



Enthesitis-related Arthritis

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Enthesitis-related arthritis (ERA) is a disease predominantly affecting the joints and entheses of the lower extremities and has the potential to eventually affect the sacroiliac joints and spine evolving to juvenile ankylosing spondylitis. ERA is also characterized by rheumatoid factor seronegativity, paucity of antinuclear antibody, and a strong association with the human leukocyte antigen-B27. ERA accounts for a higher proportion of juvenile idiopathic arthritis (JIA) cases in the Asian population compared to other populations. Advances in the understanding of ERA pathogenesis continue to progress and have led to the development of new treatments targeting pro-inflammatory cytokines. In particular, tumor necrosis factor- α inhibitors have become a mainstay of therapy for patients in whom therapy with anti-inflammatory drugs and/or disease-modifying anti-rheumatic drugs are inadequate or contraindicated. Compared to other JIA subtypes, ERA is associated with a poorer quality of life, worse function, and a higher likelihood of ongoing active disease after the initial treatment. Because the current guidelines for the management of ERA is not considered separately from other categories of JIA, there is a need for treatment guidelines specific to ERA to improve the overall disease outcomes. (**J Rheum Dis 2018;25:221-230**)

Key Words. Juvenile arthritis, Enthesitis-related arthritis, Pathogenesis, Therapeutics, Prognosis

INTRODUCTION

Enthesitis-related arthritis (ERA) is a term introduced in the International League of Associations for Rheumatology (ILAR) classification of juvenile idiopathic arthritis (JIA) [1]. The definition of ERA in the ILAR classification criteria for JIA is based on the inclusion and exclusion criteria (Table 1). ERA is characterized by the presence of predominantly lower limb arthritis and enthesitis and can eventually affect the sacroiliac (SI) joints and spine evolving to juvenile ankylosing spondylitis (JAS). For this reason, identification of individuals with axial disease is required for early and appropriate therapeutic interventions. Both ERA and JAS are characterized by rheumatoid factor (RF) seronegativity, paucity of antinuclear antibody (ANA), and a strong association with the human leukocyte antigen-B27 (HLA-B27). However, the fact that a radiologic evidence of bilateral SI joint inflammation is a prerequisite for the diagnosis of

JAS discriminates JAS from ERA. ERA and JAS may represent the peripheral and axial forms of spondyloarthritis (SpA) based on the Assessment in Spondyloarthritis International Society (ASAS) classification system [2,3].

Epidemiological studies of ERA have been hampered by a lack of standardized criteria and case ascertainment, resulting in wide-ranging results [4-11]. The proportion of patients with ERA was 8.6%~39.2% among children with JIA in previous published studies. A study with multi-ethnic cohort reported that ERA was the commonest category of JIA in children of Asian descent [8], suggesting inherent genetic differences between Asian population and other populations. The mean age at diagnosis of ERA is around 10~15 years. There is a predominance of boys in ERA as reflected by high male-to-female ratios among cohorts from several countries. However, this gender-based difference in the prevalence of ERA may result from underestimation of the occurrence of diseases in girls.

This review will provide an update on the latest under-

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Table 1. International League of Associations for Rheumatology (ILAR) classification 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, Enthesitis-related arthritis, sacroiliitis with inflammatory bowel disease, reactive arthritis, or acute anterior uveitis
- Acute anterior uveitis

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, RF: rheumatoid factor, JIA: juvenile idiopathic arthritis.

standing regarding pathogenesis, clinical manifestations, treatments and expected outcomes in children with ERA.

MAIN SUBJECTS

Pathogenesis

The etiology of ERA is unknown. The role of enteric bacteria in the pathogenesis of ERA has been an area of active investigation. In particular, the association between enteric bacteria and ERA was reported by one study showing altered microbiota in children with ERA [12]. Elevation of a marker of intestinal inflammation such as fecal calprotectin in children with ERA indicates the linkage of ERA with enteric infectious conditions as well [13]. Interestingly, a complex interrelationship between enteric bacteria and HLA-B27 has been described in the HLA-B27 transgenic rat with a disease similar to AS [14,15] and human with AS [16,17]. Alteration in the repertoire of the gut microbiome by HLA-B27 is one possible mechanism for this interaction [18].

