Evaluation of clinical outcomes in systemic juvenile idiopathic arthritis patients treated with biological agents in Turkey: the TURSIS study

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Abstract

Objective

Biological drugs are one of the most effective treatment methods for systemic juvenile idiopathic arthritis (SJIA) and can significantly prevent morbidity and mortality. This study aimed to evaluate the efficacy and safety of biologics in patients with SJIA and provide real-life data that might help improve the outcomes.

Methods

TURSIS was a retrospective multicentre study carried out in patients with SJIA for whom a biological treatment had been initiated between 1st March 2013 and 30th December 2018. Data include patients' characteristics, laboratory-clinical results, outcomes, and safety-related variables. The 24-month follow-up data of the patients and the efficacy and safety of biological drugs were evaluated.

Results

147 patients were enrolled. The clinical course of the disease was as follows; it was monocyclic in 38.1%, polycyclic in 49%, and persistent in 12.9% of patients. First-choice biologics were interleukin (IL)-1 blockers in the majority of patients (56.5%), followed by the anti-IL-6 (25.2%) and anti-TNF-alpha drugs (18.4%). Anakinra was the most preferred biologic agent in patients with macrophage activation syndrome (MAS), and tocilizumab was used more frequently in patients with persistent type (p=0.000 and p=0.003). The most frequent switch rate was seen in patients receiving anakinra (n=40/68, 58.8%), and it was most frequently switched to canakinumab (n=32/40, 80%). Better physician's global assessment scores were achieved in patients treated with anakinra in Month 3, compared to other treatments (p=0.04).

Conclusion

The results of our study support the efficacy of biological drugs in particular anti-IL-1 and anti-IL-6 drugs, in the treatment of SJIA. These treatments resulted in improvement in activity of disease and provide a considerable decrease in the frequency of MAS.

Key words

paediatric rheumatology, systemic juvenile idiopathic arthritis, macrophage activation syndrome, biological therapy, outcome

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Introduction

Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatic condition in paediatric patients (1). Systemic JIA (SJIA) is the most acute and severe form and that account for 10–20% of JIA patients. It is distinct from other forms with no gender predominance and systemic manifestations such as daily, spiking fever, rash, myalgia, lymphadenopathy, hepatosplenomegaly, serositis, and elevated acute phase reactants (*e.g.* C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR)) that reflect systemic inflammation. Arthritis is usually symmetrical and polyarticular. However, it may be absent at onset and develop later during the course of the disease (2, 3).

Genetic studies have proven that SJIA-associated loci differ from other JIA subtypes (4). There is also a multisystemic inflammation in this disease, which is caused by activation of the innate immune system and excessive increase in pro-inflammatory cytokines (*e.g.* interleukin (IL)-1 and IL-6). As a result of this exaggerated inflammation, the clinical course progresses to macrophage activation syndrome (MAS), which is the most severe complication of SJIA in 5–8% of patients (2).

In the treatment of SJIA, corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs), and disease-modifying anti-rheumatic drugs (DMARDs) are used in the first steps, as in all JIA patients (5, 6). After elucidating the pathogenesis of the disease, many studies have shown superior therapeutic efficacy of cytokine-directed therapies against IL-1 and IL-6 (5, 7, 9). Dysregulation of innate immunity may not be stopped by cytokine-targeted therapy strategies. Moreover, the disease phenotype can change and turn into destructive arthritis where adaptive immunity is active at the forefront (2, 4). Nigrovic *et al.* reported the hypothesis of a "window of opportunity" in 2014. They stated that early biological treatment has provided a favourable long-term outcome in SJIA patients (10, 12). The prognosis of SJIA depends on the control of systemic inflammation. Mortality can occur as a result of MAS, amyloidosis, and infections associated with corticosteroid use (3).

The American College of Rheumatology (ACR) published recommendations for the effective and safe treatment of JIA in 2011 (13). The recommendations were updated in 2013 focusing specifically on SJIA due to the advances in the understanding of the pathophysiology of this condition and a significant increase in published data. The initial and subsequent use of several biologic agents has been suggested for the treatment of various clinical phenotypes of SJIA (14).

Despite the substantial evidence supporting the effectiveness of biological drugs in the treatment of SJIA, the clinical response to these treatment options had not been largely investigated in Turkey. The Turkish Systemic Juvenile Idiopathic Arthritis Registry (TURSIS), the multicentre, retrospective study aimed to assess the clinical response to the available treatment modalities for SJIA and to provide real-life data that might help improve the disease outcomes in Turkey.

Materials and methods

TURSIS was a retrospective and multicentre study in patients with SJIA for whom a biological treatment had been initiated during the index period. Real-life study based on secondary data collection from medical records of patients evaluated at the eight paediatric rheumatology clinics in Turkey from July 2019 to December 2020. Patients' characteristics, clinical inactivity, safety-related variables, physician global assessment (PGA) score's and ACR30/50/70 response were assessed.

