Retrospective Evaluation of Patients with Systemic Juvenile Idiopathic Arthritis: A Single-centre Experience

Retrospektive Bewertung von Patienten mit systemischer juveniler idiopathischer Arthritis: eine Single-Center-Studie

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ABSTRACT

Objective Systemic juvenile idiopathic arthritis is one of the subtypes of juvenile idiopathic arthritis. This type of disease accounts for approximately 10–20 % of all cases of juvenile idiopathic arthritis. It typically affects both sexes equally and is usually present in children under 5 years. This study aimed to evaluate the demographic and clinical features of patients who were followed up for the diagnosis of sJIA in a single centre, the treatments they received, the responses to the treatment and the course of the disease.

Methods All patients with systemic juvenile idiopathic arthritis who were evaluated at Dr Sami Ulus Maternity Child Health and Diseases Training and Research Hospital, Department of Paediatric Rheumatology, between January 2017 and January 2020 were included in this study. Descriptive features, clinical information, medications, treatment responses and long-term prognosis of patients were evaluated retrospectively.

Results The study included 40 patients. 60 % (n = 24) of the patients were female and 40 % (n = 16) were male. The diagnosis age of the patients was 7.77 ± 4.82 years and the patients were followed up for an average of 48 ± 41 months. All of the patients had fever at the time of diagnosis. The 3 most common clinical signs after fever were arthralgia, hepatomegaly and lymphadenopathy (65, 55 and 50 %, respectively). Ten patients (32.5 %) had macrophage activation syndrome at admission. No significant difference was detected between the groups with and without macrophage activation syndrome concerning age, gender and clinical findings. Leukocyte, haemoglobin, platelet and erythrocyte sedimentation rates were significantly lower in the macrophage activation syndrome group compared with the other group, and ferritin was significantly higher. The C-reactive protein value was higher in the group without macrophage activation syndrome, but the difference was not statistically significant. While all patients received corticosteroid therapy as the initial therapy, 87.5 % of these patients were administered pulse methylprednisolone therapy. In the follow-up, 21 patients (52.5 %) needed biological treatment. Twenty-seven patients (67.5 %) had a monocyclic course, 3 patients (7.5 %) had a polycyclic course and 10 patients (25 %) had a persistent polyarticular course.

Conclusion Early diagnosis and treatment of systemic juvenile idiopathic arthritis are important because of the risk of develo-

ping macrophage activation syndrome – the most lethal complication. In our evaluation, it was seen that laboratory parameters could provide more guidance than clinical findings. Although steroids are the cornerstone of therapy, biological agents are effective in patients who are not responsive to steroid therapy.

ZUSAMMENFASSUNG

Hintergrund Die systemische juvenile idiopathische Arthritis ist ein Subtyp der juvenilen idiopathischen Arthritis. Auf diesen Krankheitstyp entfallen etwa 10 bis 20 % aller Fälle von juveniler idiopathischer Arthritis. Er betrifft üblicherweise beide Geschlechter gleichermaßen und tritt in der Regel bei Kindern unter fünf Jahren auf. Ziel dieser Studie war die Bewertung der demografischen und klinischen Merkmale der in einem einzigen klinischen Zentrum mit sJIA diagnostizierten Patienten sowie deren Behandlungen, Reaktionen auf die Behandlung und Krankheitsverlauf.

Methoden Alle zwischen Januar 2017 und Januar 2020 in der Abteilung für pädiatrische Rheumatologie des Dr.-Sami-Ulus-Kinderkrankenhauses untersuchten Patienten mit systemischer juveniler idiopathischer Arthritis wurden in diese Studie eingeschlossen. Deskriptive Merkmale, klinische Informationen, Medikamente, Ansprechen auf die Behandlung und die Langzeitprognose der Patienten wurden retrospektiv ausgewertet.

