

Biological treatment in resistant adult-onset Still's disease: A single-center, retrospective cohort study

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ABSTRACT

Objectives: The aim of this study was to assess the demographic and clinical characteristics of patients with adult-onset Still's disease (AOSD) under biological treatment.

Patients and methods: This retrospective cohort study included a total of 19 AOSD patients (13 males, 6 females; median age: 37 years; range, 28 to 52 years) who received biological drugs due to refractory disease between January 2008 and January 2020. The data of the patients were obtained from the patient files. The response to the treatment was evaluated based on clinical and laboratory assessments at third and sixth follow-up visits.

Results: Interleukin (IL)-1 inhibitor was prescribed for 13 (68.4%) patients and IL-6 inhibitor prescribed for six (31.6%) patients. Seventeen (89.5%) patients experienced clinical remission.

Conclusion: Biological drugs seem to be effective for AOSD patients who are resistant to conventional therapies. Due to the administration methods and the high costs of these drugs, however, tapering the treatment should be considered, after remission is achieved.

Keywords: Adult-onset Still's disease, anakinra, tocilizumab, treatment.

Adult-onset Still's disease (AOSD) is a rare systemic inflammatory disease with an unknown etiology. The main clinical manifestations of the disease are fever, maculopapular salmon-pink rash, arthralgia, and arthritis. Additionally, sore throat or pharyngitis, lymphadenopathy, hepatomegaly and splenomegaly, serositis, and myalgia can be seen.¹ Laboratory examination may indicate hyperferritinemia, elevated erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and transaminases, also anemia, and neutrophilic leukocytosis.^{1,2} A cautious differential diagnosis is mandatory to exclude different conditions such as malignancies, other inflammatory and infectious

diseases that may lead to similar clinical and laboratory findings.

It is well known that proinflammatory cytokines such as ferritin, interleukin (IL)-1, IL-6, IL-8, IL-18, tumor necrosis factor-alpha (TNF- α), and interferon-gamma (IFN- γ) are responsible for manifestations of AOSD.^{1,3,4} Macrophage activation syndrome, amyloidosis, disseminated intravascular coagulation, thrombotic thrombocytopenic purpura, microangiopathy, diffuse alveolar hemorrhage, and death may be seen due to the unsuppressed disease activity and continuing proinflammatory cytokine release.¹

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Although the primary treatment option for AOSD is corticosteroids, it may be insufficient for one-third of patients.⁵ Conventional immunosuppressive drugs (methotrexate, cyclosporine, leflunomide) may be necessary for remission induction and tapering corticosteroids.⁵ Biological drugs may be required for refractory disease. Due to the well-known effects of IL-1, IL-6, and TNF- α in the pathogenesis of the disease, inhibition of these pathways are favorable treatment options.⁶

There is a limited number of data in the literature regarding biological drug usage in refractory AOSD, and the clinical manifestations affecting the preference of biological drugs. In the present study, we aimed to assess the demographic and clinical characteristics of the patients with AOSD receiving biological drugs who were resistant to conventional therapies.

PATIENTS AND METHODS

This single-center, retrospective cohort study was conducted at Ankara Gulhane Training and Research Hospital, Rheumatology outpatient clinic between January 2008 and January 2020. A total of 59 patients with AOSD were screened. A total of 19 AOSD patients (13 males, 6 females; median age: 37 years; range, 28 to 52 years) who were resistant to conventional treatment and under biological treatment were included in the study. Data regarding the demographic and clinical characteristics of the patients and treatment regimens were received from the patient files. All patients were diagnosed with AOSD according to the Yamaguchi et al.'s criteria.⁷ The patients with missing data and without follow-up were excluded. Malignancies, infectious diseases and other inflammatory diseases were also excluded, before the diagnosis of AOSD. A written informed consent was obtained from each patient. The study protocol was approved by the Gülhane Training and Research Hospital Ethics Committee (No: 2020-301, Date: 30/06/2020). The study was conducted in accordance with the principles of the Declaration of Helsinki.

The biological drugs were prescribed to the patients with clinical and laboratory active disease. Before starting a biological drug, all patients received at least one conventional therapy

(corticosteroids, methotrexate, leflunomide, and cyclosporine-A). Anakinra (IL-1 inhibitor) and tocilizumab (IL-6 inhibitor) were used as biological therapy depending on the clinical and laboratory findings of the patients.