HLA-B27 remains the major genetic factor in ERA. Of over 105 molecular subtypes of HLA-B27, HLA-B27*04 and B27*05 appear to be the most common subtypes in patients with ERA [19,20]. Although numerous theories about the pathogenic role of HLA-B27 have been proposed, the exact mechanism underlying the effect of HLA-B27 on disease susceptibility has still not been

determined. It has been proposed that molecular mimicry between a microbial antigen and the HLA-B27 molecule or peptides it presents brings about an HLA-B27-restricted cytotoxic T-cell response found only in joints and other affected tissues (arthritogenic peptide hypothesis) [21-23]. Another theory comes from misfolding of the HLA-B27 heavy chain in the endoplasmic reticulum [23-25]. As a result of this, the accumulation of misfolded protein leads to induction of the proinflammatory response and stimulates the release of proinflammatory cytokines through the interleukin (IL)-23/IL-17 axis. In addition, an alternative concept implies that expression of HLA-B27 β 2 microglobulin-free homodimers on the cell surface leads to activation of the killer cell immunoglobulin-like receptors (KIRs) such as KIR3DL1/2 and promotes the production of Th17 cytokines involved in the pathogenesis of SpA [26-28]. Besides HLA-B27, endoplasmic reticulum aminopeptidase 1 (ERAP1) has been known to be associated with ERA, but not with other JIA subtypes [29]. However, its role in the pathogenesis in ERA has not been determined.

In contrast to other subtypes, ERA is not characterized by autoantibodies. Instead, high levels of monocyte-derived cytokines such as IL-1 and IL-6 in synovial fluid reflect the close relationship between the innate immune system and ERA [30]. Additionally, the increases of Th17 cells and $\gamma\delta$ T cells in ERA patients suggest the contribution of these cells to the development of ERA [31-33].

Clinical manifestations

1) General features

ERA usually has insidious onset, but may begin abruptly [34]. Systemic symptoms including low-grade fever, fatigue, and rashes may develop although these symptoms are usually absent at onset. Intermittent musculoskeletal pain and stiffness of peripheral joints develop along with enthesitis mainly in knee, ankle and foot. Arthritis in the back (spondylitis) and at the SI joint (sacroiliitis) is not common at first, but can occur later [35,36].

2) Enthesitis

Enthesitis is defined as inflammation of an enthesis, which is a site where a tendon, ligament, or joint capsule attaches to bone. It is characterized by pain and swelling especially at knee, foot, or heel. The presence of enthesitis is helpful to differentiate ERA from other subtypes of JIA. However, tenderness or pain at enthesal sites may occur

in other rheumatic diseases including other JIA subtypes and even in children without diseases [37]. In addition, Osgood-Schlatter syndrome and fibromyalgia should be excluded because these conditions are also accompanied by similar symptoms [38]. Enthesitis can be documented by the careful examination of localized tenderness or swelling at the enthesal insertion sites. The most common anatomic regions for enthesitis in children are the infrapatellar ligament insertion to patella, the plantar fascia and the Achilles tendon insertions to calcaneus, and the plantar fascia insertion to the metatarsal heads [39]. Avoidance of weight bearing on inflamed entheses can be detected during stance and gait tasks in patients with enthesitis in the lower limb.

3) Peripheral arthritis

Peripheral arthritis in ERA is usually asymmetric and mainly involves large joints of lower extremities. Although polyarticular involvement may occur at onset or during the course of disease, oligoarticular disease is more common in most instances [9,40]. Male sex, age at onset, and distribution of the affected joints may become useful tools in distinguishing ERA from other subtypes. The usually involved joints are knee, hips, ankles, and small joints of the foot and toes. Contrasting to other subtypes of JIA, hip involvement in ERA is relatively frequent [41]. Because the small joints of the hands are rarely affected, disease of these joints is less likely to be ERA [34]. Tarsitis, manifested as pain and tenderness in the mid-foot, is more common than other subtypes of JIA [42,43].

4) Axial arthritis

Involvement of spine and SI joints is relatively rare at disease onset, but may occur several years after onset [44]. Axial involvement may be asymptomatic [45-47], although it is manifested by pain particularly at the lower back and buttock areas or stiffness and limitation of motion of axial skeleton. Prolonged periods of inactivity can aggravate these symptoms. Clinical examination may reveal tenderness over SI joint, pain on flexion, abduction and external rotation of hip (Patrick or FABER test), restricted forward flexion (modified Schober's test) (Figure 1), or abnormal spinal contour on maximal forward flexion. Arthritis of the cervical spine may occur and cause severe damage [48].

