What Has Changed Over the Last Decade in Systemic Juvenile Idiopathic Arthritis?

Sistemik Juvenil İdiyopatik Artritte Son On Yılda Neler Değişti?

Fatma AYDIN[1], Tuba KURT[1], Nilüfer TEKGÖZ[1], Müge SEZER[1], Özge BAŞARAN[1], Nilgun ÇAKAR[2], Banu CELİKEL ACAR[1]

[1]Ankara City Hospital, Department of Pediatrics, Division of Pediatric Rheumatology, Ankara, Turkey
[2]Ankara University School of Medicine, Department of Pediatrics, Division of Pediatric Rheumatology, Ankara, Turkey

ABSTRACT

Objective: Systemic juvenile idiopathic arthritis (sJIA) is one of seven subtypes of JIA. The aim of this study was to investigate the characteristics, the course and the outcome of sJIA patients in our clinic and to identify what has changed over the last decade in sJIA.

Material and Methods: Files of sJIA patients that were followed between March 2002 and April 2019 were evaluated.

Results: During the study period 36 patients were diagnosed with sJIA in our clinic (19 were male). Mean age of patients was 81.7±50.1 months at the onset of disease. Most common presenting features were fever (100%), arthritis (83.3%), rash (66.7%) and hepatosplenomegaly (38.9%). Seven patients (19.4%) were diagnosed as macrophage activation syndrome (MAS) due to sJIA. All patients had received corticosteroids. Additional treatments (disease-modifying drugs, intravenous immunoglobulin and biological agents) were given to 29 patients. In our clinic, anti-IL-1 agents have been used since 2011. In this group 26 (72.2%) patients were diagnosed after 2011. After the usage of biological agents, the duration of steroid exposure significantly decreased (p= 0.001).

Conclusion: After the introduction of biological agents in the treatment of sJIA, the duration of steroid exposure decreased significantly. Considering anti interleukin (IL)-1 and anti IL-6 treatments among the priority treatments in sJIA patients is important in terms of both providing rapid disease control and reducing side effects related to drugs.

Key Words: Biological agents, Clinical features, Macrophage activation syndrome, Systemic juvenile idiopathic arthritis

ÖZ

Amaç: Sistemik juvenil idiyopatik artrit (sJİA), JİA'nın yedi alt tipinden biridir. Bu çalışmanın amacı, kliniğimizdeki sJİA hastalarının özelliklerini, seyrini ve sonuçlarını araştırmak ve son on yılda sJİA'da nelerin değiştiğini belirlemektir.

Gereç ve Yöntemler: Mart 2002 ile Nisan 2019 arasında takip edilen sJİA hastalarının dosyaları geriye dönük olarak değerlendirildi ve verileri kaydedildi.

AYDIN F : 0000-0003-0306-7473
KURT T : 0000-0003-3711-8347
TEKGÖZ N : 0000-0002-2235-4489
SEZER M : 0000-0002-9254-9935
BAŞARAN O : 0000-0002-8534-0930
ÇAKAR N : 0000-0002-1853-0101
ÇELİKEL ACAR B : 0000-0002-1808-3655

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Correspondence Address / Yazışma Adresi:
Fatma AYDIN
Ankara City Hospital, Department of Pediatrics,
Division of Pediatric Rheumatology, Ankara, Turkey
E-posta: fatma4326@yahoo.com

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Bulgular: Çalışma süresince kliniğimizde 36 hastaya sJİA tanısı konuldu (19 erkek). Hastalığın başlangıcında hastaların ortalama yaşı 81.7±50.1 aydı. Başvuru esnasında en sık saptanan bulgular ateş (%100), artrit (%83.3), döküntü (% 66.7) ve hepatosplenomegali (%38.9)'du. Yedi hasta (%19.4) sJİA'ya bağlı gelişen makrofaj aktivasyon sendromu (MAS) tanısı aldı. Tüm hastalara kortikosteroid tedavisi verildi. 29 hastaya ek tedaviler (hastalığı modifiye edici ilaçlar, intravenöz immünoglobulin ve biyolojik ajanlar) verildi. Kliniğimizde 2011 yılından itibaren anti interlökin (İL) -1 ajanlar kullanılmaktadır. Bu grupta 26 (%72.2) hasta 2011 yılından sonra tanı almıştır. 2011 yılından sonra tanı alan ve biyolojik ajan tedavisi kullanılan hastalarda (n: 26) 2011 yılından önce tanı alan hastalara (n:10) göre steroid maruziyet süresi anlamlı olarak kısalmıştır (p = 0.001).

