Original Article

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Comparison of Treatment Options for Enthesitis-Related Arthritis with the Juvenile Spondyloarthritis Disease Activity Index

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Abstract

Aim: The Juvenile Spondyloarthritis Disease Activity Index (JSpADA) is the only disease activity score specifically validated for children with enthesitis-associated arthritis (ERA). It was developed to address the need for an effective measurement tool to assess disease activity in this population. We aimed to evaluate the clinical course of patients with ERA using JSpADA and to compare the effects of treatment modalities using JSpADA.

Methods: This cross-sectional observational study enrolled 61 patients with ERA who were followed up between January 2020 and 2023. Clinical features, treatment options, and JSpADA were noted in electronic medical files. The effectiveness of treatment modalities was compared by JSpADA.

Results: The median age of onset of the group was 10 [interquartile range (IQR), 9-15] years. The study cohort included three groups of patients: 1) DMARD received (n=34); 2) biologic drug received (n=14); 3) DMARD and biological combination received (n=13). Forty-three cases (70%) presented with peripheral arthritis, including enthesitis, whereas 18 (30%) patients had axial involvement. At disease onset, the median JSpADA scores were 2 (IQR, 2-3), 2.5 (IQR, 2-3), and 3.5 (IQR, 2.5-5) in groups 1, 2, and 3, respectively (p=0.27). At the first year of follow-up, there was a significant improvement in the disease activity of groups 1 and 2 (p=0.02 and p=0.04). However, there was no significant reduction in JSpADA values in the third group.

Conclusion: In patients with ERA, intermittent JSpADA evaluation during visits can guide the objective and accurate follow-up and treatment response of patients.

Keywords: Biologic drug, enthesopathy, spondyloarthritis

Introduction

Enthesitis-associated arthritis (ERA) is a subcategory of juvenile idiopathic arthritis (JIA) characterized by enthesitis and sacroiliitis that can affect peripheral and axial joints. According to previous studies, peripheral involvement is more common in pediatric patients than in adults. Because the course, long-term complications, and treatment responses of the disease may differ, cases with peripheral and axial involvement are thought to be on different spectrums of ERA (1-4).

As in all diseases, detailed anamnesis is still considered to be the best parameter in the diagnosis, evaluation of disease activity, and follow-up of ERA. Clinicians' opinions and experiences come to the fore in the interpretation of subjective symptoms such as inflammatory low back pain or morning stiffness. For laboratory evaluation, inflammatory markers, including erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), are assessed in the follow-up of patients with ERA. However, there is still an effort among clinicians to create a practical method for disease follow-up by combining objective measurements and subjective findings with various composite scales. Because the Juvenile Arthritis Disease Activity Score (JADAS) is insufficient to evaluate axial involvement in JIA, which is more specific to ERA, the Juvenile Spondyloarthritis Disease Activity Index (JSpADA) was developed specifically for the patient group diagnosed with ERA. It is the first disease activity assessment tool constructed for children with spondyloarthropathy (5-8).

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Juvenile Spondyloarthritis Disease Activity Index evaluates disease components, including active joint and enthesitis count, morning stiffness, back mobility, clinical sacroiliitis, uveitis, patient pain assessment, and inflammatory markers. Although there are studies on the validation of JSpADA and whether it can reliably predict the duration of clinical remission, further research on real-life data for clinical use is required.

ERA is considered to have a poorer prognosis than other JIA categories in terms of its resistant course and treatment response. Although non-steroidal anti-inflammatory drugs are prescribed as first-line treatment, second-line disease-modifying antirheumatic drugs (DMARDs) are usually required during follow-up with patients. Biological drugs, particularly tumor necrosis factor inhibitors (anti-TNF), are considered in patients who are resistant and usually have axial involvement. In our country, due to the health system circumstances, a switch to biological drugs can be achieved after using conventional DMARDs for at least 3 months.

