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REVIEW

Recent updates in enthesitis-related arthritis

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Abstract

Enthesitis-related arthritis (ERA) is a category of juvenile idiopathic arthritis which belongs to the spectrum of diseases that are included in juvenile spondyloarthropathy. In recent years, there have been significant advances in understanding pathogenesis, tools to assess disease activity, early recognition of the axial disease, and targeted therapy using IL-17 inhibitors and small molecule inhibitors. The current narrative review highlights these new advances. Among many hypotheses linking HLA B27 to ERA, one of them is the effect of HLA B27 on gut dysbiosis. However, recent data suggest that gut dysbiosis is probably not determined by HLA B27. Though children present with arthritis and enthesitis, axial disease is present in 50–60% on MRI. Using data-driven approach, discriminative MRI finding for active and chronic diseases has been defined for children. This will help in the early recognition of disease. An abridged version of juvenile spondyloarthropathy disease activity (JSpADA) score without the need for acute phase reactants and Schober test performed as well as the original score may increase its acceptance in routine practice. Secukinumab (anti-IL-17 antibody) has shown a more than 75% response rate in children with ERA and may be a good alternative to anti-TNF therapy. Initial data with tofacitinib also look promising. All these will translate into better outcomes for children with ERA.

Keywords Arthritis, juvenile · HLA B27 · Outcome measures · Juvenile Spondyloarthropathy · Biologics

Abbreviations

ACR	American college of rheumatology
ANA	Antinuclear antibody
AS	Ankylosing spondylitis
ASAS	Assessment of spondyloarthritis international society
ASDAS	Ankylosing spondylitis disease activity score
BASDAI	Bath ankylosing spondylitis disease activity index
BASFI	Bath ankylosing spondylitis functional index
CD	Cluster differentiation
CHAQ	Childhood health assessment questionnaire
CIMT	Carotid artery intima media thickness
cJADAS	Clinical juvenile arthritis disease activity score
CRP	C reactive protein
CT	Computed tomography
DMARDs	Disease-modifying anti-rheumatic drugs
ERA	Enthesitis-related arthritis
ERAP1	Endoplasmic reticulum aminopeptidase 1
ESR	Erythrocyte sedimentation rate
FMD	Flow-mediated dilation
FMF	Familial Mediterranean fever
HLA	Human leucocyte antigen
IL	Interleukin
ILAR	International league of associations for rheumatology
JADI-A/E	Juvenile arthritis damage index—articular/extra-articular
JAK	Janus kinase
JIA	Juvenile idiopathic arthritis
JADAS10	Juvenile arthritis disease activity score 10
JSpADA	Juvenile spondyloarthropathy disease activity
KIR3DL	Killer immunoglobulin-like receptors
MHC	Major histocompatibility complex
MIF	Macrophage migration inhibitory factor
MMP	Matrix metalloproteinase

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MRI	Magnetic resonance imaging
MRP	Myeloid-related protein
NK cell	Natural killer cell
NLRP	Nucleotide-binding oligomerization domain, Leucine-rich Repeat and Pyrin domain-containing proteins
NSAIDs	Non-steroidal anti-inflammatory drugs
PTPN	Protein tyrosine phosphatases non-receptor type
RCT	Randomized control trial
ROR	Retinoic acid receptors
SEA	Seronegative enthesopathy arthritis
SpA	Spondyloarthritis
TLR	Toll-like receptors
TNF	Tumor necrosis factor
SoJIA	Systemic-onset juvenile idiopathic arthritis
SIJ	Sacroiliac joint
STIR	Short tau inversion recovery

Introduction

Juvenile idiopathic arthritis is an umbrella term that encompasses all chronic arthritis affecting children (less than 16 years) lasting more than 6 weeks and for which no cause is known. For a better understanding of pathogenesis and treatment strategies, the International league of associations for rheumatology (ILAR) categorized JIA into 6 mutually exclusive categories and the last as undifferentiated arthritis based on features in first 6 months of disease and some exclusions [1]. The categories include oligoarticular JIA, polyarticular RF-positive JIA, polyarticular RF-negative JIA, JIA enthesitis-related arthritis, systemic JIA, psoriatic arthritis, and undifferentiated arthritis.