Ergebnisse In diese Studie wurden 40 Patienten eingeschlossen. 60 % (n = 24) der Patienten waren weiblich und 40 % (n = 16) waren männlich. Das Diagnosealter der Patienten lag bei 7,77 ± 4,82 Jahren, und die Patienten wurden durchschnittlich 48 ± 41 Monate nachbeobachtet. Alle Patienten hatten zum Zeitpunkt der Diagnose Fieber. Die drei häufigsten klinischen Symptome nach Fieber waren Arthralgie (65 %), Hepatomegalie (55 %) und Lymphadenopathie (50 %). Zehn der Patienten (32,5 %) hatten bei Aufnahme ein Makrophagenaktivierungssyndrom. Es wurde kein signifikanter Unterschied zwischen den Gruppen mit und ohne Makrophagenaktivierungssyndrom in Bezug auf Alter und Geschlecht sowie klinische Befunde festgestellt. Die Erythrozytensedimentationrate von Leukozyten, Hämoglobin, Blutplättchen und Erythrozyten war in der MAS-Gruppe im Vergleich zur anderen Gruppe signifikant niedriger und der Ferritinspiegel war signifikant höher. Die Konzentration des C-reaktiven Proteins war in der Gruppe ohne Makrophagenaktivierungssyndrom höher, doch diese Erhöhung war statistisch nicht signifikant. Laborparameter scheinen wichtiger zu sein als klinische Befunde. Alle Patienten erhielten als Ersttherapie eine Kortikosteroidtherapie, 87,5 % von ihnen wurde eine Methylprednisolon-Stoßtherapie verabreicht. In der Nachuntersuchung benötigten 21 Patienten (52,5 %) eine biologische Behandlung. 27 Patienten (67,5 %) zeigten einen monozyklischen, 3 Patienten (7,5 %) einen polyzyklischen und 10 Patienten (25 %) einen persistierenden polyartikulären Verlauf.

Schlussfolgerung Eine frühzeitige Diagnose und Behandlung der systemischen juvenilen idiopathischen Arthritis ist wichtig, da das Risiko besteht, ein Makrophagenaktivierungssyndrom zu entwickeln – die tödlichste Komplikation. In unserer Bewertung wurde festgestellt, dass Laborparameter richtungsweisender sein können als klinische Befunde. Obwohl Steroide den Eckpfeiler der Therapie darstellen, sind biologische Wirkstoffe bei Patienten wirksam, die nicht auf eine Steroidtherapie ansprechen.

Introduction

Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatic disease in childhood. Systemic juvenile idiopathic arthritis (sJIA) has different characteristics from other JIA subtypes. It is considered as an autoinflammatory disease. Patients are classified as sJIA according to International League of Associations for (ILAR) criteria with the presence of a documented quotidian fever of at least 2 weeks duration and arthritis, and one of the following: typical rash, generalized lymphadenopathy, hepatomegaly or splenomegaly, or serositis[1]. According to Pediatric Rheumatology International Trials Organization 2019 reccommendations sJIA may be diagnosed even without presence of arthritis if a typical rash and additional 2 minor criteria are observed. Minor criteria are: 1)generalized lymph node enlargement and/or hepatomegaly and/or splenomegaly; 2) serositis; 3) arthralgia lasting 2 weeks or longer (in the absence of arthritis); and 4) leukocytosis (≥ 15,000/mm3) with neutrophilia[2]. The diagnosis requires adequate exclusion of infectious, oncologic, autoimmune, and autoinflammatory diseases.

Children with sJIA may have a monocyclic, relapsing or chronic progressive course. A significant proportion of patients experience detrimental effects, such as joint destruction and deformity, local growth abnormalities and growth retardation, osteoporosis, limitation in activities of daily living and impaired psychological health. According to the 2013 update of the 2011 American College of Rheumatology recommendations for the treatment of sJIA, glucocorticoids are initial treatment options. In some patients, disease modifying agents and biological agents are brought up to reduce steroid doses for the side effects that may arise from steroid therapy[3]. Methotrexate is the most frequently used disease-modifying anti-rheumatic drug (DMARD), followed by cyclosporine A and leflunomide. Cyclosporine A is more effective in controlling systemic disease in sJIA compared to arthritis[4]. Among the biological agents, especially anakinra, canakinumab and tocilizumab are preferred.

Macrophage activation syndrome (MAS) is a severe complication of sJIA that can appear at the first diagnosis or during disease activation. MAS criteria are determined according to Ravelli criteria as persistent fever and hyperferritinemia (> 684 ng/dL) in patients with a diagnosis of sJIA and any 2 of the following: platelet count < 181 × 109/L, aspartate aminotransferase (AST) > 48 U/L, triglycerides > 156 mg/dL, fibrinogen < 360 mg/dL[5].