Treatment response and reaching and maintaining remission in ERA can be more challenging than in other JIA categories (9,10). In patients with ERA, intermittent JSpADA evaluation during visits can guide the objective and accurate follow-up and treatment response of the patients. We evaluated the clinical course of patients with ERA through JSpADA and compared the effects of treatment modalities by comparing JSpADA in these patients.

Methods

Compliance with Ethical Standards

Ethical approval was obtained from the Istanbul University, Istanbul Faculty of Medicine Clinical Research Ethical Committee (date: 17.05.2022, and approval number: 871316). Written informed consent was obtained from parents or patients as appropriate.

Study Design

Patients treated in a tertiary pediatric rheumatology department between January 2020 and 2023 were included in the study. All patients met the diagnosis of ERA according to the International League of Associations for Rheumatology (ILAR) criteria. According to the ILAR criteria, ERA is defined as arthritis and enthesitis of ≥6 weeks' duration in children aged <16 years, or arthritis or enthesitis plus two of the following: sacroiliac tenderness or inflammatory spinal pain, HLA-B27 positivity, onset of arthritis in boys aged more than 6 years, anterior uveitis associated with pain, redness, or photophobia, and family history of HLA-B27-associated disease. Psoriasis or a history of psoriasis in the patient or a first-degree relative, the presence of IgM RF on at least two occasions at least 3 months apart, systemic JIA findings in the patient, and a follow-up period of less than 6 months were exclusion criteria (2).

The patients were followed up in the outpatient clinic at 3-month intervals. Juvenile Spondyloarthritis Disease Activity Index scores, clinical findings, laboratory parameters, and treatments were noted at each visit.

Enthesitis was defined as localized tenderness at the enthese points or the demonstration of inflammation of the enthesal sites of the respective extremities demonstrated by ultrasonography.

Axial ERA was diagnosed if the patient met the Assessment of SpondyloArthritis International Society criteria. Axial involvement includes the following characteristic features: presence of inflammatory back pain for more than 3 months, detection of sacroiliitis on imaging, and one additional spondylarthropathy feature (11).

The items of JSpADA were as follows: (1) active joint count (0 joint=0 points, ≤2 joints=0.5 points, >2 joints=1 point), (2) active enthesitis number (0 entheses=0 points, ≤2 entheses=0.5 points, >2 entheses=1 point), (3) patient global assessment of well-being (0=0 points, <5=0.5 points, ≥5=1 point), (4) ESR or CRP related to SpA activity (normal=0, ≤2 times normal=0.5 points, >2 times normal=1 point), (5) morning stiffness >15 min (present=1 point), (6) clinical sacroiliitis (present=1 point), (7) uveitis (present=1 point), (8) modified Schober test (abnormal=1 point). The range of scores is between 0 and 8, with higher scores indicating more active disease. There are still no validated cut-off values for JSpADA (5,6,8).

Patients were categorized into three groups according to the type of treatment received. Group 1 included patients who received only conventional DMARDs; Group 2 consisted of patients who received biological drugs; and cases in Group 3 required DMARD and biological combination therapy during the disease course.

Statistical Analysis

Data analysis was performed using IBM SPSS (IBM Corp., Armonk, NY) version 26. The distribution of normality was evaluated using the Shapiro-Wilk test. Descriptive statistics are defined for numerical variables as mean and SD if normal distributed and median and interquartile range (IQR) if non-normal distributed. Frequency and percentages were used for categorical variables. Comparisons between groups were made by the Student's t-test for normally distributed numerical variables, the Mann-Whitney U test for non-normally distributed numerical variables, and the χ^2 or Fisher's exact test for categorical data. A statistically significant difference is considered if $p \leq 0.05$.

Results

Demographics Features

In this study, the data of 66 patients with ERA was retrospectively analyzed. Five patients with a follow-up period of <6 months were excluded. The remaining 61 cases were enrolled in the study and grouped according to the treatments prescribed (Figure 1).