Systemic JIA is defined as the presence of arthritis in ≥ 1 joints with, or preceded by, fever of at least 2 weeks' duration that is documented to be daily and quotidian (fever that rises to ≥ 39 °C once a day and returns to ≤ 37 °C between fever peaks) for at least 3 days, and accompanied by one or more of the following: evanescent erythematous rash, generalized lymphadenopathy, hepatomegaly and/or splenomegaly, and serositis. Polyarticular JIA is defined as a child having arthritis in more than four joints, and it is classified as RF-positive poly JIA if RF is positive twice at least 3 months apart or as RF-negative polyarticular JIA. Psoriatic arthritis is defined as the presence of psoriasis and arthritis or arthritis and at least two of the following: dactylitis; nail pitting; psoriasis in a first-degree relative. Oligoarticular JIA is defined as a child having four or less joints involved. Undifferentiated arthritis includes all children with arthritis not fulfilling any categories or having features of ≥ 2 categories [1].

Enthesitis-related arthritis is defined as children with arthritis and enthesitis or arthritis/enthesitis with at least two of the following features: boy more than 6 years of age, sacroiliac joint tenderness, inflammatory back pain, presence of HLA B27, acute symptomatic anterior uveitis, or history of SpA in a first-degree relative [1]. The prevalence of different categories varies across the World. In Southeast Asia, ERA accounts for nearly 30% of children with JIA [2].

There have been significant advances in classification to include patients who present with inflammatory back pain without arthritis, role of gut microbiome and innate immune cells in pathogenesis, early use of MRI for diagnosis of axial disease, disease activity assessment using ERA-specific tools rather than generic JIA tools, and treatment options like anti-IL-17 therapy in ERA category of JIA over the last few years. This narrative review looks at these advances.

Search strategy

We did a review of the literature based on previously published guidelines [3]. The search was conducted on 21 September 2022 for the articles published in PubMed in the last 10 years in English language using the following search strategy: enthesitis-related arthritis OR juvenile spondyloarthritis. We could identify 792 such articles. They were screened for observational study ($n = 201$) or interventional study ($n = 16$) related to ERA by two of the authors. Review articles ($n = 59$), case reports/series ($n = 31$), letters/editorials ($n = 8$), and topics not related to ERA ($n = 477$) were excluded from the review. The review included articles predominantly from the 217 studies from the search, but also other relevant references wherein appropriate.

Epidemiology

JIA has a prevalence of 3.8–400 per 100,000 [4]. The prevalence is noted to be lower in Africa and the Middle East [5]. The incidence rate varies between 2 and 40 cases per year per 100,000 population [4]. Though oligoarticular JIA is the most common across the World, in Southeast Asia, ERA and systemic-onset JIA are the common categories [2]. In India which has one-sixth of the world's population and nearly 20% of the world's children, ERA constitutes 33–36% of JIA both in the community-based survey as well as in hospital-based data [6]. A multi-ethnic study from Canada also showed that Asians have a higher prevalence of ERA [7]. This may be related to differences in genetic susceptibility or environmental influences.

Classification criteria

Arthritis like ERA was initially called seronegative enthesopathy arthritis (SEA) syndrome [8]. In ILAR

classification, a child with JIA is classified as ERA if the child has both enthesitis and arthritis or if only one of the two is present then two additional features of the following features should be present: boy more than 6 years of age, sacroiliac joint tenderness, inflammatory back pain, presence of HLA B27, acute symptomatic anterior uveitis, or history of SpA in a first-degree relative [1]. Thus, a child may not have arthritis and yet have the ERA category of JIA. Purists would question that should that child be really classified as JIA?

ERA shares a lot of its clinical features with adult SpA like HLA B27 association, acute anterior uveitis, enthesitis, sacroiliac joint involvement, and family history of SpA. Further, a lot of children continue to have the disease after they reach adulthood and can be classified as Ankylosing spondylitis. Thus, there has been a suggestion to rename ERA as juvenile SpA [9]. However, a group of pediatric rheumatologists met in 2018 and proposed to call ERA as enthesitis/spondylitis-related arthritis to emphasize the two major features, i.e., enthesitis and spondylitis along with arthritis [10]. The classification of ERA is a work in progress and in the future, and we might see a new name for this disease.

Pathogenesis

Though the exact pathogenesis of ERA is not known, it is postulated that a complex interaction of genetic risk factors along with gut microbiome alterations and mechanical stress induces a cascade of immune events that culminate in synovitis, enthesitis and spondylitis (Fig. 1).