Clinical remission was defined as the absence of clinical and laboratory findings of active disease for at least two consecutive months. A flare was defined as a need for additional treatment or an increase in dosage of the currently used drugs due to a new clinical and laboratory activation in a patient with remission. The disease with flares was accepted as refractory disease. Resistant disease was defined as ongoing disease activity, regardless of the treatment for at least two consecutive months. The definitions of disease activity were determined based on the available studies in the literature.^{8,9}

Statistical analysis

Statistical analysis was performed using the SPSS for Windows version 11.5 (SPSS Inc., Chicago, IL, USA). The Kolmogorov-Smirnov test was used to assess the normality assumption. Normally distributed continuous variables were expressed in mean \pm standard deviation (SD), while non-normally distributed continuous variables were expressed in median and (interquartile range [25th-75th percentiles]). Categorical variables were expressed in number and frequency.

RESULTS

The median follow-up was 66.7 (range, 23.4 to 111.3) months. The median duration of biological treatment was 17 (range, 6 to 60) months. Disease pattern was chronic in 12 (63.2%) patients and polycyclic in seven (36.8%) patients. All patients had fever at presentation. Sixteen (84.2%) patients had a sore throat, 15 (78.9%) had arthralgia, 10 (52.6%) had a salmon-pink rash, 11 (57.9%) had hepatomegaly and splenomegaly, nine (47.4%) had arthritis, and seven (36.8%) had lymphadenopathy. Musculoskeletal manifestations occurred as polyarthritis, which was mostly seen in knees. All patients had increased levels of ESR, CRP, and ferritin, while 18 (94.7%) patients had neutrophilic leukocytosis. Serological tests (such as anti-nuclear antibody, rheumatoid factor, etc.) were negative in all patients. Conventional

Table 1. Demographic and clinical characteristics of the study groups

Study groups	All patients (n=19)			Anakinra (n=13)			Tocilizumab (n=6)								
	n	%	Mean±SD	Median	Q1-Q3	n	%	Mean±SD	Median	Q1-Q3	n	%	Mean±SD	Median	Q1-Q3
Age (year)			37		28-52			30		25.5-48.5			50.5		44.5-57
Sex															
Female	6	31.6				4	31.0				2	33.3			
Male	13	68.4				9	69.2				4	66.7			
16-35 years old patients	8	42.1				8	61.5				0	0			
Follow-up time (months)			66.7		23.4-111.3			99.1		26.8-135.6			38.8		21.1-83.8
bDMARD using duration (months)			17		6-60			14		5-85			22		9-43.5
Disease pattern															
Polycyclic	7	36.8				6	46.2				1	16.6			
Chronic	12	63.2				7	53.8				5	83.4			
Fever	19	100				13	100				6	100			
Salmon-pink rash															
Yes	10	52.6				6	46.2				4	66.7			
No	9	47.4				7	53.8				2	33.3			
Polyarthritits															
Yes	9	47.4				4	30.8				5	83.4			
No	10	52.6				9	69.2				1	16.6			
Arthralgia															
Yes	15	78.9				11	84.6				4	66.7			
No	4	21.1				2	15.4				2	33.3			
Sore throat															
Yes	16	84.2				12	92.3				4	66.7			
No	3	15.8				1	7.7				2	33.3			
Lymphadenopathy															
Yes	7	36.8				5	38.5				2	33.3			
No	12	63.2				8	61.5				4	66.7			
Hepatomegaly, splenomegaly															
Yes	11	57.9				7	53.8				4	66.7			
No	8	42.1				6	46.2				2	33.3			
Elevated transaminases															
Yes	9	47.4				7	53.8				2	33.3			
No	10	52.6				6	46.2				4	66.7			
Serositis															
Yes	3	15.8				3	23.1				1	16.7			
No	16	84.2				10	76.9				5	83.3			
Leucocyte (mm ³)			20,000		11,800-30,350			20,000		118,00-30350			17,750		15,000-21,725
Ferritin (ng/mL)			3,764		1,878-10,953			3,764		1,087-24,340			5,300		23,44.5-7,975.8
ESR (mm/h)			92.4±16.6					92.8±15.9					91.6±19.5		
CRP (mg/dL)			112		67-235			130		63.5-247.5			100.4		71-247.8
Conventional therapies															
Corticosteroids	19	100				13	100				6	100			
Methotrexate	16	84.2				11	84.6				5	83.3			
Leflunomide	7	36.8				4	30.8				3	50			
Cyclosporin-A	6	31.6				6	46.2				0	0			
Hydroxychloroquine	4	21.1				4	30.8				0	0			

SD: Standard deviation; Q: Quartile; bDMARD: Biological disease-modifying anti-rheumatic drug; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein.

immunosuppressive drugs used to treat AOSD were methotrexate (n=16, 84.2%), leflunomide (n=7, 36.8%), and cyclosporine-A (n=6, 31.6%). All patients were using corticosteroids before or during the first third months of the biological treatment (Table 1). Seventeen (89.5%) patients achieved clinical and laboratory remission, of whom 11 (84.6%) were using anakinra and six (100%) were using tocilizumab.