The data regarding visits that had been made at months 0 (initiation of biologic treatment), 3, 6, 12, 18, and 24 were secondarily extracted from electronic or hand-written hospital medical records and transferred to printed Data Collection Forms. The allowed index period for the initiation of biologics (in both biologic naïve and non-naive patients) was between March 01, 2013 and December 30, 2018. The exclusion criteria were patients with disease onset age above 18 years or classified in one of the other JIA subtypes, or SJIA patients who received non-biological treatment. The study protocol was reviewed and

approved by the Ethics Committee of the University of Health Sciences, Umraniye Training and Research Hospital, Istanbul. Patient informed consent was not required since the data were retrospectively collected from secondary sources. The study amendment was also approved by the Ethics Committee. This study was designed, implemented, and reported in accordance with the Guidelines for Good Pharmaco-epidemiology Practices (GPP) issued by the International Society for Pharmaco-epidemiology (ISPE) (Public Policy Committee, ISPE 2016), with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (15), and with the ethical principles laid down in the Declaration of Helsinki.

Study variables

Baseline disease characteristics were assessed, including the patient's date of birth, gender, weight, and height at the time of diagnosis and date of onset of symptoms, date of diagnosis, type of SJIA [monocyclic, polycyclic, persistent], and global assessment of disease activity by the physician before being included in the study. Efficacy and safety data were collected at months 3, 6, 12, 18, and 24.

Patients having met the following 5 criteria were accepted as clinically inactive; no joints with active arthritis, absence of fever, rash, serositis, splenomegaly, or generalised lymphadenopathy attributable to JIA, no active uveitis, ESR or CRP levels within normal limits (ESR:0–20 mm/h, CRP:0–0.5 mg/dl). If both ESR and CRP were analysed, the results of both tests should have been normal. Physician's global assessment of disease activity score of best possible on the scale was used. The assessment of the ACR 30/50/70 response was made as described in the ACR core set (16). Articular involvement was assessed based on the count and location of the affected joints and the presence or absence of pain, swelling, and limitation of motion.

Statistical methods

Descriptive analyses included number (n), mean, standard deviation (SD), median, minimum-maximum (min-max) for continuous variables, and frequencies and percentages for categorical variables. IBM SPSS package programme was used for the analysis of data. Statistical differences and analyses were examined with chi-square analysis for categorical variables, and differences between groups for continuous variables were analysed using the Mann-Whitney U-test. Changes over time were examined using the Friedman test. A p-value of <5% was accepted as significant. Missing values were not counted in the percentages or frequencies unless otherwise specified.

Table I. Demographic and clinical findings of all patients at baseline.

Gender (F-M, n/%)	76/51.7 – 71/48.3
Age at disease onset (year) *	4.25 (2.91)
Age at onset of biological therapy (year) *	8.00 (4.99)
Arthralgia / Arthritis, n (%)	120 (81.6)
Number of affected joints **	4 (1-14)
Rash n (%)	103 (70)
Organomegaly (Splenomegaly and /or hepatomegaly) n (%)	50 (34)
Serositis (pleuritis and/or pericarditis and/or peritonitis) n (%)	14 (9.5)
Days with fever **	15 (1-90)
Frequency of affected joints, n (%)	
Ankle	106 (36.30)
Knee	98 (33.56)
PIP & MCP	56 (19.18)
Wrist	43 (14.73)
Hip	18 (6.16)
Elbow	11 (3.77)
MTP & Foot	6 (2.05)
Shoulder	4 (1.37)
Global assessment score **	7.00 (0.00-10.00)
SJIA attack, n (%)	83 (56.5)
1 attack	38 (25.8)
>1 attack	45 (30.6)
History of MAS	35 (23.8%)
SJIA subtype, n (%)	
Monocyclic	56 (38.1)
Polycyclic	72 (49.0)
Persistent	19 (12.9)
Biologic drugs, n (%)	
Anakinra	68 (46.3%)
Canakinumab	15 (10.2%)
Tocilizumab	37 (25.2%)
Anti TNF-α (etanercept and adalimumab)	27 (18.4%)
Inflammatory markers **	
CRP (mg/dl)	5.55 (0.01-185)
ESR (mm/h)	52 (1-145)
Ferritin (ng/ml)	1033 (11.15-165371.2)

*mean (± SD), **median (min-max), CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; F: female; M: male; MAS: macrophage activation syndrome; MCP: metacarpo-phalangeal joints; MTP: metatarso-phalangeal joints; PIP: proximal interphalangeal joints; SJIA: systemic juvenile idiopathic arthritis.

Results

Demographic, clinical, and laboratory findings

The study population of 147 patients consisted of 76 females (51.7%). The mean age (± SD) at diagnosis and onset of biologic therapy was 4.25 (2.91) and 8.00 (4.99) years, respectively. At the diagnosis, 120 (81.6%) patients had active arthritis (median 4 joints), 103 (70%) had rash, 50 (34%) had hepatomegaly and/or splenomegaly and 14 (9.5%) had serositis. The median fever days were 15 days (min-max, 1–90). The disease subtypes of the patients during the period from diagnosis to the start of the study were as follows; 38.1% of patients were monocyclic (n=56), 49% were polycyclic (n=72) and 12.9% were persistent (n=19) clinical course, respectively. The most frequently affected joints at baseline were the ankles (36.30%) followed by the knees (33.56%) and the proximal interphalangeal joints & metacarpophalangeal joints (19.18%). The