HLA B27 is present in nearly 40–90% of the children with ERA [11, 12]. HLA B27 being a class I MHC molecule can present arthritogenic peptide to CD8 cells, however, neither a major expansion of CD8 T cells nor any arthritogenic peptide has been isolated in ERA or SpA [13]. Alternatively, due to the presence of cysteine at position 67 or improper loading of peptides in the endoplasmic reticulum, HLA B27 homodimers can form. These homodimers can activate NK and T cells via KIR3DL to produce cytokines [14, 15].

ERAP1 rs37018 C/T polymorphism is another genetic factor linked to ERA [16]. The aberrant function of ERAP1 can lead to improper loading of peptides resulting in misfolding of HLA B27 heavy chain or dimerization. Misfolded HLA B27 induced unfolded protein response, leads to the production of pro-inflammatory cytokines including IL-23. IL-23 in turn promotes IL-17 production, the key cytokine by CD4 T cells, NK cells, and $\gamma\delta$ T cells [15, 17]. Other genes involved are TLR4, NLRP3, CXCR4, and PTPN12 which affect innate and T cell activation [18].

As only a small proportion of children with HLA B27 ever develop ERA environmental factors such as gut dysbiosis and mechanical stress are probably important players in the pathogenesis of ERA. The studies done in children with ERA show gut dysbiosis with a reduction in *Faecalibacterium prausnitzii* and an increase in *Bacteroides* [19]. In children of patients with AS, bacterial diversity did not depend on HLA B27 status. Children who had HLA B27 + juvenile SpA had alterations in *B. fragilis* and *F. prausnitzii* as compared to HLA B27+ offspring suggesting that HLA B27 may not work by altering gut flora [20]. The fecal microbiota can alter the metabolic pathways; a reduction in the production of butyrate and tryptophan metabolism may contribute to a more pro-inflammatory effect of gut dysbiosis [21]. Gut dysbiosis leads to gut inflammation and patients with ERA having active sacroiliitis have increased fecal calprotectin levels, a surrogate marker of gut inflammation [22]. Mechanical

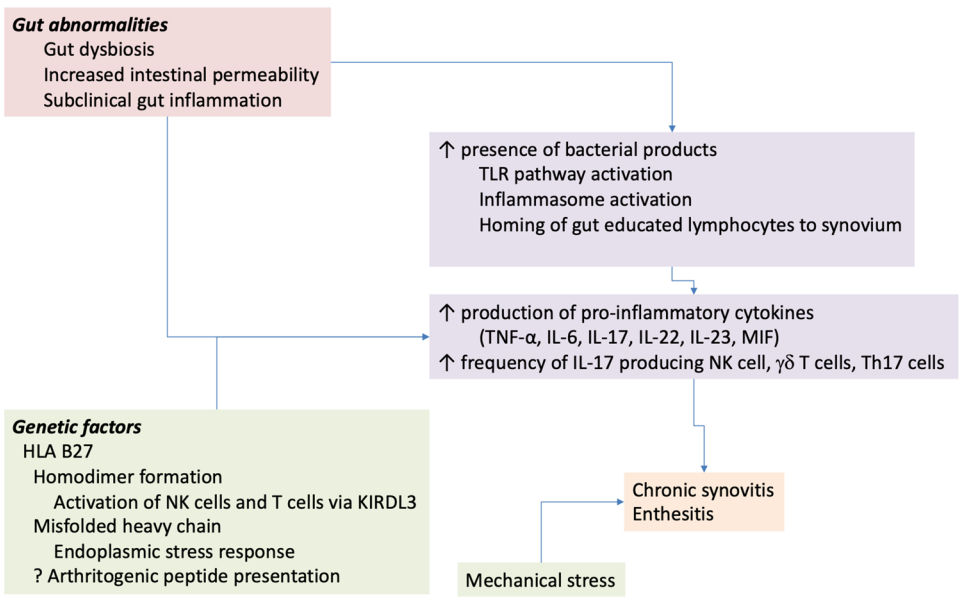

Fig. 1 Pathogenesis of enthesitis-related arthritis showing an interplay of genetic and environmental factors leading to immune inflammation mainly mediated by IL-17. *TLR* Toll-like receptor, *IL* Interleukin, *NK cell* natural killer cell, *MIF* macrophage inhibitory factor, *KIRDL3* killer cell immunoglobulin-like receptor domain 3, *HLA* human leucocyte antigen

stress at entheseal sites can initiate inflammation by inducing IL-23 production by innate immune cells.