Sonuç: Biyolojik ajanların sJİA tedavisinde kullanılmaya başlamasından sonra steroid maruziyet süresi önemli ölçüde azalmıştır. Anti İL-1 ve anti İL-6 tedavilerinin sJİA hastalarında öncelikli tedaviler arasında düşünülmesi hem hızlı hastalık kontrolünü sağlamak hem de ilaçlara bağlı ortaya çıkabilecek yan etkileri azaltmak açısından önemlidir.

Anahtar Sözcükler: Biyolojik ajanlar, Klinik özellikler, Makrofaj aktivasyon sendromu, Sistemik juvenil idiyopatik artrit

INTRODUCTION

Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatologic disease of childhood starting before 16 years of age (1). The diagnosis of JIA requires exclusion of all possible causes of chronic arthritis (2). The disease may present with a wide variety of findings and due to lack of definitive features for diagnosis different classifications have been developed to obtain homogeneous clinical groups (3,4). According to the classification criteria proposed by the International League of Associations for Rheumatology (ILAR) for the first time in 1997 and last updated in 2001, the JIA is divided into 7 subtypes as systemic, oligoarthritis, rheumatoid factor (RF) positive polyarthritis, RF negative polyarthritis, psoriatic arthritis, enthesitis related arthritis (ERA) and undifferentiated arthritis (4,5). More recently, the International Pediatric Rheumatology Organization (PRINTO) revised the classification criteria and divided JİA into 6 subtypes (Systemic, RF positive, enthesitis/spondylitis related, early-onset anti-nuclear antibody (ANA) positive, other and unclassified JIA) (6). Among these subtypes, systemic JIA (sJIA) is distinguished from others by its different phenotype and clinical course. PRINTO reported a consensus to maintain the term systemic JIA, even if some patients may not have arthritis (6).

Systemic JIA includes 10-20% of all JIA patients in childhood (7). Based on the absence of high-titer autoantibodies or autoreactive T cells, sJIA is considered as an "autoinflammatory" disease, rather than an autoimmune disease (8). The inflammatory situation underlying systemic JIA distinguishes it from other subtypes (9). Macrophage activation syndrome (MAS), which is a devastating complication develops in 5-10% of sJIA patients. This life-threatening condition characterized by prolonged-continue high fever, hepatosplenomegaly, neurologic dysfunction, hemorrhagic manifestations, and laboratory abnormalities (7,9).

The systemic use of corticosteroids is recommended as fast acting drugs in highly active sJIA, but long-term use is not recommended due to advers effects (10). The pathogenesis of sJIA is not understood completely. Systemic JIA is considered as an "autoinflammatory" disease with a central role for both interleukin-1 (IL-1) and IL-6 (8). Subsequently, IL-1 and IL-6 inhibitors have been observed significantly effective for many patients with sJIA (11).

The purpose of the present study is to describe the complaints, laboratory and physical features, response to treatments, the course and the outcome of patients who had been diagnosed as sJIA in our clinic and to determine what has changed over the last decade in sJIA.

MATERIAL and METHODS

Patients who were diagnosed with sJIA according to ILAR criteria in our clinic between March 2002 and April 2019 were enrolled into the study. The ILAR criteria are as follows: Arthritis with a fever of at least two weeks duration that is documented to be daily (quotidian) for at least 3 consecutive days and is accompanied by one or more of the following four criteria: 1.Evanescent erythematous rash, 2. Generalized lymphadenopathy, 3.Hepatomegaly and/or splenomegaly, 4. Serositis. Four following conditions must be excluded: 1. Psoriasis or a history of psoriasis in the patient or a first-degree relative, 2. Arthritis in an HLA-B27 positive boy starting after the age of six, 3. Ankylosing spondylitis, enthesitis related arthritis, inflammatory bowel disease with sacroiliitis, reactive arthritis or acute anterior uveitis in a patient or a first degree relative, 4.The presence of immunoglobulin M (IgM) rheumatoid factor (RF) on at least two occasions at least 3 months apart (5). Patients who completed the first 6 months of follow-up were included in the study. Patients who lost their follow-up visits were excluded.

