly recommend that MRI of the pelvis be performed for any ERA patient in whom axial disease is suspected as its presence may influence the medication regimen, specifically initiation of a biologic. The recent development of a spondyloarthritis (including ERA)-specific disease activity tool called the Juvenile Spondyloarthritis Disease Activity Score (JSpADA) will hopefully allow pediatric rheumatologists to better monitor disease activity over time. Over the last decade, there has been a plethora of research to help advance our understanding of the etiopathogenesis of spondyloarthritis. Future promising treatments for ERA are evidenced by research implicating the role of the IL-12/23 and IL-17 axis in spondyloarthritis. Investigations examining the microbiome will further elucidate the interactions between genetics and the environment that lead to the development of ERA. With more randomized therapeutic trials and more microbiome and genetics-

related research, we will likely see the development of targeted therapies for the treatment of ERA in the near future.

Introduction

Childhood enthesitis-related arthritis (ERA) is a category of juvenile idiopathic arthritis that is characterized by arthritis, enthesitis (inflammation at the sites where tendons and ligaments insert into bone), risk of axial disease, and an underlying genetic predisposition. Under the International League of Associations for Rheumatology (ILAR) juvenile arthritis classification criteria, ERA is one of the three categories that is included under the umbrella term juvenile-onset spondyloarthritis (JSpA). The other two categories of JSpA, according to the ILAR criteria, are psoriatic arthritis (PsA) and undifferentiated arthritis (which includes children who have features of both ERA and PsA) [1]. In order to meet criteria for ERA, children must have arthritis and enthesitis *or* arthritis or enthesitis with at least two of the following: sacroiliac joint tenderness or inflammatory lumbosacral pain, human leukocyte antigen (HLA)-B27 positivity, onset of arthritis in a male patient older than 6 years of age, acute anterior uveitis, or a first degree relative with HLA-B27-associated disease (ankylosing spondylitis (AS), ERA, sacroiliitis with inflammatory bowel disease, reactive arthritis) or acute anterior uveitis. Children cannot be classified as having ERA if they have a personal or family history of psoriasis (first-degree relative), positive testing for IgM rheumatoid factor on at least two occasions 3 months apart, or systemic juvenile idiopathic arthritis (JIA) (Table 1). More recently, there has been an emphasis on categorizing adult patients based on whether or not they have axial disease. However, this is also highly relevant to the pediatric population since we do not know the consequences of untreated axial disease on axial skeleton growth. The Assessment of Spondyloarthritis (SpA) International Society (ASAS) strongly supports a simplified classification for adult disease: (1) peripheral SpA (when spine and sacroiliac joints are spared) and (2) axial SpA (when spine and sacroiliac joints are involved with or without peripheral skeletal involvement) [2–4].

Standard treatment guidelines for ERA are lacking, and the majority of treatment recommendations for ERA are based on studies performed in adult SpA and rheumatoid arthritis or in children with the other categories of JIA [5]. However, the clinical phenotype of ERA differs significantly from both adult-onset SpA and from the other types of JIA. Pediatric patients have more peripheral arthritis and enthesitis and fewer symptoms of spinal involvement at disease onset than adults [6•]. Hip arthritis and tarsal joint arthritis (tarsitis) are more common in ERA than in adult SpA. In comparison to other categories of JIA without a predisposition to enthesitis or axial arthritis, children with ERA tend to have higher disease activity, higher pain intensity, and poorer health outcomes [7]. Children with ERA are also less likely to achieve and to sustain inactive disease than children with one of the other categories of JIA [8, 9]. The development of new disease activity scores such as the Juvenile Arthritis Disease Activity Score (JADAS) and the JSpA Disease Activity Score (JSpADA) will help better assess and address the poorer disease outcomes in children with ERA. Additionally, there is increased use of radiologic studies, specifically ultrasound with Doppler and magnetic resonance imaging, to help detect the presence of enthesitis and/or sacroiliitis in patients with ERA. These modalities will help improve the phenotyping and provision of care to these children.

Diagnosis and disease monitoring

Diagnostic procedures

- Enthesitis and sacroiliitis are challenging to detect on physical examination, and thresholds for diagnosis vary between practitioners.
- The application of ultrasound with Doppler and whole-body magnetic resonance imaging (MRI) to evaluate enthesitis has been studied; their

Table 1. International League of Associations for Rheumatology (ILAR) criteria for enthesitis-related arthritis

Arthritis and enthesitis **OR**
Arthritis or enthesitis with at least two of the following: • 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, ERA, sacroiliitis with IBD, reactive arthritis, or AAU • AAU
Exclusions: • Psoriasis or a history of psoriasis in the patient or a first-degree relative • Presence of IgM RF on at least two occasions at least 3 months apart • Systemic JIA in the patient

HLA human leukocyte antigen, *IBD* inflammatory bowel disease, *AAU* acute anterior uveitis, *RF* rheumatoid factor, *JIA* juvenile idiopathic arthritis

applicability to routine clinical practice remains unclear.

- MRI is becoming increasingly routine in the evaluation of sacroiliitis.
- The standardization of the definition of sacroiliitis based on imaging findings will allow for an objective means of determining whether or not a patient has axial disease and warrants treatment with a tumor necrosis factor alpha (TNF-α) blocker.

Ultrasound with Doppler

Enthesitis in children is typically defined as localized pain, tenderness, or swelling over the entheses. However, physical examination is not perfect as evidenced by studies in adults that have shown that ultrasound can detect enthesitis that was not identified during the physical examination [10, 11]. The most common ultrasound abnormalities seen with enthesitis include increased power Doppler signal, enthesophytes, calcifications, tendon thickening, and hypoechogenicity [12]. In a pediatric study, the positive and negative predictive values of tenderness on standardized physical exam for detection of enthesitis by USD were low [13••]. Additionally, USD is useful in distinguishing enthesitis from other possible noninflammatory causes of pain. Identification of abnormalities at the entheses in children, however, mandates knowledge of the appearance of cartilage and tendons in growing children. Two studies demonstrated that tendon thickness increases with age and that a small degree of cartilage vascularity is normal, especially in younger children [14, 15]. As additional studies are performed to further our understanding of the normal appearance of pediatric cartilage and tendons on USD, we will hopefully be able to more precisely and accurately identify enthesitis using USD as part of routine clinical practice. More research is needed to determine an optimal ultrasound scoring method for enthesitis, the clinical importance of subclinical enthesitis, and the role of USD for monitoring disease activity [5].