Transcriptomic analysis of synovial fluid mononuclear cells of ERA patients suggested dysregulation of the genes related to monocytes and NK cells [23]. NK cells in ERA patients produce higher levels of IL-17 than controls [15]. Monocytes from patients with ERA are pre-activated and produce a higher amount of pro-inflammatory cytokines in response to TLR 4 ligands. Intermediate monocyte (CD14 + CD16 +) contribute to pathogenesis by producing IL-23 which in turn acts on IL-23 receptor bearing CD4, γδT, and NK cells leading to the production of IL-17 and IL-22 [17, 24]. A recent study showed that the ROR+γδ+IL-23R+T cells are the main producers of IL-17 in the enthesis and ciliary body [25]. IL-27, the regulatory cytokine of the IL-23/17 pathway, is reduced in patients with ERA [26].

Patients with AS had higher MIF levels that went hand in hand with radiological progression. In an animal model, MIF induced TNF-alpha production by monocytes and induced bone formation [27]. MIF serum levels are increased in ERA patients [28]. Thus, the immune pathogenesis of ERA involves an interplay of genetic factors, gut dysbiosis, and inflammation leading to persistent inflammation and tissue damage.

Clinical features

The typical clinical picture of ERA is a young boy, above 6 years of age with lower limb asymmetrical oligoarthritis, with or without enthesitis. Table 1 summarizes the clinical features in various cohorts of ERA patients [29–41]. The common entheseal sites involved are tendoachilles insertion, plantar fascia insertion, enthesis around the knee joint, anterior superior iliac spine, posterior superior iliac spine, and iliac crest [32]. Entheses above the waist are less frequently involved.

Unlike adults with AS, children have more peripheral arthritides over axial involvement. Oligoarthritis is the most common presentation and is seen in 60–75%. Monoarticular (5%) and polyarticular (20%) presentations can also be seen. Midfoot involvement also termed tarsitis is a common presenting feature of ERA. This may be seen in up to two-thirds of the children with ERA [36, 42]. Hip joint involvement is also common in ERA and predicts severe disease and poor long-term outcomes. Symptomatic sacroiliitis and hip involvement are seen in 30% and 10–15% at disease onset. Over time, sacroiliitis and hip arthritis involvement progress to 70% and 40%, respectively [43]. Low body mass index and juvenile-onset SpA predict hip joint involvement in AS [44].

Acute anterior uveitis is seen in 5–11% at presentation and 27% over time [45]. Unlike ANA+poly/oligo JIA, the uveitis in ERA is acute and symptomatic with redness and blurring of vision [46]. Hence, regular screening for uveitis is not needed [47].

Fever can be present in up to one-third of the patients at disease onset and the presentation may mimic SoJIA [39]. However, unlike SoJIA, the fever is usually low grade (78%). The presence of weight loss, bone pains, sternal tenderness, hepato-splenomegaly, dactylitis, nail changes, moderate–severe anemia, cytopenia, hypertension, and proteinuria should suggest an alternate diagnosis. In areas with a high prevalence of FMF 10–26% of FMF, patients can have ERA [48].

Investigations

Multiple markers have been associated with disease activity in SpA [49]. These include conventional markers such as ESR, CRP and products of inflammation such as MRP8/14, MMP3, and Tenascin C [49], but they are still used. The only activity score for children with juvenile SpA, i.e., juvenile spondyloarthropathy disease activity (JSpADA) score includes ESR or CRP. However, a subset of patients may have normal ESR and CRP [50]. Levels of MRP 8/14 were found to be higher in children with ERA and they had modest correlation with disease activity [51]. Similarly, levels of Tenascin C and MMP3 also showed good correlation with disease activity [52, 53]. These markers need to be tested in different populations before they can be used in clinic.