Data were collected from the files of patients. Age, gender, presenting features and all initial laboratory results such as white blood cells (WBC), platelet count, C-reactive protein (CRP), erythrocyte sedimentation rates (ESR), ferritin, IgG, lactate dehydrogenase (LDH), triglyceride (TG), the serology of viral markers, brucella, ANA, anti-double-stranded DNA antibody (anti ds DNA), bone marrow aspiration (BMA), echocardiography (ECHO) and abdominal ultrasonography (US) findings were recorded. All joints of patients with complaints were evaluated by US. The drugs used in the follow-up of the disease, the course and the final status of the patients were included in the data. The patients were divided into two groups as those

diagnosed before 2011 and after 2011 and the duration of steroid exposure was compared.

The diagnosis of MAS was made according to the classification criteria that were reported by Ravelli and et al. (12) in 2016: Ferritin > 684 ng/mL is accompanied by at least two out of the following four criteria; 1.Platelet count ≤181x109/L, 2.Aspartate aminotransferase > 48 U/L, 3.TG >156 mg/dL, 4.Fibrinogen ≤360 mg/dL.

The criteria defined by Wallace et al. (13) have been used for the definition of clinical remission with medication and clinical remission without medication. According to this criteria it is considered a clinically inactive disease in the absence of active arthritis, systemic findings and uveitis, normal ESR and/or CRP values and optimal physician's global assessment and less than 15 minutes of morning stiffness. At the time of enrollment, if a patient with JIA met these criteria for six consecutive months while under treatment, it was considered clinical remission with medication and it was defined as clinical remission without medication if the patient met these criteria for 12 consecutive months without medications for arthritis and uveitis.

The clinical course of the disease was divided into three categories. Monocyclic disease was defined with a single episode of systemic symptoms and arthritis. Polycyclic disease was characterized by recurrent flares and patients with persistent systemic features and arthritis who could not be followed up without treatment were accepted as the persistent sJIA (15).

Enzyme-linked immunosorbent assay (ELISA) was used for detecting and measuring ANA and anti ds DNA.

The study was approved by the Ankara City Hospital, No.1 Clinical Research Ethics Committee (16.09.2020/1055).

Statistical analysis

Results are given as mean±SD, median (minimum-maximum) or proportion as appropriate. Comparison between the two groups for the non-normally distributed continuous variables was assessed by the Mann-Whitney U test. A p value<0.05 was considered significant. All of the analyses were performed using SPSS for Windows 15.0 (Chicago, IL).

RESULTS

During the study period 36 patients were diagnosed with sJIA in our clinic, 19 (52.7%) were male and 17 (47.3%) were female. Mean age of patients was 81.7±50.1 months at the onset of disease. Mean duration of follow-up was 62.7±50.9 months. All of the patients (100%) had fever of at least 2 weeks' duration (mean± SD:25.9±16.5 days) and 30 (83.3%) patients had arthritis, 6 (16.6%) patients had arthralgia. Ten (27.7%) patients had monoarticular, 12 (33.3%) had oligoarticular, 8 (22.2%) had polyarticular arthritis during the course of the diseases. Synovitis in the joints of 30 patients was detected by US. Twenty four (66.7%) patients had rash. Viral and brucella serology were negative in all patients. Physical examination and US revealed hepatomegaly in 7 (19.4%) patients, splenomegaly in 5 (13.8%), hepatosplenomegaly in 14 (38.8%) and lymphadenopathy in 10 (27.7%) patients. Median duration from onset of disease to diagnosis was 20 days and range was 15-60 days. Table I and II show demographic, clinical features and laboratory findings

Table I: Demographic and clinical characteristics of the patients.

	n=36 (%)
Age at disease onset (months) (Mean ± SD)	81.7 ± 50.1
Fever (n)	36 (100)
Fever (days)(Mean ± SD)	25.89 ± 16.5
Rash	24 (66.7)
Arthritis	30 (83.3)
Monoarthritis	10 (27.8)
Oligoarthritis	12 (33.3)
Polyarthritis	8 (22.2)
Arthralgia	6 (16.7)
Hepatomegaly	7 (19.4)
Splenomegaly	5 (13.9)
Hepatosplenomegaly	14 (38.9)
Lymphadenopathy	14 (38.9)
Serositis	11 (30.5)
Pleural effusion	3 (8.3)
Pericardial effusion	5 (13.9)
Pleural + pericardial effusion	2 (5.6)
Myopericardisit	1 (%2.8)
MAS*	7 (19.4)

***MAS:** *Macrophage activation syndrome*

Table II: Laboratory parameters of all systemic JIA patients at the time of diagnosis.