This study aimed to evaluate the demographic and clinical features of the patients who were followed up with sJIA diagnosis in a single center. The treatments, responses and disease course were evaluated.

Materials and Methods

Patients who were diagnosed as sJIA, according to criteria defined by ILAR and were admitted for at least one year of follow-up between January 2017 and January 2020 to the Dr Sami Ulus Maternity Child Health and Diseases Training and Research Hospital, Department of Rheumatology. Patients who were followed for less than 1 year were not included in the evaluation in order to better evaluate the course of the disease and its treatment effects. Other subtypes of JIA, patients with follow-up shorter than one year, patients over 16 years of age at diagnosis and underlying other inflammatory conditions were excluded. Patient data obtained retrospectively from medical records included: clinical and demographic data of patients, such as age at diagnosis, gender, symptoms, and findings of physical examinations, at admission and each visit, and laboratory findings, such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) levels, complete blood count (leukocyte, hemoglobin, platelet), ferritin, liver function tests, triglyceride. Disease complications, drug types, duration of treatment, frequency and number of attacks, and response to treatment were evaluated. In this study, 43 sJIA patients were analyzed. Three patients could not be evaluated because they were not regularly followed up. In the presence of fever and rash that lasted for 2 weeks, 14 patients without joint involvement were found to be diagnosed with systemic JIA by excluding other causes. Clinical and laboratory features of the patients with and without MAS were compared.

The course of the disease was evaluated in 3 separate sections (monocyclic, polycyclic and persistent polyarticular). Monocyclic sJIA course is characterized by a single episode of systemic symptoms and arthritis, resolving within 24 months. Polycyclic course has multiple recurrences of active disease alternating with periods of remission. The persistent sJIA is characterized by ongoing active systemic features and arthritis, possibly leading to severe joint deformities[6].

Treatment response has been classified into 3 groups: patients with active disease, remission on medicine (minimal disease activity) and drug-free remission (no usage of any anti-rheumatic drugs during the last 12 months). Disease remission (no disease activity) was defined as lack of fever, rash, serositis, splenomegaly, lymphadenopathy, and arthritis, as well as normal levels of ESR and CRP[7].

Other important disease complications as growth retardation, low bone mineral density (*Z*-score of bone density ≤ −2 of standard deviation), joint damage and prosthesis replacement, drug adverse effects, methotrexate intolerance and severe adverse effects of biological treatment were also recorded.

All the patients' parents provided written informed consent for their children to be included in this study and the study protocol was approved by our hospital ethics committee. (Number 112019/2001)

Statistical analyses

Statistical Package for the Social Sciences (SPSS) 21.0 was used for statistical analysis. In order to determine whether the variables are normally distributed or not, they were examined using visual (histogram, probability graphs) and analytical methods (Kolmogorov-Smirnov).

Descriptive analysis data were expressed as median, minimum and maximum values. The Mann-Whitney U test was used to compare continuous data without normal distribution between the 2 groups. $p < 0.05$ was considered statistically significant.

Results

The mean age of sJIA patients was 7.77 ± 4.82 years and 24 (60 %) of them were girls. Fever was a consistent finding in all patients at first admission. Clinical and demographic features of all patients and comparisons between the with and without MAS were compared for the patients' group are shown in ▶ **Table 1**. There was no significant difference between the groups with and without MAS concerning age and gender, and clinical findings (▶ **Table 1**). The time between the onset of the disease findings and the diagnosis was 15 ± 10 days. Monocyclic course was observed in 27 (67.5 %) of all patients, polycyclic course in 3 (7.5 %) patients and persistent course 10 (25 %) patients.

Clinical and demographic features at admission were compared between patients with and without MAS (▶ **Table 1**). Only 7 patients who had MAS were followed up in the intensive care unit. None of the patients without MAS were followed up in the intensive care unit. Laboratory features of the patients at the time of admission are shown in ▶ **Table 2**. Leukocyte, hemoglobin, platelet and ESR were significantly lower in the MAS group compared to the other group, and ferritin was significantly higher. CRP value was higher in the group without MAS, but it was not statistically significant. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) values were statistically higher in the group with MAS. Renal failure during MAS was developed in one patient requiring renal replacement therapy and creatinine returned to normal values within 2 weeks.