Plain X-rays of involved joints may show soft tissue swelling or may be normal. Only a small proportion of children have radiological sacroiliitis at presentation and this is also dependent on delay in diagnosis in different studies [37–39, 43]. MRI is the preferred modality to assess sacroiliitis. STIR sequences help in delineating bone marrow edema and osteitis (Fig. 2a). T1W and T2W fat suppressed images aid in detecting erosions. Gadolinium contrast administration is not done routinely though it can help in delineating capsulitis and synovitis better [54]. MRI changes of active sacroiliitis include bone marrow edema, synovitis, capsulitis, and enthesitis. Chronic or structural changes include subchondral sclerosis, erosions, periarticular fat deposits, and ankylosis. Recently data-driven definitions for sacroiliitis by MRI for children with juvenile SpA have been defined as (a) the presence of inflammatory lesion (bone marrow edema) in ≥ 3 SIJ (sacroiliac joint) quadrants across all SIJ slices, (b) structural lesions erosion in ≥ 3 quadrants or sclerosis or fat lesion in ≥ 2 SIJ quadrants or backfill or ankylosis in ≥ 2 joint halves across all SIJ MRI slices [55].

Among the children with symptomatic sacroiliitis, 77% have positive MRI findings [56]. Among unselected 50 patients with juvenile SpA MRI revealed sacroiliitis in 32 (64%) and hip arthritis in 23 (45%) children. Children with sacroiliitis had higher prevalence (79%) of hip arthritis

Table 1 Characteristics of JIA-ERA patients in various studies

	Vilaiyuk et al. (Thai) [33]	Ozdel et al. (Turkish) [34]	Goirand et al. (French) [35]	Weib et al. (German) [36]	Arkachaisri et al. (Singapore) [37]	Shih et al. (Taiwan) [38]	Guo et al. (China) [39]	Kavadichanda et al. (Indian) [29]	Rumsey et al. (American) [30]	Glerup et al. (Nordic) [31]	Gmuca et al. (American) [40]	Srivastava et al. (Indian) [41]
Year of publication	2016	2021	2018	2017	2021	2019	2015	2019	2021	2020	2017	2015
Study period	1997–2012	2017–2019	2008–2015	2002–2007	2009–2019	1993–2018	1998–2013	2015–2017	2015–2018	1997–2000	1989–2012	NA
Type of study	Retrospective	Retrospective	Retrospective	Inception cohort	Retrospective	Retrospective	Retrospective	Cross-sectional	Retrospective	Longitudinal cohort	Retrospective	Cross-sectional
Number of ERA patients	39	89	114	118	146	73	146	160	522	45	234	107
Proportion of ERA patients within JIA (%)	24.8	29.2	NA	NA	NA	39.9	NA	NA	NA	10.4	NA	NA
Follow-up period (years)	3.1 (0.5–15.0)	NA	2.6 (1.0–7.2)	4	4.9 (2.6–8.3)	7.7 ± 5.9	2	NA	NA	18	3	NA
Age at disease onset (mean, SD) or median (IQR)	10.4 ± 2.8	11.1 ± 3.3	9.55 ± 2.7	12 ± 2.7	11.9 (9.4–14.0)	11.0 ± 3.2	10.3 mean age of diagnosis	12.69 (2.4)	10.8 ± 3.4	9.4 ± 3.6	11.6	12 (4–16)
Male (%)	76.9	68	63	73	87	86	81.5	82	56	69	72.2	91.5
HLA B27+	71.4	42	43	66	82.2	97	58.9	68	38	79.5	59	Only HLA B27+ included
Arthritis at onset/ever (%)	NA	NA	38.5/87	75.4/95.8	89.7/76.0	97%/97% had arthritis or enthesitis	45.2/NA	NA/66	NA	NA	NA/62.8	NA/96
Enthesitis at onset/ever	NA	NA	72/86	16.1/44.1	24/42.5	97% had arthritis or enthesitis/ NA	40.4/NA	NA/67	NA/78	NA	69% enthesitis and arthritis/ NA	NA/59
Sacroiliitis at onset/ever (%)	NA	NA	30/47	NA	39.7/61	16/ NA	43.8/NA	NA/51.2	NA/40	NA	NA	NA/21
IBP ever (%)	NA	NA	20	32.2	NA	NA	NA	91.8	NA	NA	NA	NA/55

Table 1 (continued)