Laboratory parameters (n:36)	Mean ± SD
Leukocyte (mm³)	15256 ± 6296
Hemoglobin (g/dl)	10.3 ± 1.76
Platelet (mm³)	423559 ± 160915
CRP (mg/dl)	18.8 ± 34
ESR (mm/h)	83.6 ± 24.7
Ferritin (mg/dl)	4089 ± 5080
Fibrinogen (mg/dl)	399.3 ± 181.2
ALT (U/L)	28.1 ± 32.4
AST (U/L)	43.1 ± 58.3
Triglyceride (mg/dl)	194.7 ± 121.8
LDH (U/L)	575.7 ± 414
Albumin (mg/dl)	3.4 ± 0.5
Immunoglobulin G (mg/dl)	1669 ± 640

***JIA:** juvenile idiopathic arthritis; **CRP:** C-reactive protein; **ESR:** erythrocyte sedimentation rate; **ALT:** alanine aminotransferase; **AST:** aspartate aminotransferase; **LDH:** lactate dehydrogenase*

Table III: All medications used in patients with systemic JIA

Treatments	Dosage	n (%)
Pulse methylprednisolone	30 mg/kg/day, max: 1gr, for 3 consecutive days	23 (63.9)
Corticosteroids	2 mg/kg/day,max:60 mg	36 (100)
Methotrexate	15 mg/m^2/week, max: 20-25 mg	12 (33.3)
Cyclosporine	2.5-5 mg/kg/day	5 (13.9)
Azathiopurine	1-3 mg/kg/day, max:100 mg	4 (11.1)
Etanercept	0.8 mg/kg/week, max:50 mg	3 (8.3)
Infliximab	6–10 mg/kg, q2 weeks– 2 months	2 (5.5)
Anakinra	1–4 mg/kg/day	8 (22.2)
Canakinumab	>2 years: 4 mg/kg/dose q 4 weeks Maximum dose: 300 mg	6 (16.6)
Tocilizumab	>2 yrs, <30 kg 12 mg/kg q2 weeks >2 yrs, >30kg 8 mg/kg q2 weeks	3 (8.3)
Intravenous immunoglobuline	1-2 mg/kg, max 75 mg	4 (11.1)

JIA: *juvenile idiopathic arthritis*

of all patients.

Autoantibodies including ANA and anti ds DNA were performed in all patients to exclude autoimmune diseases. Positive ANA was found only in three patients with low titer (1/100 titer with ELISA).

Skin biopsy was done to five patients and the results were non-spesific (3 perivascular dermatitis, 2 leucocytoclastic vasculitis, 1 interface dermatitis).

Genetic mutations were studied in 10 patients for suspicion of familial Mediterranean fever (FMF) and one heterozygous polymorphism R202Q and one heterozygous mutation E148Q were found.

BMA and ECO were performed in all patients. BMA revealed no pathologic signs for malignancy. Hemophagocytosis was found in six patients. Serositis was observed in 11 (30.5%) patients.

All patients received intravenous corticosteroids at the onset of the diagnosis and then oral corticosteroids in the course of disease. Twenty three (63.8%) patients were initially treated with pulse methylprednisolone (PMP) (30 mg/kg/day, max: 1gr, for 3 consecutive days). Additional treatments (disease-modifying drugs, intravenous immunoglobulin (IVIG) and biological agents) were given to 29 patients. Treatment details are given in the table III.

Seven patients (19.4%) were diagnosed as MAS due to sJIA. Three patients were initially diagnosed with MAS at the time of diagnosis of systemic sJIA. In four patients, MAS developed mean 35.7±41.5 days after the diagnosis of sJIA. Three patients had two MAS attacks during the follow-up. Clinical features, laboratory findings and treatments of MAS patients are given in the table IV.

In our clinic, anti-IL-1 agents have been used since 2011. In this group, 10 patients were diagnosed before 2011 and 26 patients after 2011. Median steroid use was 18 months (range: 6-84 months) before 2011, and median steroid use was 8 months (range: 3-18 months) after 2011. Patients with persistent disease had a steroid intake for a maximum of 84 months prior to 2011, while patients with persistent course had a steroid intake for a maximum of 18 months after 2011 in our study. The duration of steroid use decreased significantly with a p value of 0.001 after 2011 compared to before.