An added benefit of USD, especially in the pediatric population, is that it is noninvasive and does not expose the patient to radiation. It is also generally cost-effective and more accessible than MRI.

Magnetic resonance imaging

The gold standard for the diagnosis of juvenile AS is the radiograph (Fig. 1); however, radiographs are not sensitive for the detection of early sacroiliitis. The presence of subchondral or periarticular bone marrow edema (BME) on MRI short-tau inversion recovery (STIR) images of the sacroiliac joints is highly suggestive of active disease (Fig. 2). Associated tendon or ligament thickening, adjacent soft-tissue swelling and edema, synovitis, and joint or bursal fluid are other important findings seen in JSpA [16]. The presence of enthesitis, synovitis, or capsulitis on MRI in the absence of BME is compatible with sacroiliitis but not sufficient for making a diagnosis of active sacroiliitis [17]. Without BME, other differential diagnoses should be considered such as infectious or oncologic processes. A recent study in children demonstrated that administration of gadolinium contrast did not add incremental value to the MRI evaluation of sacroiliitis [18]. Therefore, given the additional risks and costs associated with contrast administration, we do not recommend the use of contrast for routine evaluation of inflammatory sacroiliitis.

In a recent study, 20 % of children with JSpA had sacroiliitis on MRI at disease onset. Of the patients with sacroiliitis, two thirds were asymptomatic and one third would have been missed if evaluated by radiograph alone [19••]. The majority of children with active inflammation also had MRI evidence of chronic damage (sclerosis and/or erosions). HLA-B27 positivity and elevated C-reactive protein levels were more prevalent in those children with active sacroiliitis. These findings suggest that there may be utility in screening JSpA patients for sacroiliitis with MRI at the time of diagnosis, especially those who are HLA-B27 positive and have elevated CRP levels.

Whole-body (WB) MRI has also been used to assess the distribution of disease activity in ERA. One study demonstrated that WB-MRI was superior to

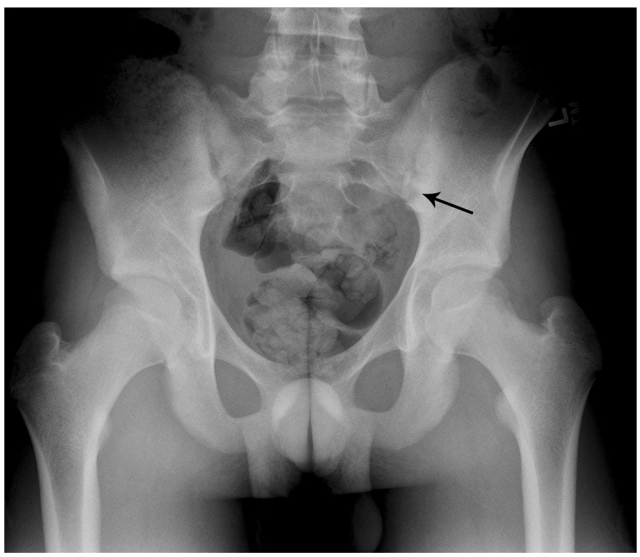

Fig. 1. AP radiograph of the pelvis in a 16-year-old boy with lower back pain demonstrating sclerosis and erosive changes of the iliac side of the left sacroiliac joint (*arrow*) suggestive of sacroiliitis. *Images courtesy of Nancy A. Chauvin, MD, Assistant Professor of Pediatric Radiology, The Children's Hospital of Philadelphia, Philadelphia, PA.*