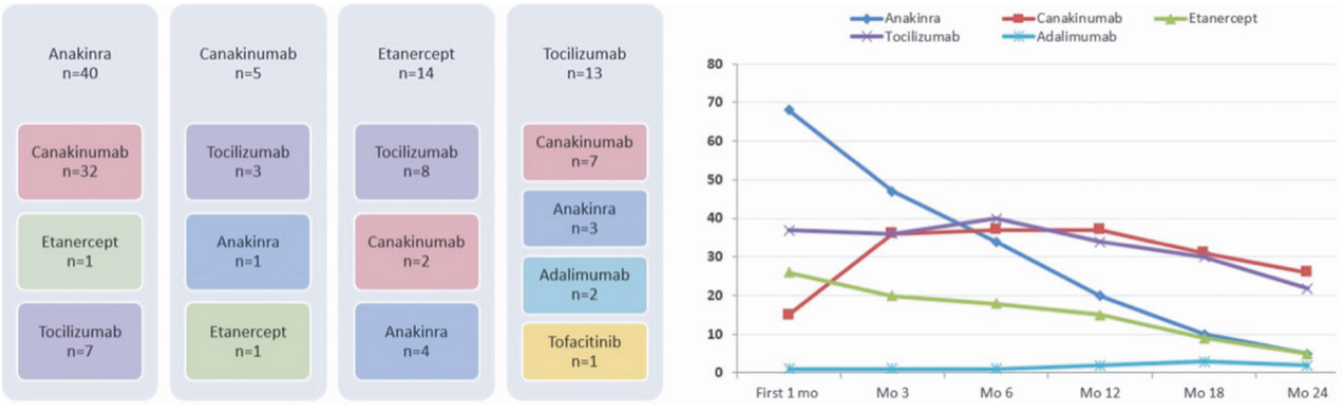


Fig. 1.A: The number of patients using the relevant biologic drug and switch rates. **B**: The number of patients on the relevant biologic drug during the study

demographic, clinical, and laboratory variables at the baseline of the study are shown in Table I.

Treatments

First-choice biologics were IL-1 blockers (anakinra or canakinumab) in the majority of patients (n=83, 56.5%), followed by the anti-IL-6 receptor monoclonal antibody tocilizumab (n=37, 25.2%). Anti-TNF-alpha drugs (etanercept or adalimumab) were observed to be preferred in fewer patients (n=27, 18.4%) (Table I). It was determined that Anakinra was the most preferred biologic agent (24/35, 68.6%) in patients with MAS, and tocilizumab was used more frequently in the group with persistent type (29/72, 40.3%) (p=0.000 and p=0.003).

Biological treatments ceased in 30.6% (n=45) of the total patients due to inactive disease during the follow-up period. Therapy was terminated in 22 of these 45 patients in the first year (48.4%), in 20 of them between 1224 months (44.4%), and in the remaining three patients in Year 3 and later. In two patients, treatment was restarted due to the disease flare.

102 patients had bolus methylprednisolone treatment before the initiation of biological therapy due to the MAS and/or active disease. The percentage of patients who were not on corticosteroids was 27.9% at the baseline of biological treatment and gradually increased throughout the visits up to month 24 (Supplementary Fig. S1). There was a numerical increase without significant difference in the percentage of steroid non-users at month 3 (p=0.524) and 6 (p=0.055) *versus* baseline, however, the differences were significant at months 12, 18, and 24 (p<0.001 for all) (Suppl. Table S1).

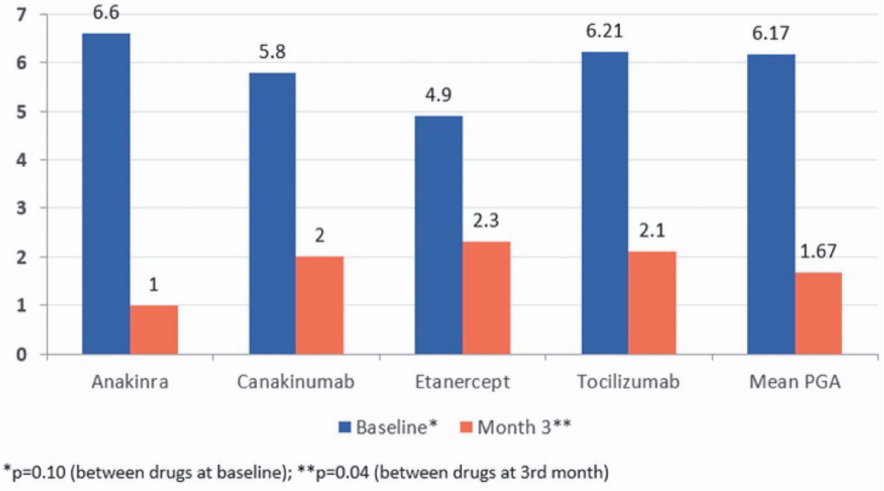


Fig. 2. Drug-specific physician's global assessment scores.