Disease course was monophasic in 18 patients (50%), polycyclic in 11 patients (30.6%) and persistent in 7 patients (19.4%). Remission (cessation of therapy) was achieved in 20 (55.6%) patients and 15 patients (41.6%) had remission on medication and one patient with MAS died due to multiorgan insufficiency.

DISCUSSION

Systemic JIA is a unique disease characterized by variable arthritis and systemic features that include fever, rash, lymphadenopathy, hepatomegaly and/or splenomegaly, or serositis. It is a more serious and acute disease than other JIA subtypes because of numerous complications of persistent inflammation. The most devastating complication of sJIA is MAS with high mortality rate (14).

Features of the disease should be well known since the disease may present with nonspesific clinical and laboratory findings. In addition, infectious etiologies, malignancies, connective tissue diseases, vasculitis and autoinflammatory syndromes should be excluded as sJIA is a diagnosis of exclusion (15). After investigating diseases that should be considered in the differential diagnosis of sJIA, patients who had no reason to explain the clinical and laboratory findings and meet the criteria for ILAR classification criteria are accepted as sJIA (5). According to ILAR criteria, it is mandatory to have arthritis with a quotidian fever of at least two weeks' duration for sJIA

Table IV: Clinical features of patients with MAS.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Age(months)/ gender/the year of MAS diagnosis	101/Female/2016	12/Female/2013	24/Male/2007	14/Male/2012	8/Male/2011	247Male/2017	129/Female//2018
Fever (days)	15	30	14	55	21	15	15
Rash	-	+	-	+	-	+	+
Arthritis	+	+	+	+	+	+	+
Organomegaly	HSM	HSM	HSM	-	+	+	HSM
Lymphadenopathy	+	-	+	-	+	-	+
Serositis	-	Pericardial effusion	-	-	-	Pleural and pericardial effusion	-
The duration between sJİA and MAS(days)	At the onset of sJİA	At the onset of sJİA	At the onset of sJİA	5	30	96	12
WBC(mm^3)/Hgb (gr/dl)/Plt (mm^3)	3200/8.7/99.000	9600/6.6/342000	6200/7.9/116000	9600/9.8/155000	10.6/20500/174000	6700/13.7/64000	14000/13.9/176000
ESH(mm/h)/ CRP(mg/dl)(<0.8)/ Fibrinogen (mg/dl) Ferritin (mg/dl)	29/10/140 3753	27/7.7/75 15000	44/7.5/236 13148	89/5/381 10964	55/9/315 2577	10/13.9/108 64650	9/1.3 1814
AST(U/L)/ALT (U/L)	321/102	96/42	67/149	120/114	24/11	375/102	66/43
Triglyceride (mg/dl) LDH (U/L)	237	462/1701	489/1935	320	189	503	119
Hemophagocytic cell in bone marrow aspiration	+	+	-	-	-		+
The course of disease	Polysiclic	Polysiclic	Monocyclic	Polysiclic	Polysiclic	Persistan	Polysiclic
The number of MAS attacks	One	One	One	Two	One	Two	Two
Treatments for MAS	Steroid, IVIG, Anakinra, Canakinumab	Steroid,CSA	Steroid,CSA	Steroid,CSA Anakinra	Steroid, CSA, AZA	Steroid, Anakinra, Canakinumab	Steroid, Anakinra, CSA, Canakinumab
Last visit	Clinical remission with medication	Clinical remission without medication	Clinical remission without medication	Clinical remission without medication	Clinical remission without medication	Exitus	Clinical remission with medication

MAS:*Macrophage activation syndrome,* ***WBC:*** *white blood cells,* ***CRP:*** *C-reactive protein,* ***ESR:*** *erythrocyte sedimentation rates,* ***LDH:*** *lactate dehydrogenase,* ***TG:*** *triglyceride,* ***CSA:*** *Cyclosporine,* ***AZA:*** *Azathiopurine,* ***IVIG:*** *Intravenous immunoglobuline,* ***sJIA:*** *systemic juvenile idiopathic arthritis*

classification (5). The fever range of the patients in our cohort was between 15 and 60 days. The time frame may extend up to 2 months as in our patients with presence of fever for some days (at least 3 days) and absent in other days.

It is controversial that arthritis is a mandatory criterion. Our six out of 36 sJIA patients had only arthralgia. All exclusion studies of these patients had been conducted and there was no reason to explain their manifestations other than sJIA. The newly reported PRINTO criteria, which have not yet been validated, exclude arthritis from being a mandatory criterion and offer arthralgia lasting 2 weeks or longer as a minor criterion (6).