Anakinra treatment

Anakinra was used in 13 (68.4%) patients. Eight (61.5%) patients were in the 16-35 years old group, in which AOSD is more common. The median duration of anakinra treatment was 14 (range, 5 to 85) months. The clinical manifestations of the patients in this group were generally systemic. Fever (100%), sore throat (92.3%),

arthralgia (84.6%), the elevation of transaminases or hepatosplenomegaly (53.8%), and salmon-pink rash (46.2%) observed. The patients in the anakinra group received methotrexate and cyclosporine as conventional immunosuppressive drugs (Table 1). The other patients received anakinra as the first biological drug. All patients used anakinra at a dose of 100 mg/day. One (7.7%) patient receiving anakinra had a disease relapse at 10 years of the treatment. Disease remission was occurred in the first month of the treatment in this patient, after increasing the anakinra dose to 200 mg/day. Corticosteroids were discontinued in all patients during the first six months of follow-up, except for one (7.7%) patient with liver transplantation (Table 2, Patient No: 9). Two (15.4%) patients died from active disease. Anakinra treatment was discontinued in five (45.5%) of 11 patients who

Table 2. Clinical characteristics of patients using anakinra treatment

Patient no.	Age/Sex	Conventional therapy	Biological drug dose	Biological drug duration	Disease status	Comorbidity	Last status
1	21/F	CS, HQ, PE, Leflunomide, MTX, Cyclosporine-A	100 mg/day	2 month	Refractory	Thrombus in four extremities, microangiopathy	Exitus
2	24/M	CS, Cyclosporine-A	100 mg/day	7 month	Remission		Anakinra and Cyclosporine-A
3	25/M	CS, MTX, Cyclosporine-A	100 mg/day	11 month	Remission	Heart failure, GBS	Without treatment (5 month)
4	26/M	CS, MTX	100 mg/day	48 month	Remission		MTX (24 month)
5	28/M	CS, HQ, MTX, Leflunomide	100 mg/day	30 month	Remission	Heart failure	Anakinra and HQ
6	29/F	CS, HQ, MTX, Azathioprine	100 mg/day	110 month	Remission		Without treatment (24 month)
7	30/M	CS, MTX, Cyclosporine-A	100 mg/day	14 month	Remission		Anakinra
8	33/M	CS	100 mg/day	60 month	Remission		MTX (24 month)
9	37/M	CS, MTX, Cyclosporine-A	200 mg/day	132 month*	Remission	Hepatic failure, DM	Anakinra, tacrolimus, CS
10	48/F	CS, MTX	100 mg/day	14 day	Refractory	GBS	Exitus
11	49/M	CS, HQ, MTX, Leflunomide	100 mg/day	110 month	Remission	Cushing syndrome	Without treatment (24 month)
12	74/M	CS, MTX, Leflunomide	100 mg/day	5 month	Remission	DM	Anakinra and Leflunomide
13	77/F	CS, MTX, Cyclosporine-A	100 mg/day	5 month	Remission	DM	Anakinra and Cyclosporine-A

F: Female; M: Male; CS: Corticosteroid; HQ: Hydroxychloroquine; PE: Plasma exchange; MTX: Methotrexate; DM: Diabetes mellitus; HT: Hypertension; GBS: Guillain-Barré syndrome; * 100 mg/day during 120 month; 200 mg/day during 12 month.

Table 3. Clinical characteristics of patients using tocilizumab treatment

Patient no.	Age/Sex	Conventional therapy	Biological drug dose	Biological drug duration	Disease status	Comorbidity	Last status
1	37/F	CS, MTX	162 mg/week	10 month	Remission		Tocilizumab and MTX
2	47/F	CS, MTX, Leflunomide	162 mg/week	27 month**	Remission	Carpal sclerosis	Tocilizumab and MTX
3	49/M	CS, MTX	8 mg/kg/month	84 month	Remission		Tocilizumab and MTX
4	52/M	CS, Leflunomide	8 mg/kg/month	17 month	Remission	DM, HT, CKF	Tocilizumab
5	56/F	CS, MTX	162 mg/week	6 month	Remission	SCLC	Chemotherapy and radiotherapy
6	60/M	CS, MTX, Leflunomide	8 mg/kg/month	30 month	Remission	DM, HT	Leflunomide