Nonsteroidal anti-inflammatory drugs (NSAIDs), especially naproxen and ibuprofen, were administered to all patients, but none of the patients responded to this treatment. All of the patients were treated with glucocorticoids: 35 (87.5 %) with high dose intravenous pulse methylprednisolone (30 mg/kg/day) and 5 (12.5 %) with prednisolone (2 mg/kg/day). Pulse methylprednisolone treatment was used for 3 consecutive days in 26 patients and 5 days in 9 patients. The steroid intake time of the patients was 152 ± 43 days. In 20 (50 %) patients, methotrexate, a disease-modifying anti-rheumatic drug was used in addition to steroid therapy. Two of these patients were started on leflunomide treatment due to the subsequent methotrexate intolerance. No side effects were observed with leflunomide treatment. Plasmapheresis was performed in 8 patients (20 %) and all of these patients were administered intravenous immunoglobulin (IVIG) treatment. Biological agents (anakinra, canakinumab, tocilizumab) were required in 21 patients (52.5 %). Most of the patients who received biological therapy were in the patient group without a diagnosis of MAS , but this was not statistically significant ($p = 0.256$). Anti-IL-1 was administered to 13 patients (32.5 %) and anti-IL-6 was administered to 8 patients (20 %) as biological agents. Only one patient was administered cyclosporine treatment. The patient with MAS did not benefit from this treatment. The treatments given to the patients are shown in ▶ **Table 3**.

▶ **Table 1** Demographic and clinical characteristics of the patients at presentations and comparison of the patients with and without MAS.

	All patients n = 40 (%)	Patients without MAS n = 30 (75%)	Patients with MAS n = 10 (25%)	p
Gender (Female)	24 (60%)	17 (42.5)	7 (17.5%)	0.46
Age, years, mean ± SD	12.41 ± 5.23	13.027 ± 5.16	9.67 ± 6.07	0.09
Age at diagnosis, years, mean ± SD	7.77 ± 4.82	8.2 ± 4.8	6.5 ± 4.8	0.34
Disease duration, months, mean ± SD	65.15 ± 30.59	71.13 ± 39.8	47.2 ± 29.8	0.47
Clinical features n, (%)				
Typical fever	40 (100)	30 (100)	10 (100)	< 0.001
Typical rash	26 (65)	19 (47.5)	7 (17.5)	0.711
Arthralgia	26 (65)	22 (55)	4 (10)	0.058
Arthritis	17 (42.5)	15 (37.5)	2 (5)	0.101
Serozitis	6 (15)	2 (5)	4 (10)	0.620
Lymphadenopathy	20 (50)	15 (37.5)	5 (12.5)	0.1
Hepatosplenomegaly	22 (55)	14 (35)	8 (20)	0.069
Disease courses				
Monocyclic	27 (67.5)	19 (47.5)	8 (20)	0.256
Polycyclic	3 (7.5)	2 (5)	1 (2.5)	
Persistent	10 (25)	9 (22.5)	1 (2.5)	

▶ **Table 2** Laboratory features of the patients at the time of admission.

	All patients	Patients without MAS at the time of diagnosis n = 30 (75%)	Patients with MAS at the time of diagnosis n = 10 (25%)	p
WBC (×10³ mm³) (mean ± SD)	13.900 (13.300–38.660)	16.935 (2.060–38.660)	8.340 (1.330–27.800)	0.010
Hb[a] (g/dL) (mean ± SD)	9.9 (7–15.5)	10.05 (7–13)	8.55 (7.5–10.5)	0.002
Plt(×10³ mm³) (mean ± SD)	444.000 (57000–1010000)	518.000 (139.000–1.010.000)	112.500 (57.000–428.000)	< 0.001
ESR[a] (mm/hr) (mean ± SD)	89.5 (14–135)	98.5 (41–135)	27 (14–60)	< 0.001
CRP[a] (mg/L) (mean ± SD)	123 (26–258)	131.5 (37–258)	103 (26–205)	0.142
ALT[a] (mean ± SD)	37 (7–1730)	16 (7–110)	191 (21–1730)	< 0.001
AST[a] (mean ± SD)	56 (17–2458)	39.5 (17–386)	587 (107–2458)	< 0.001
Fibrinogen (mean ± SD)	323 (44–867)	533 (112–867)	105 (44–201)	< 0.001
Trigliserid (mean ± SD)	197 (55–2018)	144 (62–460)	594 (164–2018)	< 0.001
Ferritin (mean ± SD)	540 (64–220000)	270 (64–7350)	30225 (4347–220000)	< 0.001