	Vilaiyuk et al. (Thai) [33]	Ozdel et al. (Turkish) [34]	Goirand et al. (French) [35]	Weib et al. (German) [36]	Arkachaisri et al. (Singapore) [37]	Shih et al. (Taiwan) [38]	Guo et al. (China) [39]	Kavadichanda et al. (Indian) [29]	Rumsey et al. (American) [30]	Glerup et al. (Nordic) [31]	Gmuca et al. (American) [40]	Srivastava et al. (Indian) [41]
Uveitis at diagnosis/ever (%)	NA	7.8/NA	NA	2.5/6.8	3.4/NA	NA/10	8.9/NA	NA/10.6	NA	NA	NA/5.6	NA/12
Midfoot arthritis (tarsitis) ever (%)	NA	NA	NA	9.3	NA	8.2	NA	15	NA	NA	NA	NA
Biologics treatment (%)	56.4	59.5	42.1	5.9	77.9	78	25.3	NA	72	51.1	15.4	NA
Outcomes												
Remission (%)	2.6	95.5	55	68	3.4% off all drugs, 15.8% clinical inactive disease, 24.7% on medication	33% non-active, 18% inactive (7& on medication, 8% off medication)	41	NA	NA	11.2 on medication, 35.3 off medications	NA	NA
Damage (bone erosions)	50.0	NA	NA	NA	NA	NA	NA	Deformities in 20%	NA	JADI-A in 19.8%, JADI-E in 12.5%	NA	NA

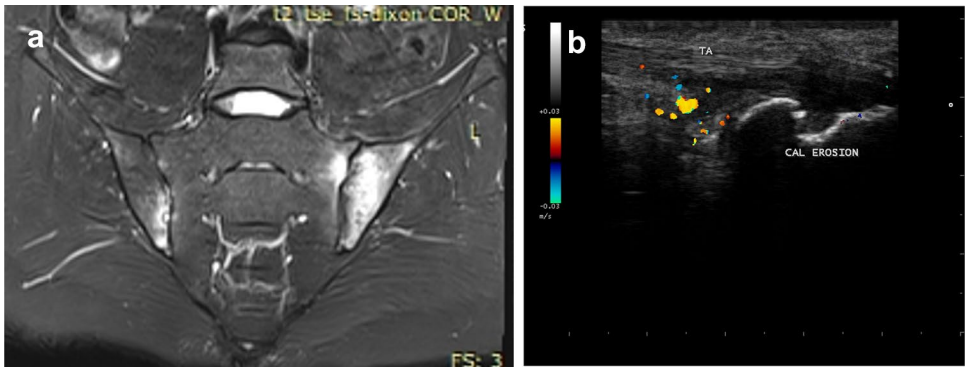

Fig. 2 **a** MRI of sacroiliac joints T2W STIR images depicting bone marrow edema; **b** enthesitis in B-mode ultrasound with color Doppler imaging showing an erosion in calcaneum as well as increased vascularity near the tendoachillies tendon insertion

[57]. Rarely, Romano's lesion (shiny vertebral corners) and Anderson's lesion (inter-discal edema) can be seen in MRI of the lumbar spine. Pelvic enthesitis can be visualized in MRI but has limited value in the diagnosis.

CT scan of sacroiliac joints is best to detect erosions. However, they are of limited value to detect active changes like bone marrow edema and also carry the risk of radiation exposure [58]. Musculoskeletal ultrasound can aid in assessing enthesitis and peripheral joint synovitis (Fig. 2b). Ultrasound can detect subclinical enthesitis and has good concordance with clinical enthesitis (89%) [59]. Minimal hip joint effusion is best detected by ultrasound and is a useful tool for a guided intra-articular steroid injection. Ultrasound is of limited value for sacroiliitis assessment [60].

Treatment

Treatment of ERA involves pharmacological and non-pharmacological measures. Non-pharmacological treatment includes spinal extension exercises, swimming, and warm water baths [61, 62]. Pharmacological management includes NSAIDs, conventional DMARDs, and biologics [63].

NSAIDs form the first line of treatment. NSAIDs alone may suffice for 20–30% of axial disease patients and 20–40% of peripheral disease patients. Methotrexate or sulfasalazine forms the next agent for treating peripheral arthritis/Enthesitis, but has a limited role in axial disease. Local intra-articular injection can be used in mono/oligoarthritis [64]. Rarely intra-articular steroid injection in SI joint has also been used to relieve inflammatory back pain. Short-course bridging low-dose steroids may be used while stepping up the therapy [63].