F: Female; M: Male; CS: Corticosteroid; MTX: Methotrexate; DM: Diabetes mellitus; HT: Hypertension; CKF: Chronic kidney failure; SCLC: Small cell cancer of lungs; ** 8 mg/kg/month for 15 months; 162 mg/week for 12 months.

were in remission. The median time for cessation anakinra was 14 (range, 5 to 85) months. Two (18.2%) of these patients were using methotrexate as maintenance therapy, three (27.3%) patients were being followed without treatment (Table 2). One (7.7%) patient had a cutaneous reaction in the injection site by anakinra which was improved with antihistaminic therapy. No other side effects were observed.

Tocilizumab treatment

Tocilizumab used in 6 (31.6%) patients. There were no patients under 35 years old in the tocilizumab group. The median treatment duration for tocilizumab was 22 (range, 9 to 43.5) months. Resistant polyarticular manifestations, as well as systemic ones, were common in the tocilizumab group. The rate of fever was 100%, arthritis was 83.4%, and arthralgia, hepatosplenomegaly, sore throat, and salmon-pink rash were 66.7% in the tocilizumab group. Methotrexate was the most frequently prescribed conventional immunosuppressive drug. The second conventional immunosuppressive drug prescribed before the introduction of a biological drug was leflunomide (Table 1). In the tocilizumab group, all of the patients received tocilizumab as the first biological drug. Four (21.1%) patients received tocilizumab as 8 mg/kg every four weeks intravenously. Two (10.5%) patients received 162 mg every week, subcutaneously. One (5.3%) patient switched to subcutaneous

form at 15 months of treatment from intravenous form (Table 3, Patient No: 2). Tocilizumab was discontinued in one (5.3%) patient at six months of the treatment due to the development of lung cancer (Table 3, Patient No: 5). Tocilizumab treatment was discontinued after 30 months in only one (16.7%) of six patients with remission. Leflunomide was used for the maintenance therapy in this patient (Table 3, Patient No: 6).

In the first three months, all of the patients in tocilizumab group achieved remission. Corticosteroids were discontinued in the first six months of follow-up. No adverse reaction was seen in the tocilizumab group.

DISCUSSION

Corticosteroids and conventional therapies are usually successful in controlling disease activity in patients with AOSD. However, in a considerable amount of patients, life-threatening clinical manifestations may occur due to the ongoing disease activity. When the disease activity cannot be suppressed with conventional therapies, biological drugs may be an option for the treatment, which inhibit the pathogenetic cytokine pathways that responsible for the clinical findings of the disease. The current study showed that tocilizumab was predominantly preferred for musculoskeletal manifestations and anakinra was

mainly prescribed for systemic involvement for patients who were resistant to the conventional therapies.

Adult-onset Still's disease is an autoinflammatory disease which presents in genetically predisposed individuals with affection of innate and adaptive immune systems.¹⁰ Although many cytokines play a role in the development of the clinical findings of AOSD, IL-1 β is the main cytokine that is responsible for the clinical manifestations.¹¹ The triggering factors, such as infections or environmental factors, lead to secretion and activation of proinflammatory cytokines IL-1 β and IL-18 by provoking dysregulation of NOD-like receptor 3 protein (NLRP3). Also, Toll-like receptor 7 stimulates dendritic cells to activate neutrophil migration by inducing T helper 17 responses. The IL-1 β may induce TNF- α , IL-6, and IL-8 secretion.¹² The IL-6 induces the production of ferritin from hepatocytes, leading to the burst of clinical findings like fever and salmon-pink rash. On the other hand, IL-18 activates the secretion of IFN- γ , which plays a role as the main cytokine of macrophage activating syndrome.^{10,13,14} Although many cytokines are implicated in the formation of the broad clinical spectrum of AOSD, particularly IL-1, IL-6, and TNF- α are target cytokines for the treatment of the patients whose clinical findings cannot be suppressed with conventional therapies.^{15,16}

Still's disease was first described by George F. Still in 1897 as systemic juvenile arthritis.² The adult form of Still's disease is a rare entity, which is commonly seen among 16 to 35-year-old female patients.^{2,17,18} The current study found a higher rate of male and elderly patients. Also, all of the patients who received tocilizumab were older than the patients in the anakinra group and chronic polyarticular form of the disease was more common. Kalyoncu et al.¹⁹ reported that male sex, young age, and having polyarthritis were related to chronic disease course and refractory disease. The higher rate of both male patients and patients with chronic articular disease courses in the current study may be related to the poor prognostic factors which lead to the occurrence of resistant disease. Additionally, a 56-year-old patient was diagnosed with lung cancer at the sixth month of the tocilizumab therapy, indicating that older patients with AOSD should be followed carefully for the development of new-

onset malignancies. Also, AOSD may present as a paraneoplastic syndrome.²⁰ Thus, a thorough screening for malignancy is required in patients with AOSD.