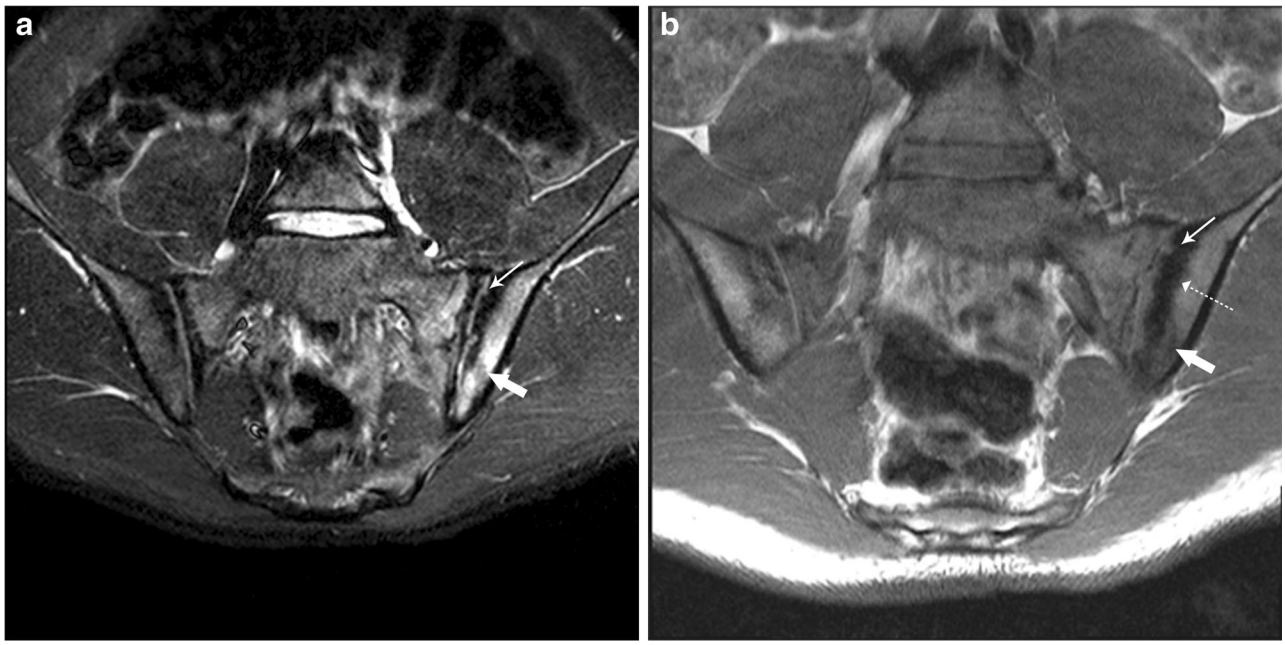

Fig. 2. Coronal MR images of the sacrum. **a** Fluid-sensitive image and **b** T1-weighted image demonstrates bone marrow edema within both aspects of the left sacroiliac joint, most pronounced within the iliac bone (*large arrows*). There are small erosive changes within the articular surface of the left ilium (*small arrows*). Sclerosis is seen along the iliac side of the joint, as demonstrated by low signal intensity, extending more than 5 mm from the articular surface (*dashed arrow*). *Images courtesy of Nancy A. Chauvin, MD, Assistant Professor of Pediatric Radiology, The Children's Hospital of Philadelphia, Philadelphia, PA*.

clinical exam for the detection of hip, sacroiliac, and spinal arthritis in JSpA [20]. Another study demonstrated poor agreement between clinical exam and WB-MRI for the detection of enthesitis in patients with JSpA [21]. Therefore, WB-MRI may play an important role in conjunction with clinical exam and radiography as an objective tool for assessing disease activity in children with JSpA, especially in the setting of a clinical trial [16]. Further research is still needed to evaluate the clinical scenarios in which WB-MRI might be more useful than dedicated MRI in JSpA.

MRI, especially considering sedation costs in younger children, is expensive. The ability to detect and treat early sacroiliitis, however, may be cost-effective in the long term and may prevent or diminish the consequences of axial damage in the growing child.

Measurements of disease activity

- Children with ERA have been reported to have higher disease activity and poorer prognosis than other categories of JIA; therefore, disease activity measures that address symptoms specific to ERA are important in monitoring these patients.
- The Juvenile Arthritis Disease Activity Scores (JADAS) and the JSpA Disease Activity Score (JSpADA) are two useful disease activity assessment tools, the latter of which is more specific to ERA.

Juvenile Arthritis Disease Activity Scores

The JADAS is a composite score consisting of four elements: the physician assessment of disease activity, parent/patient global assessment of well-being, erythrocyte sedimentation rate (ESR), and active joint count (in 10, 27, or 71 joints) [22]. The validation study for the JADAS included children with ERA, but they were a minority (<1 % of subjects). Cutoff values for defining remission, minimal disease, and acceptable symptom state with the JADAS have been validated [23]. A three-item JADAS without the sedimentation rate (JADAS3) correlated well with the original JADAS [24], suggesting that the simplified tool is sufficient for robust assessment of JIA disease activity if laboratory tests are unavailable [25]. Another version of the JADAS (JADAS-CRP), using the CRP in lieu of the ESR, was also found to be clinically effective in monitoring disease activity and correlated closely with the JADAS based on ESR [26, 27].

Juvenile Spondyloarthritis Disease Activity Score

The JSpADA is the first disease activity assessment tool developed and validated for use in JSpA (which includes ERA) [28]. It is a continuous disease activity score that was retrospectively validated in a multicenter cohort of children. This index includes eight equally weighted items: (1) active joint count, (2) tender entheses count, (3) clinical sacroiliitis, (4) morning stiffness, (5) patient assessment of pain, (6) uveitis, (7) back mobility, and (8) inflammatory markers. All items are transformed to values of 0, 0.5, or 1, and the total score ranges from 0 to 8. The JSpADA specifically includes measures of axial symptoms and enthesitis, which have been shown to independently predict poorer outcomes in JSpA [29]. The strengths of this tool include the limited number of items, inclusion of disease features specific to ERA, and the feasibility of assessing all of the items during the limited time of a routine clinic visit. This disease activity tool needs to be validated in a prospective sample, and cutoff values defining remission and minimal disease activity should be determined.

Role of the microbiome and considerations for diet modification

- The close relationship between inflammatory bowel disease and SpA has highlighted the role of the gut microbiome in the etiopathogenesis of SpA.
- A better understanding of the link between microbial dysbiosis and SpA may lead to the development of novel therapeutic approaches for the treatment of ERA [30].

Gut microbiome and starch

Approximately two thirds of adults with SpA have inflammatory intestinal changes similar to those detected in inflammatory bowel disease [31]. Similar prevalence of intestinal inflammation was reported in a pediatric study [32]. The true prevalence of inflammatory bowel disease in JSpA has yet to be determined, but it is likely very common as evidenced by research demonstrating subclinical IBD in JSpA [33]. The gut microbiome is the microbial community that resides in the intestines. Gut inflammation is thought to either cause or be a product of permeability of the epithelial lining of the gut, leading

to loss of mucosal tolerance. Some hypothesize that HLA-B27 leads to mucosal immunodeficiency secondary to effects on intestinal permeability or alterations in the gut microbiome such as a loss of protective bacterial species [34]. Stoll et al. demonstrated that in comparison to controls, ERA patients had decreased levels of *Faecalibacterium prausnitzii* in their stool [35••]. This bacterium is known to have anti-inflammatory effects, and decreased levels have been demonstrated in the stool of patients with inflammatory bowel disease [36]. On the other hand, the presence of *Klebsiella pneumoniae* is suspected to be a causative agent in the development of SpA [37]. *Klebsiella* growth in the colon appears to be dependent on starch [37]; therefore, one might hypothesize a role for decreased starch consumption. However, there are no studies to date regarding diet modification in ERA. Whether it be through diet or new targeted therapies, there is future promise that recalibration of the gut microbiome may have a beneficial impact on ERA.