TNF inhibitors such as Adalimumab, Etanercept and infliximab have shown good improvement in active joints and other disease parameters in ERA patients [65, 66]. Adalimumab has shown a 53% ASAS40 response compared to the placebo at 12 weeks in conventional DMARD treatment refractory active ERA patients in a randomized controlled trial [67]. Etanercept has shown 93%ACR Pedi30 and Pedi50 scores in a 24-week randomized control trial [68]. Following an initial response to TNF inhibitors, continuing methotrexate with adalimumab has shown better drug survival than adalimumab or etanercept-monotherapy [69] (Table 2).

Secukinumab (IL-17 inhibitor) has recently shown excellent response with improvement in JSpADA score and JADAS10 score [70]. Further, Secukinumab has shown a longer time to flare compared to placebo in an RCT withdrawal study of ERA and juvenile psoriatic arthritis patients [71]. Secukinumab has shown clinically meaningful improvement in Achilles tendon enthesitis score on MRI although not statistically significant in adult spA patients with enthesitis [72]. The long-term drug retention rates for TNF inhibitors were similar in ERA and AS (38%), however, inefficacy due to anti-drug antibody formation remained the commonest reason for infliximab discontinuation, more so among adults with AS [73].

The newer class of drugs JAK inhibitors have been approved for polyarticular JIA and adult AS [74, 75]. The withdrawal RCT of tofacitinib in polyarticular JIA also had an exploratory arm which included 21 ERA patients. In an open label phase, 75% of children with ERA showed response and in double-blind withdrawal phase 4 of 9 in the tofacitinib arm and 4 of 7 in the placebo arm had flares by 44 weeks [74].

Patients should also be informed about the risks and warning signs of acute anterior uveitis. Topical steroids form the main stay of treatment during the acute attacks. It is recommended to continue DMARDs or biologics the patient is getting for joint disease at the time of acute uveitis. Patients with repeated attacks (> 3/year) should be given DMARDs/biologics. Conventional DMARDs (methotrexate and sulfasalazine) show moderate efficacy in preventing recurrent attacks of uveitis [76, 77]. TNF inhibitors adalimumab and infliximab are the preferred biologics over etanercept in acute anterior uveitis [78, 79].

Table 2 Trials of biologics or small molecule inhibitors

Trial	Type of study	Number of study participants	Drugs given	Primary outcome
Burgos Vargas et al. [65]	RCT	46 ERA	Adalimumab	Change from baseline of active joint count by 12 weeks; -62.6% in adalimumab arm vs -11.6% in placebo arm
Burgos Vargas et al. [66]	RCT	26 Juvenile onset spA	Infliximab	Number of active joints at 12 weeks; mean (SD) of 1.4 (2.4) in infliximab arm vs 4.1 (3.0) in placebo arm
Horneff et al. [67]	RCT	32 Juvenileonset spA	Adalimumab	ASAS 40 response at week 12: 53% adalimumab vs 33% placebo
Horneff et al. (CLIPPER study) [68]	Open label	127 (38 ERA)	Etanercept	JIA ACR 30 response at week 12: 83.3% with ERA, 89.7% for extended oligo JIA, 93.1% for psoriatic arthritis
Shipa et al. [69]	Retrospective observational study	188 ERA	Adalimumab vs Etanercept	Discontinuation of treatment due to primary or secondary failure and adverse drug reactions: 108 Etanercept, 80 Adalimumab. Adalimumab–methotrexate combination was associated with longer drug survival, compared to adalimumab-monotherapy (HR 0.41, 95% CI 0.20–0.85), etanercept-monotherapy (HR 0.28, 95% CI 0.15–0.53), and etanercept–methotrexate combination (HR 0.39, 95% CI 0.21–0.73)
Baer et al. [70]	Retrospective	17 ERA	Secukinumab	JSpADA and JADAS10 significantly improved between baseline and 24-month follow-up
Brunner et al. [71]	RCT, withdrawal study	86 (52 were ERA)	Secukinumab	Time to flare: HR 0.28; 95% CI 0.13–0.63; $p < 0.001$
Behrens et al. (ACHILLES study) [72]	RCT	204 (adult axial spA or psoriatic arthritis)	Secukinumab	Clinical resolution of heel enthesitis at 24 weeks: 33.3% in secukinumab vs 23.5% in placebo arm; OR 1.65; 95% CI 0.85, 3.25
Ruperto et al. [74]	RCT, withdrawal study	225 (21 were ERA)	Tofacitinib	Flare rate by week 44: 29% tofacitinib vs 53% placebo arm, HR 0·46, 95% CI 0·27–0·79; $p = 0·0031$
Tynjala et al. [78]	Observational	45 JIA (4 were ERA)	Etanercept, Infliximab	Uveitis improved in 14 (31%). Inflammatory activity improved more frequently ($p = 0.047$) in the patients taking infliximab. The number of uveitis flares/year was higher ($p = 0.015$) in the patients taking etanercept (mean 1.4) than in those taking infliximab (mean 0.7)
Jaffe et al. [79]	RCT	217 (Adults with active non-infectious uveitis)	Adalimumab	The time to treatment failure occurring at or after week 6: 24 weeks in adalimumab vs 13 weeks in placebo (HR 0.5; 95% CI 0.36–0.7, $p < 0.001$)