The study cohort included 12 (19.6%) female and 49 (80.3%) male patients. The median duration of illness of patients in group 1 who received only DMARDs was significantly shorter than that of patients in groups 2 and 3. Eleven patients (18%) had a family history of ankylosing spondylitis. Table 1 summarizes the demographic features of the cohort.

Clinical Findings

When the findings of the systems questioned in the routine visits were examined, morning stiffness (33, 54%), heel pain (31, 51%), and hip pain (25, 41%) were the most common complaints. At disease onset, peripheral arthritis and enthesitis were in 35 (57%) and 31 (51%) subjects, respectively. At the time of diagnosis, 43 (70.4%) patients presented with peripheral involvement, and 27 (44.2%) had isolated peripheral involvement. Sacroiliitis was in 15 (24.5%) patients. Heel pain was significantly more common in group 1 than in the other groups, and sacroiliitis was seen more frequently in group 3 among the three groups. Clinical features at disease onset are shown in Table 2.

Treatment

Nonsteroidal anti-inflammatory drugs were prescribed as the first-line treatment in almost half of the patients. Sulfasalazine (n=37, 61%) was the most commonly preferred conventional DMARD for the groups, and methotrexate (n=24, 39%) was the second most common DMARD choice. In the whole cohort, sulfasalazine was the most widely used concomitant DMARD for biological therapy. The median duration of receiving DMARDs was 6 (IQR: 4-24) months.

Biologic DMARDs were prescribed to 22 (36%) patients with axial involvement and 5 (8.1%) patients with peripheral involvement. The two main biologics preferred were etanercept (22; 36%) and adalimumab (5; 8.1%). Adalimumab and etanercept were prescribed at similar rates for peripheral and axial involvement.

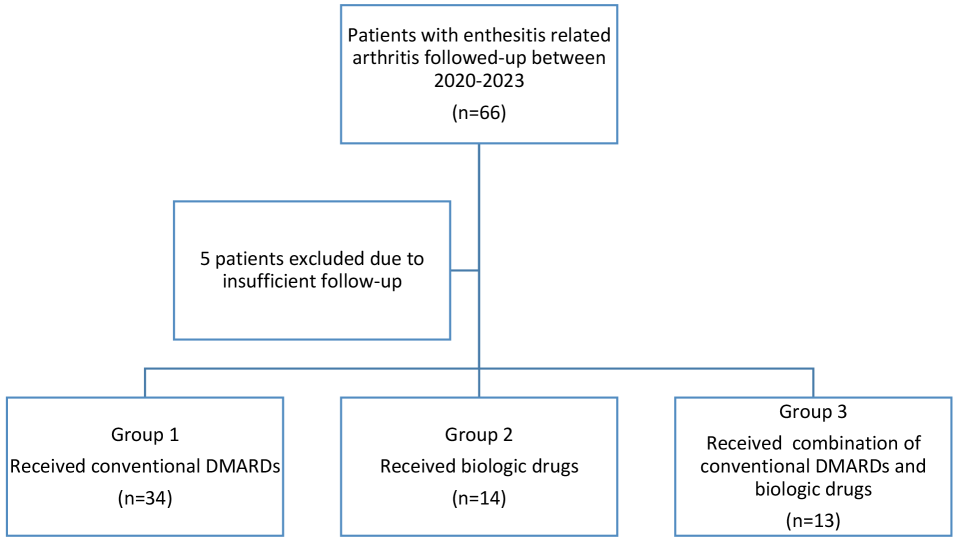

Figure 1. Study population

Table 1. Demographics of cohort (n=61)

Features	Group 1 (n=34)	Group 2 (n=14)	Group 3 (n=13)	p-value*
Gender (male), n, %	27 (73.5%)	10 (71.4%)	12 (92%)	0.3
Age, median (IQR 25-75), years	16 (11-17)	15 (10-12)	15 (11-18)	0.09
Age of onset of disease, median (IQR 25-75), years	11 (10-15)	8 (7-14)	9 (7.5-12)	0.2
Duration of illness, median (IQR 25-75), months	10 (8-15)	11.5 (9-22)	12.5 (10-22.5)	0.001*
Rheumatologic disease history in family n, %	5 (8.1%)	3 (21.4%)	3 (23%)	0.07