Treatment

Currently, most pediatric rheumatologists determine a child's treatment regimen based on the number of affected joints and the presence of axial disease. The 2011 American College of Rheumatology (ACR) recommendations [38] do not consider the treatment of children with ERA separate from those children with other categories of JIA. According to these recommendations, an initial trial of nonsteroidal anti-inflammatory drugs (NSAIDs), with or without intraarticular corticosteroid injection(s), is recommended in patients with four or fewer affected joints [38], particularly those with predominant enthesitis. For patients with five or more active joints, the initiation of methotrexate or other traditional disease-modifying anti-rheumatic drugs (DMARDS) such as sulfasalazine is recommended. For patients with sacroiliitis, treatment with TNF-α blockade is the first-line treatment and has also been found to be of benefit in the treatment of refractory enthesitis [8, 39–43]. More recently, there have been new emerging treatments for SpA including medications that target the IL-12/23 and IL-17 axis (ustekinumab and secukinumab, respectively) as well as phosphodiesterase 4 (PDE4) inhibitors (apremilast). Therefore, clinical trials are warranted to establish the efficacy of these new treatments in the treatment of ERA. Lastly, as our understanding of the role of the microbiome becomes better elucidated, there may prove to be some utility in dietary modifications or gastrointestinal-targeted treatments in the near future.

Pharmacologic treatment

- The goal of therapy with pharmacologic agents for ERA is to alleviate pain and decrease inflammation at the entheses and the synovial lining to preserve joint function and improve mobility.

Nonsteroidal anti-inflammatory drugs

NSAIDs are effective for the short-term, more immediate relief of pain in ERA and are commonly used for such purpose. NSAIDs are particularly effective for those children with predominantly enthesitis. NSAIDs typically do not suffice

as monotherapy for the treatment of active arthritis. Some studies in adult SpA have suggested that continuous use of an NSAID not only improves symptoms but also reduces the radiographic appearance of axial inflammatory lesions and may slow spinal radiographic progression, but this remains to be demonstrated in ERA [44, 45]. A recent study in adults, however, suggested that outcomes were similar for adults with AS who received scheduled versus on demand diclofenac [46]. These medications are generally inexpensive. Commonly used NSAIDs include piroxicam, diclofenac, and meloxicam. NSAIDs are contraindicated in patients with inflammatory bowel disease, glucose-6-phosphate dehydrogenase (G6PD) deficiency, or gastrointestinal ulcers. They should be taken with food to prevent gastritis, as gastrointestinal upset is one of their main side effects. Toxicity monitoring should include a complete blood count (CBC), creatinine measurement, liver function test (LFT), and urinalysis 4–6 weeks after initiation of treatment and then every 6–12 months thereafter.

Oral corticosteroids and intraarticular corticosteroids

Oral corticosteroids (CS) were previously used more frequently for the treatment of ERA but are no longer acceptable as monotherapy for persistent, active arthritis. Oral CS can be effective in ameliorating the symptoms of an acute flare and quickly restoring mobility. They are relatively inexpensive. However, there are significant risks of oral CS use. In the immediate period, patients may experience hyperactivity, insomnia, or transient hypertension. These aforementioned symptoms, along with diabetes, glaucoma, weight gain, increased appetite, and mood changes, are potential reversible side effects from oral CS. Pediatric-specific long-term side effects include delayed puberty and short stature. There are also some significant potential irreversible side effects including cataracts, striae, osteopenia, and avascular necrosis. Included in this category of treatments are intraarticular corticosteroids (IACS), which involves injection of triamcinolone hexacetonide, or triamcinolone acetonide directly into the joint space. Triamcinolone hexacetonide is no longer commercially available. Localized injections may spare the child from exposure to systemic medication. The cost of the intervention is dependent on whether the child requires sedation services, which is typically age-dependent. If sedation is not needed, the procedure can be easily performed in the physician's office. The beneficial effects of an IACS injection are rapid (within days). The associated risks include infection, atrophy, hypopigmentation, chemical irritation, and calcium deposits. Especially for patients who present with oligoarticular (≤4 joints) arthritis, initiation of treatment with an IACS is strongly recommended, especially before the initiation of a DMARD.

Disease-modifying anti-rheumatic drugs

Methotrexate

Methotrexate (MTX) is the most commonly used DMARD for JIA, but there are no studies to support its use specifically in the ERA population. In randomized controlled trials of MTX in the other categories of JIA, MTX has shown significant improvement in joint count, patient/physician global assessment, and erythrocyte sedimentation rate (ESR) [47–49]. Unfortunately, MTX (and DMARDS, in general) has not been proven to be effective for axial disease or

enthesopathy [50, 51]. Therefore, MTX is recommended for ERA patients who demonstrate peripheral arthritis without axial involvement. The optimal dose and route of administration, despite MTX's common use, is still uncertain, and dosing varies among practitioners. Most physicians typically initiate treatment as a single weekly dose of 10 mg/m^2 and titrate as needed up to 30 mg/m^2 weekly. The route of administration of MTX is not standardized. Evidence suggests that bioavailability with oral dosing often does not increase significantly beyond 20 mg/m^2 per week [52]. Our practice is to start patients on subcutaneous MTX to gain initial control of arthritis as subcutaneous MTX has better bioavailability and fewer side effects and may improve patient compliance [53]. Once remission is maintained, we wean the dose and transition to oral MTX as tolerated. Patients are advised to take folic acid 0.4–1 mg/day to help ameliorate the gastrointestinal side effects of MTX including nausea and vomiting. Additional side effects include hair thinning, oral ulcers, headaches, hepatitis, cytopenias, and pneumonitis. Medication toxicity monitoring should include a CBC, aspartate aminotransferase (AST)/alanine transaminase (ALT), and creatinine drawn 4 weeks after the initiation of treatment and, if normal, every 3 months thereafter. The cost of the medication ranges from inexpensive to moderate.

Sulfasalazine

Sulfasalazine (SSZ) is another DMARD that may be beneficial in the treatment of ERA [54, 55]. In a phase II, exploratory, 26-week prospective, randomized, double-blind, placebo-controlled trial of SSZ in active JSpA, SSZ improved both doctor and patient assessments compared to placebo [54]. This study was limited by its small number of patients but suggests that SSZ may be useful in JSpA. The usual dose is 30–50 mg/kg/day, and it is titrated over the course of several weeks. Patients are expected to demonstrate clinical improvement 6–8 weeks after initiation of treatment. Potential side effects include gastrointestinal issues, cytopenias, hypogammaglobulinemia, hepatotoxicity, and Stevens-Johnson syndrome. Toxicity monitoring labs include CBC, AST/ALT, and creatinine performed 4–6 weeks after starting treatment and every 3–4 months thereafter.