The arthritis prevalence was lower in the current study than the studies performed with AOSD patients using conventional therapies.^{10,19} The patterns of arthritis were mainly oligoarticular or monoarticular in the studies evaluating conventional therapies, whereas, in the current study, all of the patients had refractory polyarthritis. The patients with monoarthritis and oligoarthritis may have benefited from conventional therapies, whereas polyarthritis may be resistant to conventional therapies.¹⁹ Also, the rate of the patients with arthritis was higher in the tocilizumab group than the anakinra group; however, the difference was not statistically significant. A recent study conducted in Italy investigated the efficacy of IL-1 inhibitory treatment in patients with AOSD and showed that the prevalence of systemic manifestations was 74.2%,²¹ similar to our study. Also, they reported an improvement in chronic articular disease with high Disease Activity Score 28 (DAS28). On the other hand, the literature data regarding the effect of IL-1 inhibitors on articular manifestations are controversial. Besides, few studies have shown that IL-1 inhibitors may not be sufficient for controlling the chronic articular disease, as well as controlling systemic disease.²²⁻²⁴ A different pathway other than IL-1 may be responsible for chronic articular manifestations. In the pathogenesis of the chronic articular form of AOSD, which resembles rheumatoid arthritis, TNF- α and IL-6 may play a more crucial role than IL-1.²⁵

Although the elevation of transaminases can be frequently observed in the course of AOSD, fulminant hepatic failure is a rare manifestation. Anakinra was prescribed for a patient (Patient No: 9) with hepatic failure who required liver transplantation. The patient is still under follow-up with remission and with normal transaminases under the treatment of low-dose corticosteroid, a calcineurin inhibitor, and anakinra.²⁶ Although the data regarding the use of anakinra in the patients with liver transplantation are limited, the patient was treated based on the data of the efficacy and safety of anakinra among the patients with renal transplantation.

Similar to the previous studies, the most commonly preferred conventional immunosuppressive drug before the commencement of biological drug was methotrexate.^{23,27,28} Cyclosporine was the second most common preferred drug for patients with hepatic transaminase elevations and who were receiving anakinra. Leflunomide was the drug secondly prescribed for the patients with mainly articular symptoms and who were receiving tocilizumab, consistent with the literature.^{22,27} Fewer adverse reactions were observed in the current study, compared to previous studies.^{22,29,30} There is no randomized-controlled study investigating the use of subcutaneous tocilizumab in patients with AOSD and most data are retrieved from case series.^{29,30} In the current study, three patients were using subcutaneous tocilizumab, two of them received subcutaneous form as the first administration, and one received subcutaneous form after achieving remission with intravenous form. A patient's treatment was discontinued after lung cancer was diagnosed. The other two patients were under follow-up with remission with subcutaneous form of tocilizumab, and no adverse events were observed.

Two patients in the study groups died from active disease and multiorgan failure eventually. The rest of the patients were followed with remission. The rate of the patients in remission and whose biological therapy was discontinued due to the remission were higher than the results of the Colafrancesco et al.'s study.²¹ In the literature, the data for cessation tocilizumab in the patients with remission are based on case reports. Frequently, lengthening the dosing interval or reducing the dose were preferred methods.²⁹ In the study presented by Reihl Crnogaj et al.,²⁸ three of four patients had disease flares after cessation of tocilizumab due to the remission of the disease.

This study has certain limitations. First, a small number of patients were included in the study. Second, there was no control group who were using only conventional therapies. Further large-scale studies including those using both conventional and biological therapies may provide more accurate results on the treatment, clinical, and laboratory course of the disease.

In conclusion, in the course of AOSD, biological drugs may be rarely required for patients with active disease and arthritis resistant to conventional therapies. However, many cytokines play a role in the pathogenesis of the disease, inhibition of the main cytokines with biological drugs is crucial. Using IL-1 inhibitors for the improvement of mainly systemic symptoms and using IL-6 inhibitors for the improvement of mainly chronic articular symptoms seem to be rational. Besides, due to both the potential adverse events and the high costs of the drugs, reducing the dose, lengthening the dosing interval, and ceasing the drugs should be the key points to be considered for patients with remission.

Declaration of conflicting interests

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