*p<0.05 is considered significant Mann-Whitney U test, IQR: Interquartile range

Comparison of the Groups

A comparison of the three groups in terms of JSpADA indexes revealed no difference in JSpADA (p=0.27) at the time of disease onset. At the sixth month and first year evaluations, JSpADA scores showed significant improvement for groups 1 and 2 (p=0.02 and p=0.04). During the disease course, there was no significant reduction in JSpADA values in the 3rd group (p=0.8). Juvenile Spondyloarthritis Disease Activity Index values are summarized in Table 3 for three groups at disease onset: 6 months, first year, and last visit.

Discussion

In this study, the efficacy of treatments used in ERA on clinical outcomes was examined using the JSpADA index. Our results revealed that patients who received a combination of biologics and conventional DMARDs had more severe disease, more frequent axial involvement, and higher activity indexes. Furthermore, this study shows that the JSpADA index is a practical and convenient tool for the follow-up of ERA patients.

Methotrexate is the most commonly prescribed DMARD for children with JIA (12,13). However, it has a limited role for treating enthesitis, sacroiliitis, and axial involvement of the ERA subtype (7) and is usually prescribed for peripheral involvement of the disease. Among conventional DMARDs, sulfasalazine is the most commonly recommended onegin axial ERA. Kısaarslan et al. (14) performed a study evaluating the response to conventional DMARDs in 52 patients with ERA. Twenty-seven patients (52%) achieved remission with DMARDs, whereas 25 (48%) patients could not achieve. Methotrexate and sulfasalazine were prescribed in 41 (78.8%) and 33 (63.5%) patients, respectively. In their cohort, the JSpADA score at disease onset had a mean value of 3.49±1.09 (1.5-5.5). They reported that the absence of factors affecting the duration of DMARD application showed that DMARDs might still be applied as the first line of treatment. Consistent with this study, the first choice for ERA treatment in our cohort was conventional DMARDs, both as monotherapy and along with biologics. However, in our study, sulfasalazine was preferred twice as frequently as methotrexate, and the scores were lower at the onset of the disease. The reason why methotrexate use was low despite the higher peripheral involvement in our study is that DMARD selection may vary depending on the clinical experience of

Table 2. Clinical manifestations of groups at the disease onset

Characteristic	Group 1 (n=34)	Group 2 (n=14)	Group 3 (n=13)	p-value*
Hip pain n, %	11 (32%)	6 (42.8%)	8 (61.5%)	0.8
Inflammatory back pain n, %	10 (29.4%)	5 (35.7%)	5 (38.4%)	0.3
Heel pain n, %	24 (70.5%)	4 (28.8%)	3 (23%)	0.03*
Morning stiffness ≥15 minutes n, %	20 (59%)	6 (42.8%)	7 (53.8%)	0.06
Arthritis n, %	22 (64.7%)	8 (57.1%)	5 (38.4%)	0.8
Enthesitis n, %	21 (61.7%)	6 (42.8%)	4 (30.7%)	0.8
Sacroiliitis n, %	6 (17.6%)	3 (21.4%)	6 (46%)	0.01*
Uveitis n, %	0	0	0	
JSpADA, median (min-max)	2 (2-3)	2.5 (2-3)	3.5 (2.5-5)	0.27
HLA-B27 positivity n, %	14 (41.1%)	5 (35.7%)	5 (48.4%)	0.08
Increasing in acute phase reactants n, %	18 (52.9%)	6 (42.8%)	7 (53.8%)	0.08
MRI findings n, % Peripheral arthritis Peripheral arthritis and sacroiliitis Sacroiliitis	 20 (58.8%) 4 (11.7%) 4 (11.7%)	 4 (28.5%) 2 (14.2%) 2 (14.2%)	 3 (23%) 1 (7.7%) 5 (38.4%)	 0.7 0.9 0.7