Anti-tumor necrosis alpha blockers

Infliximab, etanercept, and adalimumab

The class of biologic agents that block TNF-α is useful in the treatment of enthesitis and peripheral and axial arthritis in adults. Additionally, TNF-α blockers have demonstrated efficacy for arthritis and enthesitis as well as symptomatic treatment of axial disease in JSpA [8, 39–43]. Therefore, they are considered first-line treatment for ERA patients with axial disease but should also be considered for those with enthesitis or arthritis that is refractory to NSAIDs and/or DMARDs. Studies in adults suggest that early inflammatory lesions in AS resolve following anti-TNF-α therapy and that treatment slows the development of new syndesmophytes [56]. Delay in initiation of TNF-α blockers is also associated with increased odds of structural progression in adults [57]. Given the potential detrimental consequences of untreated axial involvement in growing, developing children, the use of TNF-α blockers in

patients with axial disease is likely cost-effective despite the expense of these medications.

The three recommended TNF-α blockers are etanercept, adalimumab, and infliximab. The typical etanercept dose is 0.8 mg/kg/week subcutaneously (maximum 50 mg). The standard adalimumab dose is 40 mg subcutaneously every other week in patients weighing at least 30 kg. Recently, a phase III, multicenter, randomized, double-blind, placebo-controlled study of adalimumab was performed in pediatric patients with ERA [58••]. Mean percent change from baseline in active joint count at week 12 was greater in the adalimumab group versus placebo (−62.6 versus −11.6 %, p=0.039). Additionally, improvement in the signs and symptoms of ERA was sustained with continued adalimumab therapy through week 52. The results of this study suggest that adalimumab is efficacious and safe for the treatment of patients with active ERA who have failed conventional treatments. The intravenously administered TNF-α blocker, infliximab, is dosed at 5–10 mg/kg/dose, administered at 0, 2 weeks, and then every 4–8 weeks. Infliximab is currently not FDA-approved for JIA. The potential risks and side effects of these medications include infection, cytopenias, hypersensitivity reactions, injection site reactions, psoriasis, demyelination, and malignancy. Given the risk of activation of latent tuberculosis with these medications, tuberculosis screening should be done prior to starting treatment. This can be done with either a tuberculin skin test or interferon-gamma release assays (IGRAs), the latter of which is approved for use in children 5 years of age or older. Patients should have a CBC and CMP checked 4–6 weeks after initiation of treatment and then every 6 months. We strongly support the concomitant use of MTX with infliximab to help prevent the development of human anti-chimeric antibodies (HACAs) and preserve the efficacy of this medication.

Other biologic agents

The potential use of other biologic agents, including rituximab (B cell-depleting therapy) and abatacept (T cell co-stimulation inhibitor), has been examined in small open-label studies in adults with AS [59, 60]. Rituximab was not effective in patients who had prior exposure to TNF-α blockers but was modestly effective in TNF-naïve patients. Neither rituximab nor abatacept, however, was effective as first-line therapy in adults, and neither has been studied in pediatric ERA. Lastly, there have been two randomized placebo-controlled studies examining the use of tocilizumab (IL-6 blocker) in AS that failed to show efficacy [61].

Emerging therapies

- Recently, the role of the IL-12/23 and IL-17 axis in the pathogenesis of SpA and drugs that target this axis are being studied.
- Drugs used for the treatment of psoriasis, including apremilast (PDE4 inhibitor), seem to be promising for the treatment of SpA [62, 63].

Ustekinumab

Ustekinumab is an anti-IL-12/23 human monoclonal antibody. In a prospective, open-label, proof-of-concept clinical trial, it effectively reduced the signs

and symptoms of active AS in 20 patients, including serum C-reactive protein level and active inflammation on magnetic resonance imaging (MRI) [64••]. In this study, patients were treated with 90 mg subcutaneously at baseline, week 4, and then every 4 weeks. This medication is expensive, and additional studies regarding its efficacy in pediatric ERA are warranted. It may, however, be considered for patients who fail the aforementioned treatments. Adverse effects include infections, nausea, injection site reactions, and allergic reactions.

Secukinumab

Secukinumab is an anti-IL-17A antibody that had favorable results in a proof-of-concept trial in AS, including the open-label extension phase up to 24 months [65, 66]. Available dosing recommendations are based on its use in PsA in adults: initially, 300 mg SQ once weekly for five doses and then once every 4 weeks. Similarly to ustekinumab, further investigative studies are warranted to determine appropriate dosing for use in children with ERA. The cost and side effects not only are also similar to ustekinumab but also include upper respiratory tract involvement such as cough and pharyngitis.

Apremilast

Apremilast is an orally available, small-molecule PDE4 inhibitor, which blocks the upstream activation of cytokines important in the pathogenesis of AS. In a double-blind, placebo-controlled, single-center, phase II study, patients with symptomatic AS with active axial disease on MRI were randomized to apremilast 30 mg orally twice daily or placebo over 12 weeks [62]. Apremilast was associated with a greater improvement from baseline for all clinical assessments compared with placebo but did not achieve statistical significance. Nonetheless, this study suggests future applicability of apremilast in the treatment of axial inflammation in ERA.

Conclusions

- The diagnosis and accurate phenotyping of ERA can be facilitated by the use of imaging modalities such as USD, conventional MRI, and WB MRI.
- Newly developed disease activity measures, including the JADAS and JSpADA, will allow physicians to better monitor ERA patients over time.
- Further research into the role of the microbiome in the development of SpA will hopefully provide new and targeted therapies for ERA.
- TNF-α blockers are first-line treatment for children with axial disease.
- New potential treatment regimens include medications used for adult psoriasis and AS patients. These include ustekinumab, secukinumab, and apremilast.

Acknowledgments

The radiologic images referenced in this article were provided courtesy of Nancy A. Chauvin, MD, Assistant Professor of Pediatric Radiology, The Children's Hospital of Philadelphia, Philadelphia, PA.