Exposure to biological therapies

During the study period, 51% of patients (n=75) remained on the same biologic drug. 63 patients (42.8%) had experienced one switch, whereas nine patients (6.1%) switched twice. The most frequent switch rate was seen in patients receiving anakinra (n=40/68, 58.8%), and it was most frequently switched to canakinumab (n=32/40, 80%). The second most frequently switched biological agent was etanercept (n=14/27, 52.8%), and it was most frequently switched to tocilizumab (n=8). The numbers of patients using the relevant biologic drug throughout the overall study and the rate of switches are presented in Figure 1. The number of patients treated with canakinumab increased from 15 (10.2%) to 36 (25.7%) in Month 3, whereas the number of those treated with tocilizumab decreased from 37 (25.2%) to 36 (25.7%). The number of patients on anakinra and etanercept also decreased from 68 to 47, and 26 to 20, respectively. Seven patients stopped biologics treatments in Month 3 (Fig. 1).

Outcome

The global assessment scores at baseline were available for 143 patients. There was no significant difference in the PGA scores of the patients using different biologic drugs at the initiation of the treatment (overall mean PGA at baseline: 6.17). Better PGA scores were achieved in patients treated with anakinra in Month 3, compared to other treatments (p=0.04) (overall mean PGA in Month 3: 1.67) (Fig. 2).

The proportion of patients without joint involvement gradually increased from baseline to 6 months. It was around

90% in Month 6 and remained almost constant until Month 24. While the presence of active joint involvement was significantly reduced in Month 3 from baseline, no significant difference was observed in the following visits. (Fig. 3) After the initiation of biological drugs, inflammatory parameters declined irrespective of the disease course. The mean (SD) CRP level was 10.05 (19.08) mg/dl at baseline. It was found 2.76 mg/dl in Month 6, 12.2 mg/dl in Month 12, 1.14 mg/dl in Month 18 and 7.74 mg/dl in Month 24. The mean ESR level was 52.81 (33.44) mm/h at baseline and was found to be lower at follow-up visits.

The numbers and proportions of patients achieving ACR 30-50-70 responses and inactive disease during the study period were presented in Figure 4. The highest number of patients reached inactive disease at 18 months. The percentage of patients achieved ACR 30/50/70 response in particular for anakinra, canakinumab, tocilizumab, and anti-TNF treatments were respectively; 89.1%/82.6%/78.2%, 88.8%/80.5%/72.2%,93.9%/75.7%/66.6%, 81.8%/72.7%/ 63.6%, in Month 3. ACR 30/50/70 responses were also achieved in Month 6 at 94.1%/88.2%/82.3% of patients for anakinra, 89.1%/78.3%/70.2% of patients for canakinumab, 87.1%/71.7%/58.9% of patients for tocilizumab, and 80%/70%/65% of patients for anti-TNF alpha treatments.

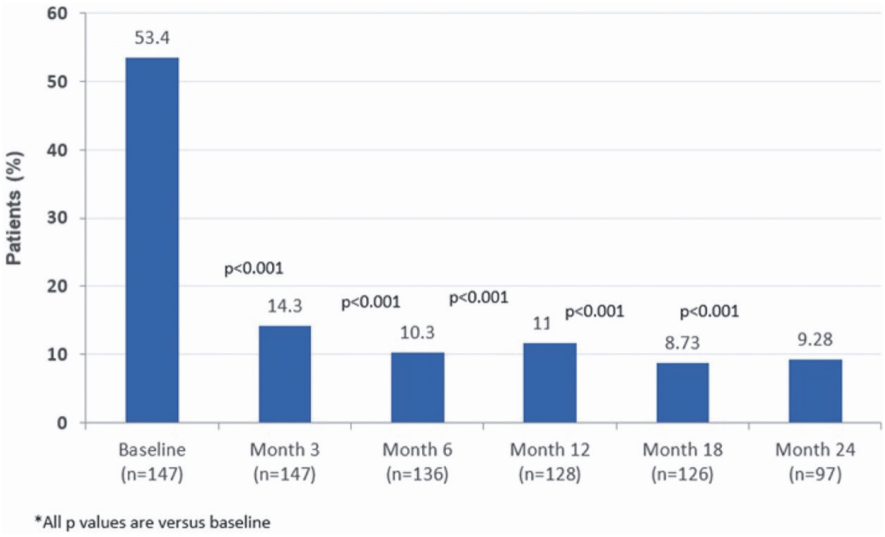


Fig. 3. Rate of patients with active joints.

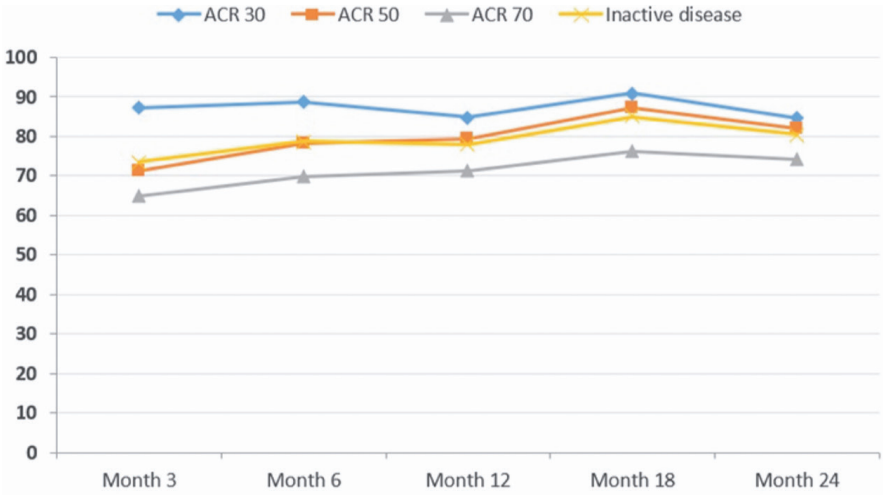


Fig. 4. ACR response and inactive disease rates achieved with all treatments.