*p<0.05 is considered significant- Pearson X^2 test, JSpADA: The Juvenile Spondyloarthritis Disease Activity Index, HLA: Human leukocyte antigen, MRI: Magnetic resonance imaging, min-max: Minimum-maximum

Table 3. Comparison of disease activity indexes among groups

JSpADA, median (min-max)	Group 1 (n=34)	Group 2 (n=14)	Group 3 (n=13)	p-value*
Disease onset	2 (2-3)	2.5 (2-3)	3.5 (2.5-5)	0.27
6-month follow-up	0.5 (0-1)	0.5 (0-2)	2.5 (1-3)	0.2
12-month follow-up	0 (0-1)	0.5 (0-1.5)	1.5 (1-2)	0.1
Last visit	0 (0-1)	0 (0-1)	1.5 (1-2)	0.1

*By Mann-Whitney U test and p<0.05 is considered significant, JSpADA: The Juvenile Spondyloarthritis Disease Activity Index, min-max: Minimum-maximum

the centers and the course of the disease. In this respect, intermittent recording of JSpADA scores during follow-up visits can be considered for managing the disease and deciding whether a second-line medication such as biologics is needed. Additionally, clinicians caring for adult patients with spondyloarthropathy claim that biologics can be the initial therapy for adults in many cases, whereas traditional DMARDs are still the first-line treatment option for patients with ERA.

In 2018, JSpADA was prospectively validated in 127 children with ERA (6). Researchers also assessed the performance of adult SpA scores. They pointed out that exclusion of back mobility from JSpADA may increase its applicability, and adult scores, including Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Ankylosing Spondylitis Disease Activity Score-ESR, showed good construct validity and good correlation with JSpADA. The results of this study provide the opportunity to use the same score in the future to follow these patients into adulthood, thus eliminating the need to switch to separate adult scores. Although our study did not make a comparison with adult scores, the fact that the scores are higher in cases requiring biological drugs during clinical follow-up suggests that JSpADA is effective in indicating the severity of the disease.

In children with ERA, axial involvement, including the hip and sacroiliac joint, may require more aggressive treatment than peripheral involvement. Because the presence of hip arthritis and sacroiliitis at disease onset has poorer prognoses, decreased clinical remission rates and thus increased biological drug requirements have been reported in previous studies (15-17). In this context, TNF-α inhibitors can significantly improve the clinical manifestations of axial ERA (15,18). However, no significant difference in long-term follow-up was detected in patients who initially had high JSpADA scores (19). A recent study by Shipa et al. investigated the drug survival of adalimumab and etanercept (and their biosimilars) in biologic-naïve patients with ERA (20). They assessed disease activity using BASDAI and JADAS-CRP. Following an initial positive primary response, continuing methotrexate with adalimumab was associated with the longest drug survival compared with adalimumab monotherapy or etanercept-based regimens. In their study, axialERA was associated with poorer drug survival, consistent with our study. They reported that elevated baseline CRP and axial disease were associated with an unfavorable initial response to TNFi, whereas patients with concomitant methotrexate were more likely to show an initial response to TNFi. In our results, patients treated with monotherapy had low JSpADA levels at disease onset, whereas combination therapy was preferred in those with high scores. There was improvement in the scores of all three groups during follow-up, but the most significant improvement was observed in groups 1 and 2. These results suggest that having low disease activity at the onset of the disease and the use of DMARDs mono- or combination therapy may facilitate disease management. A study by Zhang et al. (15) showed that anti-TNF therapy was effective in children with ERA after 18 months of diagnosis. They compared magnetic resonance imaging (MRI) and clinical manifestations of joint inflammation in children before and after TNF-α inhibition and reported significant improvement ($p<0.013$). They also speculated that children with ERA, who have no characteristic symptoms of the disease, might show inflammatory reactions during MRI re-examination in the subclinical affected joints. In our study, comparisons of the three groups revealed that patients in groups 2 and 3 had more frequent axial involvement and thus required biological drugs. The JSpADA scores of these two groups were also higher than those of group 1. Comparable with previous studies (13,21-23), cases in our research with active disease scores during the follow-up had more sacroilities and required more frequent biological drugs. Eventually, axial ERA is a risk factor for poor prognosis, the need for combination therapy, and high activity indexes. MRI can also be considered in the follow-up of cases with severe and refractory disease (24).