Compliance with Ethics Guidelines

Conflict of Interest

Dr. Weiss' work is supported by the National Institute of Arthritis and Musculoskeletal and Skin Disease grant 1-K23-AR059749-01A as well at a 1R03 AR062665-01 grant. Dr. Gmuca is supported by the National Institute of Health Rheumatology Research Training Grant T32-AR007442-28.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Petty RE, Southwood TR, Manners P, Baum J, Glass DN, Goldenberg J, et al. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. J Rheumatol. 2004;31:390–2.
2. Palazzi C, D'Angelo S, Gilio M, Leccese P, Padula A, Olivieri I. Pharmacological therapy of spondyloarthritis. Expert Opin Pharmacother. 2015;16:1495–504.
3. Rudwaleit M, van der Heijde D, Landewe R, Akkoc N, Brandt J, Chou CT, 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.
4. Rudwaleit M, van der Heijde D, Landewe R, Listing J, Akkoc N, Brandt J, 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;68:777–83.
5. Gmuca S, Weiss PF. Juvenile spondyloarthritis. Curr Opin Rheumatol. 2015;27:364–72.
6.• Tse S, Burgos-Vargas R, Colbert RA. Juvenile spondyloarthritis treatment recommendations. Am J Med Sci. 2012;343:367–70.

This article provides a summary of current treatment recommendations for juvenile spondyloarthritis.

7. Weiss PF, Beukelman T, Schanberg LE, Kimura Y, Colbert RA. Enthesitis-related arthritis is associated with higher pain intensity and poorer health status in comparison to other categories of juvenile idiopathic arthritis: cross-sectional analysis of the Childhood Arthritis and Rheumatology Research Alliance (CARRA) Registry. J Rheumatol. 2012;39:2341–51.
8. Otten MH, Prince FH, Twilt M, Ten Cate R, Armbrust W, Hoppenreijs EP, et al. Tumor necrosis factor-blocking agents for children with enthesitis-related arthritis—data from the Dutch arthritis and biologicals in children register, 1999-2010. J Rheumatol. 2011;38:2258–63.
9. Donnithorne KJ, Cron RQ, Beukelman T. Attainment of inactive disease status following initiation of TNF-alpha inhibitor therapy for juvenile idiopathic arthritis: enthesitis-related arthritis predicts persistent active disease. J Rheumatol. 2011;38:2675–81.
10. D'Agostino MA, Said-Nahal R, Hacquard-Bouder C, Brasseur JL, Dougados M, Breban M. Assessment of peripheral enthesitis in the spondylarthropathies by ultrasonography combined with power Doppler: a cross-sectional study. Arthritis Rheum. 2003;48:523–33.
11. Jousse-Joulin S, Breton S, Cangemi C, Fenoll B, Bressolette L, de Parscau L, et al. Ultrasonography for detecting enthesitis in juvenile idiopathic arthritis. Arthritis Care Res. 2011;63:849–55.