[*] White blood count (WBC: 5000–10000 / mm³), Hemoglobin (Hb:10.9–15 g/dl), Platelet count (PLT: 150000–400000 mm³), ESR(Sedimentation rate: 0–20 mm/hour), C-reactive protein(CRP: 0–5 mg/dl), Alanine aminotransferase (ALT: 0–35 units/L), Aspartat-aminotransferase (AST: 0–33 units/L), Fibrinogen (200–400 mg/dL), Trigliserid(150–199 mg/dL), Ferritin(20–250 ng/mL).

In 27 patients (67.5 %) whose steroid treatment was discontinued within 3–6 months, the disease was monocyclic and did not recur. Three patients (7.5 %) showed polycyclic and 10 patients (25 %) showed persistent course. Four MAS attacks were observed in a patient with a polycyclic course. 15 (37.5 %) of the patients were in remission without any treatment, 25 patients were in remission with the drug. There were no patients with active disease who were followed up with medication.

During the follow-up, many disease and drug-related complications were noted out of the 40 patients who suffered from some complication either due to the disease itself and/or drugs used. Recurrent infection due to biological agents was not observed in any patient. In only one sJIA patient who received canakinumab treatment (she was in remission with the drug), pulmonary tuberculosis developed in the first year of the treatment and treatment was started for tuberculosis. Etanercept was started as an anti-tumor

▶ **Table 3** Initial treatments of the sJIA patients.

Treatment, n (%)	All patients n = (%)	Patients without MAS at the time of diagnosis n = 30 (75%)	Patients with MAS at the time of diagnosis n = 10 (25%)	p
High dose methylprednisolone	35 (87.5)	25 (62.5)	10 (25)	0.306
Corticosteroid 2 mg/kg/day	5 (12.5)	5 (12.5)	0 (0)	0.217
Methotrexate	20 (50)	17 (42.5)	3 (7.5)	0.273
IVIG + plasmaphresis	8 (20)	0 (0)	8 (20)	<0.001
Biological therapy	21 (52.5)	15 (37.5)	6 (15)	0.42
Anti-IL1	13 (32.5)	8 (20)	5 (12.5)	0.24
Anti-IL6	8 (20)	7 (17.5)	1 (2.5)	0.653

necrosis factor (anti-TNF) treatment in 2 patients, but then it was switched to tocilizumab treatment because because no response was observed with this treatment in these 2 patients. Tocilizumab improved joint involvement in these patients. Three patients had growth retardation; 5 patients had osteoporosis in bone mineral densitometry. There was no need for additional treatment other than vitamin D and calcium treatment. No cases of malignancy or death were reported.

Discussion

Systemic JIA is a polygenic autoinflammatory disease that differs in many respects from other JIA subtypes. The clinical features include fever, rash, arthralgia and arthritis, myalgia, lymphadenopathy, hepatomegaly, splenomegaly, and serositis. Arthritis may be absent at onset and appear during the disease course[8]. It is important to evaluate the musculoskeletal examination in detail in patients with resistant fever and rash in suspected systemic JIA. As seen in our systemic JIA patients, 42.5% of all cases have arthritis, while 65% have arthralgia.

In a retrospective analysis by Mansi et al., in their patient cohort of 53 patients, 9 (17%) patients had a monocyclic course, 31 (58.5%) had an intermittent course and 13 (24.5%), a persistent course[9]. Lomater et al. reported 80 children with sJIA and 11.2% of the patients had a monocyclic course , 33.7% had polycyclic and 55.0% had persistent disease course before the era of biologics[10]. In Barut's cohort, 31.5% of patients had monocyclic, 13.7% of patients polycyclic and 54.8% of patients had a persistent clinical course[11]. In Çakan's cohort, 45.2% had monocyclic, 30.1% had polycyclic and 24.5% had persistent disease course[12]. Monocyclic course is higher in our patient population. 67.5% of our patients showed a monocyclic course. Our percentage of cases with monocyclic progress is closer to the numbers reported from outside our country. Polycyclic course is the least common course of our sJIA patients.