Study Limitations

The retrospective and single-center design are the main limitations of our study. Because the patients are from a reference center for pediatric rheumatology, the possibility of including cases with severe and active disease seems to be more frequent. Despite these limitations, this study demonstrates the practicality, importance, and value of JSPADA in evaluating ERA treatment options and managing the disease with sufficient patients for a single center.

Conclusion

Evaluation of treatment response and reaching and maintaining inactive disease in ERA patients can be more challenging than in other JIA categories. Because the clinical picture of ERA is highly variable, treatment strategies may vary in parallel, and it becomes difficult to standardize. In addition to JSpADA at the time of diagnosis, high JSpADA values that do not decrease during follow-up may indicate the severity of the disease and the need for more aggressive treatment. Multicenter studies are needed to reveal the use of disease activity measures such as JSpADA developed for children in the follow-up of ERA patients on treatment decisions.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Istanbul University, Istanbul Faculty of Medicine Clinical Research Ethical Committee (date: 17.05.2022, and approval number: 871316).

Informed Consent: Written informed consent was obtained from parents or patients as appropriate.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Concept: F.G.D., O.A., V.G., N.A.A., Design: F.G.D., O.A., V.G., N.A.A., Data Collection or Processing: F.G.D., O.A., V.G., N.A.A., Analysis or Interpretation: F.G.D., O.A., V.G., N.A.A., Literature Search: F.G.D., O.A., V.G., N.A.A., Writing: F.G.D., O.A., V.G., N.A.A.