12. Spadaro A, Iagnocco A, Perrotta FM, Modesti M, Scarno A, Valesini G. Clinical and ultrasonography assessment of peripheral enthesitis in ankylosing spondylitis. Rheumatology (Oxford). 2011;50:2080–6.
13.•• Weiss PF, Chauvin NA, Klink AJ, Localio R, Feudtner C, Jaramillo D, et al. Detection of enthesitis in children with enthesitis-related arthritis: dolorimetry compared to ultrasonography. Arthritis Rheumatol. 2014;66:218–27.
This article establishes that ultrasonography is superior to dolorimetry for the detection of enthesitis.
14. Chauvin NA, Ho-Fung V, Jaramillo D, Edgar JC, Weiss PF. Ultrasound of the joints and entheses in healthy children. Pediatr Radiol. 2015.
15. Jousse-Joulin S, Cangemi C, Gerard S, Gestin S, Bressollette L, de Parscau L, et al. Normal sonoanatomy of the paediatric entheses including echostructure and vascularisation changes during growth. Eur Radiol. 2015;25:2143–52.
16. Aquino MR, Tse SM, Gupta S, Rachlis AC, Stimec J. Whole-body MRI of juvenile spondyloarthritis: protocols and pictorial review of characteristic patterns. Pediatr Radiol. 2015;45:754–62.
17. Sieper J, Rudwaleit M, Baraliakos X, Brandt J, Braun J, Burgos-Vargas R, et al. The Assessment of SpondyloArthritis international Society (ASAS) handbook: a guide to assess spondyloarthritis. Ann Rheum Dis. 2009;68(2):ii1–44.
18. Weiss PF, Xiao R, Biko DM, Johnson AM, Chauvin NA. Detection of inflammatory sacroiliitis in children with magnetic resonance imaging: is gadolinium contrast enhancement necessary? Arthritis Rheumatol. 2015;67:2250–6.
19.•• Weiss PF, Xiao R, Biko DM, Chauvin NA. Sacroiliitis at diagnosis of juvenile spondyloarthritis assessed by radiography, magnetic resonance imaging, and clinical examination. Arthritis Care Res (Hoboken). 2015.
This article highlights the useful of MRI at the time of diagnosis to help detect sacroiliitis.
20. Rachilis ACBP, Lobo-Mueller E, et al. Whole body magnetic resonance imaging in juvenile spondyloarthritis: will it provide vital information compared to clinical exam alone? Arthritis Rheum. 2011;63:749.
21. Srinivasalu H, Hill SC, Montealegre Sanchez G, et al. Whole body magnetic resonance imaging in evaluation of enthesitis in spondyloarthropathy. Arthritis Rheum. 2012;64:S848.
22. Consolaro A, Ruperto N, Bazso A, Pistorio A, Magni-Manzoni S, Filocamo G, et al. Development and validation of a composite disease activity score for juvenile idiopathic arthritis. Arthritis Rheum. 2009;61:658–66.
23. Consolaro A, Bracciolini G, Ruperto N, Pistorio A, Magni-Manzoni S, Malattia C, et al. Remission, minimal disease activity, and acceptable symptom state in juvenile idiopathic arthritis: defining criteria based on the juvenile arthritis disease activity score. Arthritis Rheum. 2012;64:2366–74.
24. McErlane F, Beresford MW, Baildam EM, Chieng SE, Davidson JE, Foster HE, et al. Validity of a three-variable Juvenile Arthritis Disease Activity Score in children with new-onset juvenile idiopathic arthritis. Ann Rheum Dis. 2013;72:1983–8.
25. Webb K, Wedderburn LR. Advances in the treatment of polyarticular juvenile idiopathic arthritis. Curr Opin Rheumatol. 2015.
26. Mourao AF, Santos MJ, Melo-Gomes J, Martins FM, Costa JA, Ramos F, et al. Using the Juvenile Arthritis Disease Activity Score based on erythrocyte sedimentation rate or C-reactive protein level: results from the Portuguese register. Arthritis Care Res (Hoboken). 2014;66:585–91.
27. Nordal EB, Zak M, Aalto K, Berntson L, Fasth A, Herlin T, et al. Validity and predictive ability of the juvenile arthritis disease activity score based on CRP versus ESR in a Nordic population-based setting. Ann Rheum Dis. 2012;71:1122–7.
28. Weiss PF, Colbert RA, Xiao R, Feudtner C, Beukelman T, DeWitt EM, et al. Development and retrospective validation of the juvenile spondyloarthritis disease activity index. Arthritis Care Res (Hoboken). 2014;66:1775–82.
29. Weiss PF, Beukelman T, Schanberg LE, Kimura Y, Colbert RA, Investigators CR. Enthesitis-related arthritis is associated with higher pain intensity and poorer health status in comparison with other categories of juvenile idiopathic arthritis: the Childhood Arthritis and Rheumatology Research Alliance Registry. J Rheumatol. 2012;39:2341–51.
30. Gill T, Asquith M, Rosenbaum JT, Colbert RA. The intestinal microbiome in spondyloarthritis. Curr Opin Rheumatol. 2015;27:319–25.
31. Mielants H, Veys EM, Goemaere S, Goethals K, Cuvelier C, De Vos M. Gut inflammation in the spondyloarthropathies: clinical, radiologic, biologic and genetic features in relation to the type of histology. A prospective study. J Rheumatol. 1991;18:1542–51.
32. Mielants H, Veys EM, Cuvelier C, De Vos M, Goemaere S, Maertens M, et al. Gut inflammation in children with late onset pauciarticular juvenile chronic arthritis and evolution to adult spondyloarthropathy—a prospective study. J Rheumatol. 1993;20:1567–72.
33. Stoll ML, Patel AS, Punaro M, Dempsey-Robertson M. MR enterography to evaluate sub-clinical intestinal inflammation in children with spondyloarthritis. Pediatr Rheumatol Online J. 2012;10:6.
34. Rosenbaum JT, Lin P, Asquith M, Costello ME, Kenna TJ, Brown MA. Does the microbiome play a causal role in spondyloarthritis? Clin Rheumatol. 2014;33:763–7.
35.•• Stoll ML, Kumar R, Morrow CD, Lefkowitz EJ, Cui X, Genin A, et al. Altered microbiota associated with abnormal humoral immune responses to commensal organisms in enthesitis-related arthritis. Arthritis Res Ther. 2014;16:486.
This article reviews the role of the microbiome in ERA.
36. Cao Y, Shen J, Ran ZH. Association between Faecalibacterium prausnitzii reduction and

inflammatory bowel disease: a meta-analysis and systematic review of the literature. Gastroenterol Res Pract. 2014;2014:872725.

37. Rashid T, Wilson C, Ebringer A. The link between ankylosing spondylitis, Crohn's disease, Klebsiella, and starch consumption. Clin Dev Immunol. 2013;2013:872632.
38. Beukelman T, Patkar NM, Saag KG, Tolleson-Rinehart S, Cron RQ, DeWitt EM, et al. American College of Rheumatology recommendations for the treatment of juvenile idiopathic arthritis: initiation and safety monitoring of therapeutic agents for the treatment of arthritis and systemic features. Arthritis Care Res (Hoboken). 2011;2011(63):465–82.
39. Tse SM, Burgos-Vargas R, Laxer RM. Anti-tumor necrosis factor alpha blockade in the treatment of juvenile spondylarthropathy. Arthritis Rheum. 2005;52:2103–8.
40.•• Hugle B, Burgos-Vargas R, Inman RD, O'Shea F, Laxer RM, Stimec J, et al. Long-term outcome of anti-tumor necrosis factor alpha blockade in the treatment of juvenile spondyloarthritis. Clin Exp Rheumatol. 2014;32:424–31.

This article provides evidence for the use of anti-tumor necrosis factor alpha blockade in ERA.