Çakan et al. compared patients with and without MAS at the time of systemic JIA diagnosis. Patients who developed MAS had higher ferritin and lower fibrinogen values than patients without MAS. In our patient cohort, as in the cohort of Çakan et al., girls were in the majority(60%). While the course of MAS in our patients is 25% compatible with the literature, in the cohort of Çakan et al., this rate is 33.9% [12].

Sağ et al. reported that serositis and HSM findings were more common in patients with MAS in sJIA; no significant difference was found in the findings of rash, arthralgia, arthritis and lymphadenopathy in these patients[13]. In our patient group, no difference was found between all these clinical features of the patients.

Non-steroid anti-inflammatory drugs, corticosteroids and DMARDs are the first-line treatments in sJIA. Sura et al. have demonstrated clinical inactive disease in 25.5% of the sJIA patients with NSAIDs[14]. No response to NSAIDs was obtained in any of our patients. The effects of DMARDs, such as methotrexate, cyclosporin and leflunomidine, are mild. Biological agents are preferable in the treatment of steroid- related side effects and in steroid treatment unresponsiveness. Anti-IL1 treatment is prominent in patients with fever and systemic findings, whereas anti-IL-6 treatment is preferred in patients with more prominent joint findings[15] .

In recent years, there have been positive developments in systemic JIA prognosis due to the increasing use of biological drugs. In the cohort of Sağ et al., 80% of the patients needed biological agents. Half of our patients needed biological agents. The high rate of use of biological agents in this study may be due to their being a pediatric rheumatology center receiving frequent referrals in our country[13]. There is also a case report which Janus kinase (JAK) inhibitors may also be useful in treatment[16]. We have not used JAK inhibitors in any of our sJIA patients.

The number of our patients who have been followed-up without medication is higher than in the literature. It is not known whether the early diagnosis- early treatment of sJIA disease and the biological agents used in maintenance are effective in the course of the monocyclic disease. Biological treatment, which is initiated especially in persistent polyarticular involvement, seems to minimize joint damage. While etanercept has been used with a high success rate of 88% in persistent disease in the past, it has been preferred more rarely in recent years due to its lower success in treatment [16]. Anti-TNF agents were preferred in 2 patients in our cohort. These patients with polyarticular involvement did not respond to this treatment and then tocilizumab treatment was started.

Biological drugs in sJIA appear to be safe in terms of the risk of serious side effects when evaluated in the short term. There was no significant increase in the risk of both hematological and solid malignancies in patients using biological agents. Our cohort of patients treated with tocilizumab and canakinumab did not experience allergic side effects. Side effects such as increased infection

frequency were not observed. Anakinra allergy developed in one patient with MAS, but the maintenance treatment of this patient was performed with canakinumab. No allergic reactions were observed with canakinumab. Growth and developmental delay was observed in 3 of our patients who were treated with a diagnosis of systemic JIA. The effective role of biological agents in the treatment, and shorter duration of steroid therapy may have led to fewer patients with growth and development retardation.

It is evident that our patient population covers the patients evaluated in the last 3 years and the role of newly released biological agents. In 2002, while the risk of irreversible joint damage in the adult age group of JIA was 75 %[17]. In our country, the risk of joint deformities has decreased – due to the increase in the number of pediatric rheumatologists in the last 10 years and the response to the biological agents selected in the treatment.

In our study, MAS was observed in 10 patients (25 %) at the time of the first diagnosis. Two patients had recurrent MAS attacks. While the risk of death from MAS is 8 % in multicenter studies, there was no death due to MAS in our patient population.

The major limitation of our study is the retrospective design with a small sample size from a single medical center.

In conclusion, sJIA is a disease that requires early diagnosis because MAS is the most important and fatal complication. Although steroids have priority in treatment, anti-IL1 and anti-IL6 therapy is also preferred and used effectively in resistant patients. There is not enough information about which biological agent is optimally effective in treatment. Biological therapy should not be delayed in steroid-resistant cases. A better understanding of disease pathogenesis in the future will shed more light on treatment.

Conflict of Interest

The authors declare that they have no conflict of interest.