Adverse events

A total of 22 adverse events, including one death, were observed in 12 patients (8.2%) (Table II). The most frequently observed adverse events were pneumonia (n=4) followed by urinary tract infection (n=3) and vomiting (n=2). A 15-year-old patient who had suffered from SJIA for 11 years was put on etanercept at baseline, then switched to tocilizumab, and died from aspiration pneumonia. The event was reported to be unrelated to biological use.

Macrophage activation syndrome

Thirty-three (22.4%) of 144 patients whose data about the presence or absence of clinical findings of MAS were available, had experienced a MAS attack between the diagnosis of SJIA and initiation of biological treatment. 9 patients experienced MAS after baseline. Most of the patients (81.3%) had experienced a single MAS (clinical) attack; the highest number of MAS (clinical) attacks per patient was 4 (observed in 2 patients [6.3%]).

The most frequently observed clinical manifestations of MAS were persistent fever (93.8%) and rash (81.3%). The data about lymphadenopathy, hepatomegaly, and splenomegaly were available for a lower number of patients and the percentage of patients who had experienced these signs as part of the MAS clinical presentation were 43.9% (13/30), 71.9% (23/24) and 70.0% (21/30), respectively. The frequencies of other clinical manifestations, such as lung and central nervous system involvement (seizures and encephalopathy), were lower during MAS attacks. None of the patients in the etanercept group had a clinical MAS before the initiation of this therapy.

The laboratory findings associated with MAS (n=32) revealed that hyperferritinaemia was the most commonly observed finding (96.9%), followed by a decrease in haemoglobin level (84.4%), and an increase in lactate dehydrogenase level (71.9%). Increased liver function tests (65.6%), decreased fibrinogen level (56.3%), hypoalbuminaemia (62.5), decrease in ESR (59.4%), and haemophagocytosis in bone marrow aspiration (53.1%) were the other laboratory findings observed in more than half of the patients with MAS.

Table II. Adverse events observed during the study period.

Adverse events	Subjects (n/%)
Pneumonia	4 (33.3)
Urinary **t**ract **i**nfection	3 (25.0)
Vomiting	2 (16.7)
Nausea	1 (8.3)
Acute gastroenteritis	1 (8.3)
Diarrhea	1 (8.3)
Empyema	1 (8.3)
Aspiration pneumonia	1 (8.3)
Zona Zoster	1 (8.3)
Local **s**kin **r**eaction	1 (8.3)
Oral candidiasis	1 (8.3)
Acute SJIA attack	1 (8.3)
Autoimmune h**a**emolytic an**a**emia	1 (8.3)
Cataract surgery	1 (8.3)
Tonsillectomy and adenoidectomy	1 (8.3)
Death	1 (8.3)
Total	12 (100)

Discussion

The TURSIS study retrospectively enrolled a large cohort of patients with SJIA treated with biological drugs between 2013 and 2018. The studies in the literature generally included a small number of patients, while our study compared the efficacy and safety of different biologic drugs head-to-head on a relatively large number of patients. This study confirmed the beneficial effects of biologics on these patients through real-life data. The effective use of biological drugs in the early period reduces the risk of disease-related joint damage and mortality in SJIA, which cause destructive joint damage and macrophage activation syndrome.

Horneff *et al*. published the results of a registry of SJIA patients in 2017. In this study, responses to etanercept, tocilizumab, and anti-IL-1 treatments were evaluated in 245 patients diagnosed with SJIA and enrolled between 2000 and 2015. Etanercept/tocilizumab/anti-IL-1 treatments were presented in their studies as the most commonly used biologic drugs at 58.3%/30%/24.5% rates, respectively. It was stated that etanercept was used more frequently in the past, but it was certainly less effective. They also found that the patients in the anti-IL-1 and tocilizumab cohorts showed high disease activity with a predominance of systemic manifestations, whereas active arthritis was the leading symptom in the etanercept cohort (17). In our study group, the most commonly used first biologic drugs were as follows; 56.5% of the patients were treated with anti-IL-1 treatments and tocilizumab was used in 25.2% of the patients with the second frequency. When the distribution of the first selected biologics were evaluated; it was determined that the patients who received anti-TNF-alpha treatments were mostly in the polyarticular and persistent group.