5) Uveitis

The uveitis is the most common extra-articular manifes-

tations of ERA. It has been reported in around 7% of ERA patients [10,49]. Acute symptomatic anterior uveitis is characteristic of ERA and its common presentations include ocular pain, redness of eye, and photophobia. It is usually unilateral and can occur repeatedly. In contrast to anterior uveitis seen in other JIA subtypes, the uveitis in ERA is more frequently symptomatic and seldom leaves any significant sequelae [34]. It may be present at diagnosis, develop during the course of disease, or be an initial manifestation usually detected in the course of routine ophthalmologic examination.

Laboratory findings

There are no diagnostic laboratory tests for ERA. A complete blood count (CBC) with differential counts is a part of the initial evaluation of any child with a joint disease. Mild anemia is a usual finding and suggests the presence of chronic disease. The number of white blood cells remains normal or increases with normal differential. The substantial elevation of inflammatory markers such as C-reactive protein or erythrocyte sedimentation rate may be noted, although these markers may be normal or only minimally increased even in patients with clinically active disease. RF are characteristically absent [38]. Compared with healthy population, the occurrence of ANAs is not more frequent in children with ERA [34]. Children with ERA were found to have higher levels of fecal calprotectin than those with other JIA subtypes [13,50]. While



Figure 1. Modified Schober's test. With patient standing upright, two points are marked on the back 5 cm below and 10 cm above the horizontal line joining the dimples of Venus which is used as a mark for the lumbosacral junction. On maximal forward flexion, keeping the knees straight, an increase of the distance between the top and bottom points reflects lumbosacral spinal mobility and is considered normal if more than 5 cm.

HLA-B27 is present in more than 95% of adults with AS, a somewhat lower prevalence of HLA-B27 was reported in recent studies of children with SpA [51,52].

Radiologic findings

1) Plain radiographs

Although plain radiographs are limited by their inability to show inflammation or soft tissue changes, it can reveal subtle thickening of tendon and ligaments and a loss of the distinct margins at the tendon insertion site. In addition, chronic bony changes such as enthesophyte formation or occasional erosions can be detected. Although radiographic evidence of sacroiliitis is often found several



Figure 2. Anteroposterior view of the pelvis shows joint space narrowing, bone erosions, and reactive sclerosis in the sacroiliac joints.

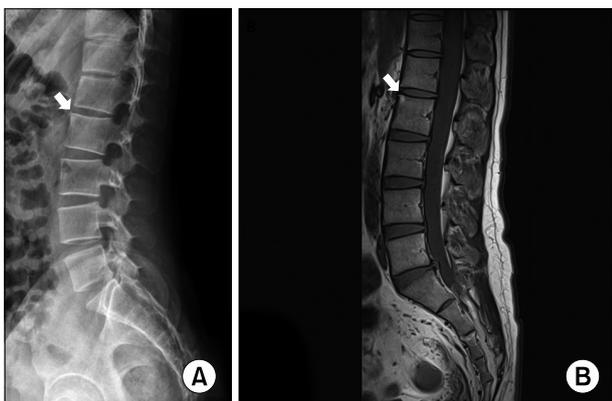


Figure 3. Corner lesion in 15 year old male with enthesitis-related arthritis. Plain radiograph (A) and T1-weighted magnetic resonance imaging (B) of spine show increased signal at the anterior aspect of the superior endplate of L2 (arrows).

years after the onset of peripheral arthritis, it may be the first radiologic finding. For radiologic evaluation of the SI joints, a standard anteroposterior view of the pelvis is usually obtained (Figure 2) and may demonstrate haziness or a punched-out appearance of the cortical margins, widening of the joint space as a result of erosion of the subchondral bone, and joint sclerosis reflecting an osteoblastic reaction. These findings are usually bilateral and symmetrical, although unilateral involvement can be seen initially. Radiological changes in the lumbosacral spine are less common and usually follow the abnormalities of the SI joints. The anterior corners of vertebral bodies may initially look bright due to periostitis with new bone formation (shiny corner sign) (Figure 3A) [38,53]. Subsequently, the anterior margin of the vertebral body loses its normal concavity and becomes flat or squared. Formation of syndesmophyte, calcifications or heterotopic ossifications inside a spinal ligament or of the annulus fibrosus, is less frequent in the pediatric population but can occur later during adulthood [54].