Outcome measures

Though in general in JIA, cJADAS is used to assess disease activity. cJADAS includes physician global assessment VAS, parent global assessment VAS, and active joint count assessed in 71, 27 or 10 joints [80]. cJADAS10 can be used in routine clinical practice. However, it does not include uveitis, inflammatory back pain or enthesitis which are the main features of ERA. A score specific for juvenile SpA, i.e., JSpADA was devised that includes active joint count, active enthesis count, ESR/CRP levels, pain VAS, morning stiffness, clinical sacroiliitis, uveitis, and back mobility (scored 0, 0.5 and 1 for each parameter, total score 0–8). It was prospectively validated and found to perform well in ERA patients [81]. Recently, an attempt has been made to make JSpADA simple to use by removing Schober's test (JSpADA7), CRP/ESR (JSpADA7 (no CRP/ESR) or by removing both [JSpADA6 (no Schober, no CRP/ESR)]. All these modifications still had good correlation with cJADAS, moderate–high correlation with physician global assessment [81].

Adult scores such as BASDAI and ASDAS-ESR also have been validated in ERA [50]. BASFI (Bath ankylosing spondylitis functional index) has also performed well in ERA patients and can be used to assess functional impact [82]. Damage assessment in ERA is challenging, as outcome measures like juvenile arthritis damage index—articular/extra-articular (JADI-A/E) underestimate joint damage, enthesitis, and spinal limitation in ERA [83]. Imaging modality such as X-ray and MRI remains the standard to assess hip damage, sacroiliac joint ankylosis, and bamboo spine. However, these are late changes and are irreversible by the time they are detected. Chronic changes in MRI of the sacroiliac joint namely erosions, subchondral sclerosis, fat replacement, and bony ankylosis have been seen in upto 60–70% of ERA patients on follow-up [43].

Course and outcomes

ERA patients have worse quality of life compared to the other categories of the JIA on follow-up [31, 84]. 40–50% of the patients have a relapsing course and persistent active disease in the long term [36, 85]. Around 40–60% require biologics over time. 85% achieve remission at some point while on drugs for more than 6 months [36], whereas only 3.4% to 33% of the patients achieve complete remission off all medications (Table 1). Early administration of biologicals portends better long-term outcomes [86].

Those with hip involvement at onset and delay in diagnosis have poor disease outcomes in the long term [43]. The presence of sacroiliitis and HLA B27 predict poor disease outcomes and chronic course [86, 87]. Tarsitis at onset predicts persistent disease activity in the long term. Articular damage by JADI-A is seen in 19.8% of patients over 18 years and extra-articular damage by JADI-E in 12.5% [31]. Children with JIA have worse lipid profiles and evidence of early cardiac dysfunction as evidenced by increased left ventricular mass index, CIMT, and reduced brachial artery FMD [88].

Conclusions

ERA is a chronic arthritis usually seen in boys beyond 6 years of age which resembles adult SpA but presents more often with asymmetrical lower limb arthritis and enthesitis than inflammatory back pain. Subclinical sacroiliitis is common and HLA B27 is present in nearly 60–70% of children. The immunopathogenesis is primarily driven by innate immune cells with major role of IL-23/IL-17 axis along with TNF-alpha. The therapies directed at these cytokines show excellent short-term results. In future, we expect to have more appropriate name, classification criteria, criteria for axial disease, advances in interpretation of sacroiliitis, and role of ultrasound in these children. Besides this, better understanding of pathogenesis will also translate to better therapeutics and long-term outcome.

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Declarations

Conflict of interest None.

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