In an Italian Cohort study, among the patients treated with canakinumab, the inactive disease was achieved in 57% of patients in Month 6 and 67% in Month 12 (18). It was also reported in the BIKER registry that clinically inactive disease was reached in 60% of SJIA patients in the Month 24, consistent with these results (17). In another German registry study, 248 patients receiving IL-1 therapy were evaluated; inactive disease was reported to be achieved in 51% of patients receiving anakinra and 85% of patients receiving canakinumab at Month 12 (19). In our study group, it was observed that 80.7% (n:67/83) of the patients who received anti-IL-1 therapy achieved inactive disease in Month 3 of treatment. We showed significant improvement in both PGA scores and active joint counts during the first 3 months of treatment, being more evident with Anakinra. Achieving inactive or mild disease activity in the early period also provides an opportunity to reduce the risk of disease-related damage in the long-term period.

In a long-term follow-up trial, researchers showed that 33% of patients achieved clinic inactive disease in Month 6 and 40% in Month 24 (20). In a recently reported AID registry, it was shown that in patients with SJIA treated with an anti-IL-6 drug tocilizumab, inactive disease/remission was achieved in 75% of patients at Year 1 of treatment (21). In our cohort, we showed that the ACR-70 response was achieved with tocilizumab in 51% of patients in Month 3 and 64% in Month 6 of treatment. Ruperto *et al*. determined that after 5 years of biological therapy in SJIA patients, 56% of the patients were still under steroid therapy at a median dose of 0.25 mg/kg/day (20). In another study evaluating the efficacy of canakinumab in Japanese SJIA patients, it was shown that only 10.3% of patients ceased the steroid at the Week 28 of treatment, while steroid dose tapering was made in 73.7% of the patients (21). We found in our cohort that the percentage of patients off corticosteroids was 79.2% at Month 24 which is higher than in other studies (Figure S1). Our study results indicate that biological treatments significantly reduce the requirement of steroids in patients with SJIA. Overall, biological therapies were well tolerated and resulted in improvement in clinical activity early after they had been initiated.

Persistence and compliance with biological drugs in patients with juvenile idiopathic arthritis are important points about which we have insufficient knowledge. In a retrospective longitudinal observational study involving 68 JIA patients, 16.2% of them required a second and 7.4% required a third biologic drug. They also found the persistence rate for biological therapy for 5 years was 64% (22). In the UK cohort and the Dutch registry, the percentage of SJIA patients who required a biologic switch was similar (26%) (23, 24). In our study, 75 patients (51%) remained on the same biologic, whereas 63 patients had at least one biologic switch. The most frequently changed biologic was anakinra, often after the first month of treatment. The reason for this high rate is the need to start treatment with a rapid and effective therapy to suppress the severe inflammation of SJIA. Furthermore, the necessity of daily anakinra practice and the presence of painful injections complicate its chronic and long-term use and require its switch after the stabilization of the SJIA flare. During the follow-up period, 58.8% of our patients treated with anakinra switched to other biological treatments. While canakinumab was the most frequently switched agent from anakinra, tocilizumab was second. Anti-TNF alpha therapies are the second most frequently switched biologic agents. A majority of anti-TNF alpha drugs were switched to anti IL-1 or anti IL-6 treatments due to insufficient efficacy.

Macrophage activation syndrome is a potentially life-threatening comorbidity

of SJIA that needs to be treated quickly and effectively (25). Especially after the widespread use of anakinra and canakinumab in SJIA and with MAS, the frequency of it has decreased significantly (17-19). We also showed in our study that the frequencies of MAS attacks, which contribute to morbidity and mortality, decreased following the initiation of biologics. The occurrence of MAS with biological therapy has been described in previous studies. Although the mechanism of occurrence of MAS during these therapies is still unclear, it has been reported that biological drugs have no significant effect on emergence of MAS and clinical features in patients with SJIA (17, 26). Our nine patients experienced MAS after baseline.

It is known that the frequency of bacterial infections increases as a result of both high disease activity, chronicity of the disease, and steroid treatments used in JIA patients (27). There are also studies that show that this risk is even higher in SJIA patients (28, 29). Similarly in our study, we observed adverse effects in 8.1% of our patients, mostly infections. In different studies, it was seen that the mortality rates in JIA patients who received biological therapy varied between 0.024–0.96/100 patient-years (30-32). Deaths in SJIA patients have generally been reported due to MAS (31, 32). In our study, one of our patients died due to aspiration pneumonia, and this was considered a situation independent of the use of biologics. In our study, no malignancy development was observed in our patients on biological therapy.

One of the biggest limitations of our study can be stated as the relatively small number of patients when evaluated on the basis of each biological drug. Evaluation of patients in a certain period of time caused this limitation. Another limitation was that the baseline PGA scores were missing in 2.7% of patients. Studies with a higher number of patients on a single biological agent may yield more valuable results in terms of efficacy and safety.

Conclusion

This study described the patient characteristics and the impact of biologics on disease activity in a real-life study of patients with SJIA in Turkey. Overall biological therapies resulted in improvement in clinical activity early after initiation. We have seen that biological treatments were well tolerated and provided a considerable decrease in the frequency of MAS. Further studies with a larger study size can reveal the differences between the biological drugs on disease outcomes and guide treatment decisions, thereby improving patient management.