References

[1] Petty RE, Southwood TR, Manners P et al. International League of Associations for Rheumatology Classification of Juvenile Idiopathic Arthritis: Second Revision, Edmonton, 2001. The Journal of Rheumatology 2004; 31: 2

[2] Martini A, Ravelli A, Avcin T et al. Toward new classification criteria for juvenile idiopathic arthritis: First steps, pediatric rheumatology international trials organization international consensus. Journal of Rheumatology 2019; 46: 190–197. doi:10.3899/jrheum.180168

[3] Ringold S, Weiss PF, Beukelman T et al. 2013 Update of the 2011 American College of Rheumatology Recommendations for the treatment of juvenile idiopathic arthritis: Recommendations for the medical therapy of children with systemic juvenile idiopathic arthritis and tuberculosis screening among c. Arthritis and Rheumatism 2013; 65: 2499–2512. doi:10.1002/art.38092

[4] Bagri NK. Cyclosporine for Systemic Onset Juvenile Idiopathic Arthritis: Current Stand and Future Directions. Indian Journal of Pediatrics 2019; 86: 576–577. doi:10.1007/s12098-019-02985-6

[5] Ravelli A, Minoia F, Davì S et al. 2016 Classification criteria for macrophage activation syndrome complicating systemic juvenile idiopathic arthritis: A European league against Rheumatism/American college of Rheumatology/Paediatric rheumatology international trials organisation collaborat. Annals of the Rheumatic Diseases 2016; 75: 481–489. doi:10.1136/annrheumdis-2015-208982

[6] Singh-Grewal D, Schneider R, Bayer N et al. Predictors of disease course and remission in systemic juvenile idiopathic arthritis: Significance of early clinical and laboratory features. Arthritis and Rheumatism 2006; 54: 1595–1601. doi:10.1002/art.21774

[7] Wallace CA, Giannini EH, Huang B et al. American College of Rheumatology provisional criteria for defining clinical inactive disease in select categories of juvenile idiopathic arthritis. Arthritis Care and Research 2011; 63: 929–936. doi:10.1002/acr.20497

[8] Pardeo M, Bracaglia C, De Benedetti F. Systemic juvenile idiopathic arthritis: New insights into pathogenesis and cytokine directed therapies. Best Practice and Research: Clinical Rheumatology 2017; 31: 505–516. doi:10.1016/j.berh.2018.02.002

[9] Dewoolkar M, Cimaz R, Chickermane PR et al. Course, Outcome and Complications in Children with Systemic Onset Juvenile Idiopathic Arthritis. Indian Journal of Pediatrics 2017; 84: 294–298. doi:10.1007/s12098-017-2293-5

[10] Lomater C, Gerloni V, Gattinara M et al. FFS onset juvenile idiopathic arthritis: a retrospective study of 80 consecutive patients followed for 10 years. JR 2000; 27: 491–496

[11] Barut K, Adrovic A, Sahin S et al. Prognosis, complications and treatment response in systemic juvenile idiopathic arthritis patients: A single-center experience. International Journal of Rheumatic Diseases 2019; 22: 1661–1669. doi:10.1111/1756-185X.13649

[12] Çakan M, Karadağ ŞG, Tanatar A et al. The frequency of macrophage activation syndrome and disease course in systemic juvenile idiopathic arthritis. Modern Rheumatology 2019; 0: 000. doi:10.1080/14397595.2019.1660026

[13] Sağ E, Uzunoğlu B, Bal F et al. Systemic onset juvenile idiopathic arthritis: A single center experience. Turkish Journal of Pediatrics 2019; 61: 852–858. doi:10.24953/turkjped.2019.06.005

[14] Sura A, Failing C, Sturza J et al. Patient characteristics associated with response to NSAID monotherapy in children with systemic juvenile idiopathic arthritis. Pediatric rheumatology online journal 2018; 16: 2. doi:10.1186/s12969-017-0219-4

[15] Tarp S, Amarilyo G, Foeldvari I et al. Efficacy and safety of biological agents for systemic juvenile idiopathic arthritis: A systematic review and meta-analysis of randomized trials. Rheumatology (United Kingdom) 2016; 55: 669–679. doi:10.1093/rheumatology/kev382

[16] Huang Z, Lee PY, Yao X et al. Tofacitinib treatment of refractory systemic juvenile idiopathic arthritis. Pediatrics 2019; 143. doi:10.1542/peds.2018-2845

[17] Packham JC, Hall MA. Long-term follow-up of 246 adults with juvenile idiopathic arthritis: Functional outcome. Rheumatology 2002; 41: 1428–1435. doi:10.1093/rheumatology/41.12.1428