Seven patients who diagnosed with MAS had continuous unremitting pattern of fever and the platelet counts were tended to decrease and ferritin was high in these patients (>500 ng/dl). MAS is a fatal complication of sJIA. The estimated prevalence of MAS in sJIA is 10% (7). In our study MAS was observed 19.4% of patients. Other two studies from Turkey presented MAS complication as 11.9% and 33.9% in their cohorts, respectively (16,17). According to these results, MAS rates differ even in the same country. Although this situation may be caused by triggering factors.

In addition, it is suggested that MAS may occur subclinically in 30-40% of sJIA patients. Early suspicion of MAS is very important to start therapy before the injury due to hypercytokinemia becomes irreversible (18). Clinicians should be very careful in terms of MAS findings, otherwise MAS may be life-threatening. Features concerning for MAS were defined as any combination of the following disease manifestations: persistent (rather than quotidian) fever, cytopenias or falling cell line counts (particularly platelets), falling ESR, hypertriglyceridemia, hypofibrinogenemia, hemophagocytosis, transaminitis, coagulopathy, organomegaly, low or absent natural killer cell activity, hyperferritinemia, or central nervous system dysfunction (19).

Despite improvements in treatment options, sJIA remains one of the most challenging pediatric rheumatologic disease. After revealing the role of IL-1 and IL-6 in the pathogenesis of sJIA, there have been changes in treatment approaches. In this study, all patients diagnosed with sJIA initially received steroid treatment. In our clinic, anti-IL-1 agents have been used since 2011 and were previously unavailable. Before 2011, patients with significant systemic symptoms were given steroid therapy for a long time, azatiopurine, and IVIG. Patients with severe arthritis were treated with methotrexate and those with unresponsive to methotrexate anti-TNF agents, such as etanercept. Two persistent patients with systemic onset polyarticular JIA didn't improve with any of the steroid, methotrexate, etanercept and infliximab treatments given before 2011. Similarly, Russo et al. (20) reported 24% of 45 sJIA patients treated with anti TNF agents (etanercept, infliximab, adalimubab) and complete remission was achieved in 13%. Regardless of the beneficial effects in other forms of JIA, anti-TNF agents show poor response rates in sJIA (18). After starting Anakinra treatment in 2011, remission was achieved in three patients who were diagnosed before 2011 and were not in remission. After 2011, azathiopurine was never used. In addition, with the introduction of biological agents in our clinic, the duration of steroid use decreased significantly after 2011 compared to before.

IL-1 inhibitors (Anakinra, canakinumab) and IL-6 inhibitor (Tocilizumab) were observed significantly effective for many patients with sJIA (21). According to ACR recommendations, anti-IL-1 was administered to patients with predominant systemic findings, and tocilizumab was administered to patients with severe arthritis (19). Moreover, Horneff et al. (22) reported a large proportion of sJIA patients in German Biologics register (BiKeR) gained significant response to treatment with tocilizumab or IL-1 inhibitors than with etanercept.

Baris et al. (23) reported that the first IL-1 blockade in sJIA patients was in 2004 at Boston Children's Hospital and they showed the proportion of monophasic disease tends to increase after 2004. In our study, disease course was monophasic in 18 patients (50%), polycyclic in 11 patients (30.6%) and persistent in 7 patients (19,4%). Barut el al. (16) found in their cohort 31.5% of patients with monocyclic, 13.7% of patients with polycyclic and 54.8% of patients with persistent clinical course. Çakan et al. (17) showed that monocyclic course was observed in 45.2%, polycyclic course in 30.1% and persistent course in 24.5% of the cases in their study. In our cohort, half of the patients had a monocyclic course. The reason for this may be that the majority of patients have been diagnosed after the presentation of biological treatments, as we mentioned above. Remission was achieved in 55.6% of our patients, similar to previously reported studies (16,17).

There were some potential limitations in our study. Patient population was small, the study is local, all data were collected retrospectively and the treatment approach is heterogeneous.

CONCLUSION

The diagnosis of sJIA may be difficult and can take a long time, because other autoinflammatory disorders, systemic autoimmune diseases, infections and malignancies should be excluded. On the other hand, clinicians shouldn't delay in diagnosis and treatment considering the complication of developing MAS. If possible, biological treatments should be used to avoid steroid side effects. Prospective studies with large number of patients can be more helpful to follow up sJIA patients.

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