2) Ultrasonography with Doppler (USD)

Ultrasound with power Doppler is a highly useful and sensitive tool in the evaluation of clinical or subclinical enthesitis (Figure 4). It has the advantage of being non-invasive and easily accessible in the clinic, although it is highly operator-dependent and needs specialized training.

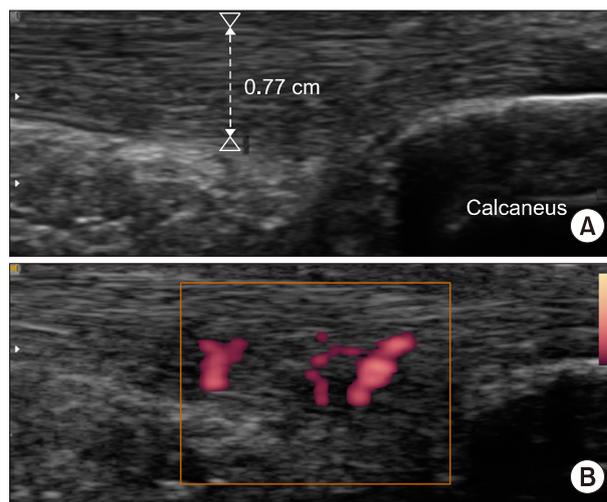


Figure 4. Achilles tendon enthesitis in a 14 year old boy. (A) Longitudinal grayscale ultrasound image demonstrates increased thickness of Achilles tendon (arrowheads) with hypoechogenicity and loss of fibrillar pattern in deep layer. (B) Power Doppler images demonstrates increased signals within the tendon consistent with hyperemia.

The common abnormalities of entheses detected by USD are hypoechoic (and/or thickened) tendon at its bony attachment and bony changes including enthesophytes, erosions or irregularity [55].

3) Magnetic resonance imaging (MRI)

Early as well as chronic inflammatory changes in the SI joints and the spine can be identified by MRI even in patients with normal conventional radiographs. MRI with gadolinium enhancement is helpful to detect active synovitis [56,57], whereas MRI using short-tau inversion recovery (STIR) images has an advantage of not requiring gadolinium administration in detecting bone marrow edema (BME) [58,59]. Subchondral or periarticular BME on STIR imaging or osteitis on T1 post-gadolinium images of the SI joints is most indicative of active sacroiliitis (Figure 5) [58,60]. In addition, tendon or ligament thickening, adjacent soft-tissue swelling and edema, synovitis, enthesitis, and capsulitis around the SI joints and other sites within the pelvis can be detected by MRI. However, these findings are compatible with sacroiliitis but not sufficient for making a diagnosis of active sacroiliitis in the absence of bone marrow edema [61]. Because spinal involvement is less frequent in children and adolescents than that in adults, a spinal MRI is not usually required in these population unless there is a substantial possibility of spinal disease [58]. The typical findings in children with ERA are fatty lesions at the vertebral edge (corner le-

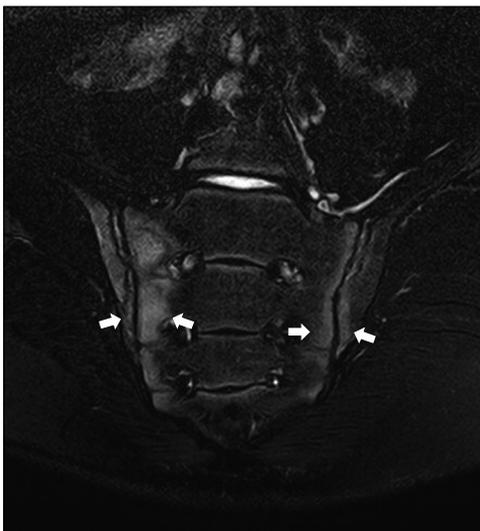


Figure 5. Coronal T1-weighted magnetic resonance imaging of pelvis in 15 year old male with enthesitis-related arthritis. There is active sacroiliitis with bone marrow edema (arrows) on both iliac and sacral sides of the sacroiliac joints.

sions) (Figure 3B).