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References

1. BRUCK N, SCHNABEL A, HEDRICH CM: Current understanding of the pathophysiology of systemic juvenile idiopathic arthritis (sJIA) and target-directed therapeutic approaches. *Clin Immunol* 2015; 159: 72-83. https://doi.org/10.1016/j.clim.2015.04.018
2. LIN YT, WANG CT, GERSHWIN ME, CHIANG BL: The pathogenesis of oligoarticular/polyarticular vs systemic juvenile idiopathic arthritis. *Autoimmun Rev* 2011; 10: 482-9. https://doi.org/10.1016/j.autrev.2011.02.001
3. MARTINI A: Systemic juvenile idiopathic arthritis. *Autoimmun Rev* 2012; 12: 56-9. https://doi.org/10.1016/j.autrev.2012.07.022
4. OMBRELLO MJ, ARTHUR VL, REMMERS EF *et al*.: Genetic architecture distinguishes systemic juvenile idiopathic arthritis from other forms of juvenile idiopathic arthritis: clinical and therapeutic implications. *Ann Rheum Dis* 2017; 76: 906-13. https://doi.org/10.1136/annrheumdis-2016-210324
5. HINZE CH, HOLZINGER D, LAINKA E *et al*.; PRO-KIND SJIA PROJECT COLLABORATORS: Practice and consensus-based strategies in diagnosing and managing systemic juvenile idiopathic arthritis in Germany. *Pediatr Rheumatol* 2018; 16: 7. https://doi.org/10.1186/s12969-018-0224-2
6. DUECKERS G, GUELLAC N, ARBOGAST M *et al*.: Evidence and consensus based GKJR guidelines for the treatment of juvenile idiopathic arthritis. *Clin Immunol* 2012; 142: 176-93. https://doi.org/10.1016/j.clim.2011.10.003
7. PASCUAL V, ALLANTAZ F, ARCE E, PUNARO M, BANCHEREAU J: Role of interleukin-1 (IL-1) in the pathogenesis of systemic onset juvenile idiopathic arthritis and clinical response to IL-1 blockade. *J Exp Med* 2005; 201: 1479-86. https://doi.org/10.1084/jem.20050473
8. MARTINI A, RAVELLI A, AVCIN T *et al*.: Pediatric rheumatology international trials organization (PRINTO). Toward new classification criteria for juvenile idiopathic arthritis: first steps, pediatric rheumatology international trials organization international consensus. *J Rheumatol* 2019; 46: 190-7. https://doi.org/10.3899/jrheum.180168
9. KUMAR S, KUNHIRAMAN DS, RAJAM L: Application of the Yamaguchi criteria for classification of "suspected" systemic juvenile idiopathic arthritis (SJIA). *Pediatr Rheumatol* 2012; 10: 40. https://doi.org/10.1186/1546-0096-10-40
10. VASTERT SJ, DE JAGER W, NOORDMAN BJ *et al*.: Effectiveness of first-line treatment with recombinant interleukin-1 receptor antagonist in steroid-naive patients with new-onset systemic juvenile idiopathic arthritis: results of a prospective cohort study. *Arthritis Rheumatol* 2014; 66: 1034-43. https://doi.org/10.1002/art.38296
11. NIGROVIC PA: Review: is there a window of opportunity for treatment of systemic juvenile idiopathic arthritis? *Arthritis Rheumatol* 2014; 66: 1405-13. https://doi.org/10.1002/art.38615
12. FOELL D, WITTKOWSKI H, HINZE C: Still's disease as biphasic disorder: current knowledge on pathogenesis and novel treatment approaches. *Z Rheumatol* 2020; 79: 639-48. https://doi.org/10.1007/s00393-020-00779-2
13. BEUKELMAN T, PATKAR NM, SAAG KG *et al*.: 2011 American College of Rheumatology recommendations for the treatment of juvenile idiopathic arthritis: initiation and safety monitoring of therapeutic agents for the treatment of arthritis and systemic features. *Arthritis Care Res* (Hoboken) 2011; 63: 465-82. https://doi.org/10.1002/acr.20460
14. RINGOLD S, WEISS PF, BEUKELMAN T *et al*.; AMERICAN COLLEGE OF RHEUMATOLOGY: 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 children receiving biologic medications. *Arthritis Rheum* 2013; 65: 2499-512. https://doi.org/10.1002/acr.22087
15. VON ELM E, ALTMAN DG, EGGER M, POCOCK SJ, GØTZSCHE PC, VANDENBROUCKE JP; STROBE INITIATIVE: Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *BMJ* 2007; 335: 806-8. https://doi.org/10.1016/j.ijsu.2014.07.013
16. GIANNINI EH, RUPERTO N, RAVELLI A, LOVELL DJ, FELSON DT, MARTINI A: Preliminary definition of improvement in juvenile arthritis. *Arthritis Rheum* 1997; 40: 1202-9. https://doi.org/10.1002/1529-0131(199707)40:7%3C1202::aid-art3%3E3.0.co;2-r
17. HORNEFF G, SCHULZ AC, KLOTSCHE J *et al*.: Experience with etanercept, tocilizumab and interleukin-1 inhibitors in systemic onset juvenile idiopathic arthritis patients from the BIKER registry. *Arthritis Res Ther* 2017; 19:

256. https://doi.org/10.1186/s13075-017-1462-2
18. DE MATTEIS A, BRACAGLIA C, PIRES MARAFON D *et al*.: Canakinumab in systemic juvenile idiopathic arthritis: real-world data from a retrospective Italian cohort. *Rheumatology* (Oxford) 2022; 61: 1621-9. https://doi.org/10.1093/rheumatology/keab619
19. LAINKA E, BAEHR M, RASZKA B *et al*.: Experiences with IL-1 blockade in systemic juvenile idiopathic arthritis - data from the German AID-registry. *Pediatr Rheum* 2021; 19: 38. https://doi.org/10.1186/s12969-021-00510-8
20. RUPERTO N, BRUNNER HI, QUARTIER P *et al*.; PAEDIATRIC RHEUMATOLOGY INTERNATIONAL TRIALS ORGANISATION (PRINTO) AND THE PEDIATRIC RHEUMATOLOGY COLLABORATIVE STUDY GROUP (PRCSG): Canakinumab in patients with systemic juvenile idiopathic arthritis and active systemic features: results from the 5-year long-term extension of the phase III pivotal trials. *Ann Rheum Dis* 2018; 77: 1710-9. https://doi.org/10.1136/annrheumdis-2018-213150.
21. NISHIMURA K, HARA R, UMEBAYASHI H *et al*.: Efficacy and safety of canakinumab in systemic juvenile idiopathic arthritis: 48-week results from an open-label phase III study in Japanese patients. *Mod Rheumatol* 2021; 31: 226-34. https://doi.org/10.1080/14397595.2020.1783163
22. NIETO-GONZÁLEZ JC, TRIVES-FOLGUERA L, MELGAREJO-ORTUÑO A *et al*.: Persistence and adherence to biologic therapies in juvenile idiopathic arthritis. *Sci Rep* 2021; 11: 16195. https://doi.org/10.1038/s41598-021-95252-8
23. KEARSLEY-FLEET L, HEAF E, DAVIES R *et al*.: Frequency of biologic switching and the outcomes of switching in children and young people with juvenile idiopathic arthritis: a national cohort study. *Lancet Rheumatol* 2020; 2: e217-e226. https://doi.org/10.1016/S2665-9913(20)30025-4
24. OTTEN MH, PRINCE FH, ANINK J *et al*.: Effectiveness and safety of a second and third biological agent after failing etanercept in juvenile idiopathic arthritis: results from the Dutch National ABC Register. *Ann Rheum Dis* 2013; 72: 721-7. https://doi.org/10.1136/annrheumdis-2011-201060
25. RAVELLI A, DAVÌ S, MINOIA F, MARTINI A, CRON RQ: Macrophage activation syndrome. *Hematol Oncol Clin North Am*. 2015; 29: 927-41. https://doi.org/10.1016/j.hoc.2015.06.010
26. YOKOTA S, IMAGAWA T, MORI M *et al*.: Longterm safety and effectiveness of the anti-interleukin 6 receptor monoclonal antibody tocilizumab in patients with systemic juvenile idiopathic arthritis in Japan. *J Rheumatol* 2014; 41: 759-67. https://doi.org/10.3899/jrheum.130690
27. BEUKELMAN T, XIE F, CHEN L *et al*.; SABER COLLABORATION: Rates of hospitalized bacterial infection associated with juvenile idiopathic arthritis and its treatment. *Arthritis Rheum* 2012; 64: 2773-80. https://doi.org/10.1002/art.34458
28. AYGUN D, SAHIN S, ADROVIC A *et al*.: The frequency of infections in patients with juvenile idiopathic arthritis on biologic agents: 1-year prospective study. *Clin Rheumatol* 2019; 38: 1025-30. https://doi.org/10.1007/s10067-018-4367-9
29. BRUNELLI JB, SCHMIDT AR, SALLUM AME *et al*.: High rate of serious infection in juvenile idiopathic arthritis patients under biologic therapy in a real-life setting. *Mod Rheumatol* 2018; 28: 264-70. https://doi.org/10.1080/14397595.2017.1349059
30. RINGOLD S, HENDRICKSON A, ABRAMSON L *et al*.: Novel method to collect medication adverse events in juvenile arthritis: results from the childhood arthritis and rheumatology research alliance enhanced drug safety surveillance project. *Arthritis Care Res* (Hoboken) 2015; 67: 529-37. https://doi.org/10.1002/acr.22487.
31. KLEIN A, KLOTSCHE J, HÜGLE B *et al*.: Long-term surveillance of biologic therapies in systemic-onset juvenile idiopathic arthritis: data from the German BIKER registry. *Rheumatology* (Oxford) 2020; 59: 2287-98. https://doi.org/10.1093/rheumatology/kez577
32. PRINCE FH, TWILT M, TEN CATE R *et al*.: Long-term follow-up on effectiveness and safety of etanercept in juvenile idiopathic arthritis: the Dutch national register. *Ann Rheum Dis* 2009; 68: 635-41. https://doi.org/10.1136/ard.2007.087411