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References

1. Naveen R, Guleria S, Aggarwal A. Recent updates in enthesitis-related arthritis. Rheumatol Int 2023;43:409-20.
2. Petty RE, Southwood TR, Manners P, et al. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. J Rheumatol 2004;31:390-2.
3. Chan OM, Lai BM, Leung AS, Leung TF, Ho AC. High prevalence of sacroiliitis and early structural changes in the sacroiliac joint in children with enthesitis-related arthritis: findings from a tertiary centre in Hong Kong. Pediatr Rheumatol Online J 2023;21:45.
4. Ferjani Hanene L, Ben Ammar L, Maatallah K, et al. Enthesitis-related arthritis and spondylarthritis: the same disease or disparate entities? Expert Rev Clin Immunol 2022;18:93-9.
5. Weiss PF, Colbert RA, Xiao R, et al. Development and retrospective validation of the juvenile spondyloarthritis disease activity index. Arthritis Care Res (Hoboken) 2014;66:1775-82.
6. Zanwar A, Phatak S, Aggarwal A. Prospective validation of the Juvenile Spondyloarthritis Disease Activity Index in children with enthesitis-related arthritis. Rheumatology (Oxford) 2018;57:2167-71.
7. Srinivasalu H, Treemarcki EB, Rumsey DG, Weiss PF, Colbert RA; CARRA Spondyloarthritis Workgroup and the CARRA Registry Investigators. Modified Juvenile Spondyloarthritis Disease Activity Index in the Childhood Arthritis and Rheumatology Research Alliance (CARRA) Registry. J Rheumatol 2023;50:532-7.
8. Polat MC, Ekici Tekin Z, Çelikel E, et al. The Juvenile Spondyloarthritis Disease Activity Index Is a Useful Tool in Enthesitis-Related Arthritis: Real-Life Data. J Clin Rheumatol 2023;29:309-15.
9. Yıldız M, Haşlak F, Adroviç A, Şahin S, Barut K, Kasapçopur Ö. Juvenile spondyloartropathies. Eur J Rheumatol 2022;9:42-9.
10. Yildiz M, Haslak F, Adrovic A, Sahin S, Barut K, Kasapcopur O. Comment on: The conundrum of juvenile spondyloarthritis classification: Many names for a single disease? Lesson learned from an instructive clinical case. Int J Rheum Dis 2020;23:1430-1.
11. Rudwaleit M, van der Heijde D, Landewé R, 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.
12. Weiss PF, Beukelman T, Schanberg LE, Kimura Y, Colbert RA; CARRA Registry Investigators. 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.
13. Ramanathan A, Srinivasalu H, Colbert RA. Update on juvenile spondyloarthritis. Rheum Dis Clin North Am 2013;39:767-88.
14. Kısaarslan AP, Sözeri B, Gündüz Z, Zararsız G, Poyrazoğlu H, Düşünsel R. Evaluation of factors affecting the duration of disease-modifying anti-rheumatic drugs application in patients with enthesitis-related arthritis. Eur J Rheumatol 2019;6:130-5.
15. Zhang T, Huang S, Guo Y, et al. Effectiveness of tumor necrosis factor inhibitors in children with enthesitis-related arthritis: a single-center retrospective analysis. Front Pediatr 2023;11:1122233.
16. Ravichandran N, Guleria S, Mohindra N, Aggarwal A. Predictors of long-term functional outcomes of juvenile idiopathic arthritis-enthesitis-related arthritis: a single centre experience. Rheumatology (Oxford) 2023;62:3110-6.
17. Baer J, Klotsche J, Foeldvari I. Secukinumab in the treatment for patients with juvenile enthesitis related arthritis non-responsive to anti-TNF treatment according the Juvenile Spondyloarthritis Disease Activity Index. Clin Exp Rheumatol 2022;40:620-4.
18. Braun J, Baraliakos X, Heldmann F, Kiltz U. Tumor necrosis factor alpha antagonists in the treatment of axial spondyloarthritis. Expert Opin Investig Drugs 2014;23:647-59.
19. Vilaiyuk S, Lerkvaleekul B, Jino J, Charuvanij S, Book YX, Arkachaisri T. Comparison of the outcomes between early and late anti-tumor necrosis factor therapy in patients with enthesitis-related subcategory of juvenile idiopathic arthritis: a multi-center study in Southeast Asia. Expert Opin Biol Ther 2022;22:1323-32.
20. Shipa MR, Heyer N, Mansoor R, et al. Adalimumab or etanercept as first line biologic therapy in enthesitis related arthritis (ERA) - a drug-survival single centre study spanning 10 years. Semin Arthritis Rheum 2022;55:152038.
21. Gmuca S, Xiao R, Brandon TG, et al. Multicenter inception cohort of enthesitis-related arthritis: variation in disease

characteristics and treatment approaches. Arthritis Res Ther 2017;19:84.

22. Goirand M, Breton S, Chevallier F, et al. Clinical features of children with enthesitis-related juvenile idiopathic arthritis / juvenile spondyloarthritis followed in a French tertiary care pediatric rheumatology centre. Pediatr Rheumatol Online J 2018;16:21.
23. Horneff G, Foeldvari I, Minden K, et al. Efficacy and safety of etanercept in patients with the enthesitis-related arthritis category of juvenile idiopathic arthritis: results from a phase III randomized, double-blind study. Arthritis Rheumatol 2015;67:2240-9.
24. Lambert RG, Bakker PA, van der Heijde D, et al. Defining active sacroiliitis on MRI for classification of axial spondyloarthritis: update by the ASAS MRI working group. Ann Rheum Dis 2016;75:1958-63.