Treatment

1) General managements

Children with ERA should be managed by a team of health professionals who can provide patient and family education, medical treatment, physical therapy, and psychosocial support. The goal of therapy should be to relieve pain, preserve joint function, achieve disease remission, and prevent long-term damage caused by the disease or its treatment. An optimal management strategy includes differentiation or stratification of children according to the severity and risk of functional disability. Although there is no medication that can cure the disease, prognosis of ERA has improved recently due to the progress in treatment modalities. The current managements for ERA are based on evidences from studies in adults with AS or rheumatoid arthritis and children with other JIA subtypes. However, application of data from these populations to children with ERA may not be ideal, as evidenced by recognized clinical differences between ERA and AS or other categories of JIA. In the 2011 American College of Rheumatology Recommendations for the treatment of JIA [62], the management of children with ERA is not considered separately from that for children with other categories of JIA and primarily based on the number of active joints and the presence of sacroiliitis. For this reason, there is a critical need for a rational therapeutic strategy focused specifically on the ERA population. The flow of treatment and the suggestions for the use of drugs based on the current recommendations for the treatment of patients with ERA are summarized in Figure 6.

2) Non-steroidal anti-inflammatory drugs (NSAIDs)

NSAIDs are often the first line of therapy for relief of both axial and peripheral symptoms and also effective for enthesitis [63]. Although disease remission may be induced by continuous use of NSAIDs, use of NSAIDs as monotherapy for more than 2 months is discouraged if disease does not remit [62]. Among various NSAIDs, naproxen (15~20 mg/day, maximum 500 mg/day) is usually selected as an initial medication because it has lower toxicity and can be administered using a convenient twice daily regimen. Toxicity monitoring includes CBC, creatinine measurement, liver function test (LFT), and urinalysis every 4~6 weeks after initiation of treatment and then every 6~12 months thereafter.

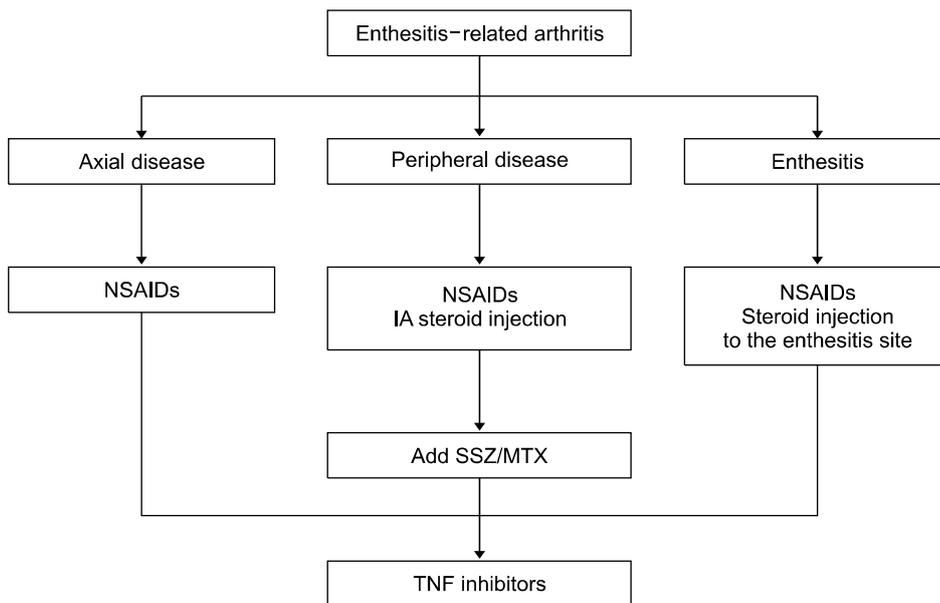


Figure 6. Flow of treatments for patients with enthesitis-related arthritis. NSAIDs: non-steroidal anti-inflammatory drugs, IA: intraarticular, SSZ: sulfasalazine, MTX: methotrexate, TNF: tumor necrosis factor.