41. Burgos-Vargas RC-VJ, Gutierrez-Suarez R. Efficacy, safety, and tolerability of infliximab in juvenile-onset spondyloarthropathies (JO-SpA): results of a three-month, randomized, double-blind, placebo-controlled trial phase. Arthritis Rheum. 2007;56:S319.
42. Henrickson M, Reiff A. Prolonged efficacy of etanercept in refractory enthesitis-related arthritis. J Rheumatol. 2004;31:2055–61.
43. Otten MH, Prince FH, Armbrust W, ten Cate R, Hoppenreijs EP, Twilt M, et al. Factors associated with treatment response to etanercept in juvenile idiopathic arthritis. JAMA. 2011;306:2340–7.
44. Jarrett SJ, Sivera F, Cawkwell LS, Marzo-Ortega H, McGonagle D, Hensor E, et al. MRI and clinical findings in patients with ankylosing spondylitis eligible for anti-tumour necrosis factor therapy after a short course of etoricoxib. Ann Rheum Dis. 2009;68:1466–9.
45. Wanders A, Heijde D, Landewe R, Behier JM, Calin A, Olivieri I, et al. Nonsteroidal antiinflammatory drugs reduce radiographic progression in patients with ankylosing spondylitis: a randomized clinical trial. Arthritis Rheum. 2005;52:1756–65.
46. Sieper J, Listing J, Poddubnyy D, Song IH, Hermann KG, Callhoff J, Syrbe U, Braun J, Rudwaleit M. Effect of continuous versus on-demand treatment of ankylosing spondylitis with diclofenac over 2 years on radiographic progression of the spine: results from a randomised multicentre trial (ENRADAS). Ann Rheum Dis. 2015.
47. Ruperto N, Murray KJ, Gerloni V, Wulffraat N, de Oliveira SK, Falcini F, et al. A randomized trial of parenteral methotrexate comparing an intermediate dose with a higher dose in children with juvenile idiopathic arthritis who failed to respond to standard doses of methotrexate. Arthritis Rheum. 2004;50:2191–201.
48. Giannini EH, Brewer EJ, Kuzmina N, Shaikov A, Maximov A, Vorontsov I, et al. Methotrexate in resistant juvenile rheumatoid arthritis. Results of the U.S.A.-U.S.S.R. Double-blind, placebo-controlled trial. The Pediatric Rheumatology Collaborative Study Group and The Cooperative Children's Study Group. N Engl J Med. 1992;326:1043–9.
49. Woo P, Southwood TR, Prieur AM, Dore CJ, Grainger J, David J, et al. Randomized, placebo-controlled, crossover trial of low-dose oral methotrexate in children with extended oligoarticular or systemic arthritis. Arthritis Rheum. 2000;43:1849–57.
50. Poddubnyy D. Axial spondyloarthritis: is there a treatment of choice? Ther Adv Musculoskelet Dis. 2013;5:45–54.
51. Haibel H, Brandt HC, Song IH, Brandt A, Listing J, Rudwaleit M, et al. No efficacy of subcutaneous methotrexate in active ankylosing spondylitis: a 16-week open-label trial. Ann Rheum Dis. 2007;66:419–21.
52. Balis FM, Mirro Jr J, Reaman GH, Evans WE, McCully C, Doherty KM, et al. Pharmacokinetics of subcutaneous methotrexate. J Clin Oncol. 1988;6:1882–6.
53. Alsufyani K, Ortiz-Alvarez O, Cabral DA, Tucker LB, Petty RE, Malleson PN. The role of subcutaneous administration of methotrexate in children with juvenile idiopathic arthritis who have failed oral methotrexate. J Rheumatol. 2004;31:179–82.
54. Burgos-Vargas R, Vazquez-Mellado J, Pacheco-Tena C, Hernandez-Garduno A, Goycochea-Robles MV. A 26 week randomised, double blind, placebo controlled exploratory study of sulfasalazine in juvenile onset spondyloarthropathies. Ann Rheum Dis. 2002;61:941–2.
55. van Rossum MA, Fiselier TJ, Franssen MJ, Zwinderman AH, ten Cate R, van Suijlekom-Smit LW, et al. Sulfasalazine in the treatment of juvenile chronic arthritis: a randomized, double-blind, placebo-controlled, multicenter study. Dutch Juvenile Chronic Arthritis Study Group. Arthritis Rheum. 1998;41:808–16.
56. Maksymowych WP, Morency N, Conner-Spady B, Lambert RG. Suppression of inflammation and effects on new bone formation in ankylosing spondylitis: evidence for a window of opportunity in disease modification. Ann Rheum Dis. 2013;72:23–8.
57. Haroon N, Inman RD, Learch TJ, Weisman MH, Lee M, Rahbar MH, et al. The impact of tumor necrosis factor alpha inhibitors on radiographic progression in ankylosing spondylitis. Arthritis Rheum. 2013;65:2645–54.
58.•• Burgos-Vargas R, Tse SML, Horneff G, Pangan AL, Kalabic J, Goss S, Unnebrink K, Anderson JK. A randomized, double-blind, placebo-controlled, multicenter study of adalimumab in pediatric patients with enthesitis-related arthritis. Arthritis Care Res. 2015:n/a-n/a.

This is a randomized controlled trial supporting the use of adalimumab in the treatment of ERA.

59. Song IH, Heldmann F, Rudwaleit M, Haibel H, Weiss A, Braun J, et al. Treatment of active ankylosing

spondylitis with abatacept: an open-label, 24-week pilot study. Ann Rheum Dis. 2011;70:1108–10.
60. Song IH, Heldmann F, Rudwaleit M, Listing J, Appel H, Braun J, et al. Different response to rituximab in tumor necrosis factor blocker-naive patients with active ankylosing spondylitis and in patients in whom tumor necrosis factor blockers have failed: a twenty-four-week clinical trial. Arthritis Rheum. 2010;62:1290–7.
61. Sieper J, Porter-Brown B, Thompson L, Harari O, Dougados M. Assessment of short-term symptomatic efficacy of tocilizumab in ankylosing spondylitis: results of randomised, placebo-controlled trials. Ann Rheum Dis. 2014;73:95–100.
62. Pathan E, Abraham S, Van Rossen E, Withrington R, Keat A, Charles PJ, et al. Efficacy and safety of apremilast, an oral phosphodiesterase 4 inhibitor, in ankylosing spondylitis. Ann Rheum Dis. 2013;72:1475–80.
63. Braun J, Kiltz U, Heldmann F, Baraliakos X. Emerging drugs for the treatment of axial and peripheral spondyloarthritis. Expert Opin Emerg Drugs. 2015;20:1–14.
64.•• Poddubnyy D, Hermann KG, Callhoff J, Listing J, Sieper J. Ustekinumab for the treatment of patients with active ankylosing spondylitis: results of a 28-week, prospective, open-label, proof-of-concept study (TOPAS). Ann Rheum Dis. 2014;73:817–23.
This article provides evidence for the efficacy of ustekinumab in ankylosing spondylitis.
65. Baeten D, Baraliakos X, Braun J, Sieper J, Emery P, van der Heijde D, et al. Anti-interleukin-17A monoclonal antibody secukinumab in treatment of ankylosing spondylitis: a randomised, double-blind, placebo-controlled trial. Lancet. 2013;382:1705–13.
66. Baraliakos XBJ, Laurent DD, et al. Long term inhibition of interleukin (IL)-17A with secukinumab improves clinical symptoms and reduces spinal inflammation as assessed by magnetic resonance imaging in patients with ankylosing spondylitis. Arthritis Rheum. 2012;64:S574.