3) Glucocorticoids

Corticosteroids can be used as a short-term oral or intravenous therapy for an acute flare and as topical treatment of acute uveitis. In addition, intraarticular administration of corticosteroids is recommended for the localized joint disease to rapidly relieve joint symptoms, to restore function, and to avoid systemic use of corticosteroids [64-66]. Triamcinolone hexacetonide (for large joints, 1 mg/kg, maximum 40 mg/dose; for smaller joints, 0.5 mg/kg, maximum 20 mg/dose) is used as the drug of choice for intraarticular steroid injections. Local injections of corticosteroids at sites of enthesitis may provide relief of symptoms but should be used cautiously due to the increased risk of tendon rupture [34].

4) Disease-modifying anti-rheumatic drugs (DMARDs)

Although DMARDs have shown efficacy for peripheral joint disease, they have not been proven effective for axial disease or enthesopathy [42,67,68]. For this reason, DMARDs are not recommended for patients with purely axial disease [66]. However, DMARDs may be used in exceptional situations of axial symptoms in which there is no other pharmacological treatment option left for a particular patient for reasons of toxicity, contraindications or costs. In clinical studies of children with SpA, sulfasalazine (30~50 mg/kg/day, maximum 3 g/day) improved both doctor and patient assessments and was found to be effective and safe compared to placebo [69,70]. Clinical improvement is usually expected several weeks after initiation of sulfasalazine. Because side effects of sulfasala-

zine include bone marrow suppression and hepatotoxicity, CBC and LFT must be regularly monitored. Despite absence of controlled studies in children with ERA, methotrexate or leflunomide can be considered for the management of peripheral disease of ERA in case of no response to sulfasalazine.

5) Biologic agents

Biologic agents blocking tumor necrosis factor (TNF)- α (TNF- α inhibitors) have offered a powerful therapeutic option for the management of patients with ERA. They have demonstrated efficacy for peripheral disease refractory to NSAIDs and DMARDs as well as symptomatic treatment of axial disease [71-74]. However, the role of TNF- α inhibitors in impeding progression of structural damage in children remains to be elucidated. If a patient is in sustained remission, tapering of TNF- α inhibitors can be considered [66,75,76]. However, complete discontinuation of TNF- α inhibitors seems to lead to a high percentage of patients that experience flares [77,78]. The choice of TNF- α inhibitors can be made according to patient preference and associated extra-articular manifestations including uveitis. It is required to perform baseline screening for tuberculosis (tuberculin skin test or interferon- γ release assays) before commencing treatment with the TNF- α inhibitor. The frequently recommended TNF- α inhibitors include etanercept (0.8 mg/kg/week, subcutaneously, maximum 50 mg), adalimumab (20 mg or 40 mg subcutaneously every other week for weight less or greater than 30 kg, respectively), and infliximab (5

mg/kg initial loading every 2 weeks for 3 infusions and then every 8 weeks). So far, the evidence for the efficacy of other biologic agents such as rituximab, anakinra, abatacept, tocilizumab, ustekinumab (anti IL-12/23 human monoclonal antibody), and secukinumab (anti-IL-17A antibody) is insufficient to support the use of these medications in patients with ERA.

Prognosis

Children and adolescents with ERA shows variable course and prognosis. The disease remission within five years of diagnosis has been reported in less than 20% of patients [79], but its rate will likely increase with the advent of additional biologic therapies. The prognosis of ERA appears to be worse than those of other JIA categories [9,80-82]. Thus, ERA is usually associated with worse physical function, poorer quality of life, higher pain scores, and a higher possibility of ongoing active disease after initial treatment compared with other JIA subtypes. Family history of AS, disease onset after 8 years of age, HLA-DRB1*08, HLA-B27, ankle and hip arthritis within the first 6 months of disease, and tarsitis are associated with a poorer prognosis [36,47,82]. ERA can progress to AS within 10 years of disease onset [36,44].

CONCLUSION

ERA is characterized by the presence of arthritis and enthesitis predominantly at the lower extremities and has a potential to eventually affect the SI joints and spine evolving to JAS. Its most common extra-articular manifestation is uveitis. Advances in the understanding of ERA pathogenesis continue to evolve and have led to the development of new treatments targeting pro-inflammatory cytokines. In particular, the TNF- α inhibitors become a mainstay of therapy for patients in whom therapy with NSAID and/or DMARDs is inadequate or contraindicated. Because the current guidelines for management of ERA is not considered separately from other categories of JIA, there is a need for treatment guidelines specific for ERA to improve the overall course of disease.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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