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ORIGINAL ARTICLE

Efficacy of anakinra treatment in pediatric rheumatic diseases: Our single-center experience

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ABSTRACT

Objectives: This study aims to present our experience on anakinra, a recombinant interleukin-1 (IL-1) receptor antagonist, and efficacy results in pediatric rheumatic diseases in our clinic.

Patients and methods: Between July 1st, 2016 and July 1st, 2020, a total of 33 pediatric patients (18 males, 15 females; mean age: 6±3.4 years; range 4 to 13 years) with pediatric rheumatic diseases who were treated with anakinra were retrospectively analyzed. The patients with over one-month treatment period and followed for at least one year were included. Demographic and clinical findings, outcomes, adverse events, prior and/or additional treatments were collected at baseline, at 3 and 12 months of therapy.

Results: There were 33 patients with different pediatric rheumatic diseases (11 with systemic juvenile idiopathic arthritis [sJIA] complicated by macrophage activation syndrome [MAS], six with hyperimmunoglobulin-D syndrome, five with cryopyrin-associated periodic syndrome, five with familial Mediterranean fever, four with idiopathic recurrent pericarditis, one with NLRP12-associated periodic fever syndrome and one with unclassified systemic autoinflammatory disease), in the study group. The complete response was observed 69.7% of patients, partial response in 24.2%, and no response in 6.1% at three months of treatment. Inactive disease status was achieved in 45.5% of the patients with remission-on medication and 18.2% of the patients with remission-off medication at the end of a year. Anakinra was switched to other biological treatments in 51.5% of patients (n=17). Biological switch to canakinumab and tocilizumab were observed in 70.6% and 29.4% of these patients. Except for local reactions (n=2), no adverse events were observed in any of the patients.

Conclusion: Anakinra appears to be a promising treatment alternative owing to its rapid effect as a result of its short half-life in autoinflammatory conditions. While short-term therapy seems to be sufficient for the sJIA complicated by MAS, the patients with systemic autoinflammatory diseases maintenance a more anakinra-dependent course.

Keywords: Anakinra, autoinflammatory diseases, familial Mediterranean fever, macrophage activation syndrome, systemic-onset juvenile idiopathic arthritis.

Interleukin-1 (IL-1) is a proinflammatory cytokine with two distinct ligands (IL-1α and IL-1β) that binds to the IL-1 receptor and stimulate the number of secondary inflammatory mediators. It plays a critical role in acute and chronic inflammation.[1] It is known that IL-1-mediated inflammation plays a role in the pathogenesis of a broad range of autoinflammatory conditions in childhood. The most common of these diseases caused by overexpression of IL-1 are familial Mediterranean fever (FMF), cryopyrin-associated periodic syndrome (CAPS), hyperimmunoglobulin-D syndrome (HIDS), systemic-onset juvenile idiopathic arthritis (SoJIA), and idiopathic recurrent pericarditis (IRP), respectively. Inhibition of IL-1 overexpression as an effective target therapy has been widely used in these diseases in the last decade.[2,3]

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Anakinra is a recombinant IL-1 receptor antagonist (IL-1Ra) that competitively binds to the IL-1 receptors, thus blocking the biological effects of the IL-1.[3] There are studies in the literature showing anakinra as an effective treatment for diseases, such as colchicine-resistant FMF, systemic juvenile idiopathic arthritis (sJIA) complicated by macrophage activation syndrome (MAS), Still disease and Muckle-Wells syndrome (MWS).[4-8] In this study, we present our anakinra experience and efficacy results in pediatric rheumatic diseases in our clinic.

PATIENTS AND METHODS

This single-center, retrospective study was conducted at Ümraniye Training and Research Hospital, Department of Pediatrics Division of Pediatric Rheumatology between July 1st, 2016 and July 1st, 2020. A total of 33 pediatric patients (18 males, 15 females; mean age: 6±3.4 years; range 4 to 13 years) with pediatric rheumatic diseases who were treated with anakinra were included. The patients treated with anakinra due to the resistant disease consisted of the following diagnoses: FMF, sJIA complicated by MAS, HIDS, CAPS, IRP, and other systemic autoinflammatory diseases (SAIDs). The diagnosis of MAS was made based on the Paediatric Rheumatology International Trials Organisation (PRINTO) MAS classification criteria.[9] The diagnosis of FMF was made based on pediatric FMF (Ankara) criteria.[10] Also, the diagnosis of other SAIDs was made based on the current diagnostic criteria.[11-13] The patients followed for at least one year after the induction of anakinra treatment were included in the study. The patients who did not attend to follow-up visits regularly or had shorter than one-month anakinra treatment period were excluded. Anakinra cessation was evaluated in patients who achieved remission by extending the treatment interval, considering the primary disease and clinical findings.

Outcomes

The demographic, clinical, and laboratory findings, outcomes, adverse events, prior and/or additional treatments were collected from the clinical database of the hospital at baseline (before starting anakinra), after three and 12 months of anakinra treatment. Outcome measures that were evaluated differently for each disease were examined from the patient records. The modified Wallace criteria were used to define inactive disease in sJIA. For a patient to achieve clinically inactive disease status based on these criteria, the following conditions must be fulfilled: no joints with active arthritis, absence of fever, rash, splenomegaly, active uveitis or generalized lymphadenopathy, no presence of erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) elevation related to juvenile idiopathic arthritis, the best possible physician's global assessment score and morning stiffness less than 15 min.[14] Auto-inflammatory diseases activity index (AIDAI) score was used to assess disease activity for FMF, HIDS, CAPS, and other SAIDs. The AIDAI score encompasses the fever >38°C, abdominal pain, nausea/vomiting, diarrhea, headaches, chest pain, painful nodes, arthralgia/myalgia, swelling of the joints, eye manifestations, skin rash, pain relief drugs taken, and calculated by the presence or absence of these symptoms daily in a month.[15] Also, the overall health status of the patients was also evaluated with a Visual Analog Scale (VAS) (1 to 10 - best to the worst) and defined as physician's and patient's global assessment (PGA) scores. According to all these criteria, inactive disease was defined as the absence of active systemic features for each specific disease, normal ESR and CRP, and with the best possible PGA score. The patients whose disease findings improved more than 50%, but inactive disease status could not be provided were defined as partial responders. Those with less than 50% improvement in disease activity were defined as non-responders. Patients with diagnoses other than sJIA were also grouped as SAIDs. The AIDAI, CRP, ESH, ferritin and platelet count results were evaluated and compared before and after treatment in patients diagnosed with sJIA and SAIDs. These outcome parameters were also compared between responsive and non-responsive patients in each group.

A treatment-emergent adverse event (TEAE) was defined as a noxious and unintended event occurs in normal prophylaxis or treatment doses and first emerged from first administration until the last visit within the treatment period which does not necessarily have a causal relationship

Table 1. Demographic and clinical characteristics of patients

Characteristics	n	%	Median	IQR
Age (year)				
At diagnosis			6	4-13
At anakinra onset			8	5-13.5
Sex				
Female	15	45.5		
Male	18	54.5		
Follow-up duration (month)			14	3.7-28
Diagnosis				
Familial Mediterranean fever	5	15.2		
SoJIA complicated with MAS	11	33.3		
Hyperimmunoglobulin-D syndrome	6	18.2		
CAPS	5	15.2		
Idiopathic recurrent pericarditis	4	12.1		
NAPS12	1	3		
Unclassified SAID	1	3		
Previously treatments				
Colchicine	22	66.6		
Methylprednisolone	11	33.3		
Methotrexate	4	12.1		
Cyclosporine	6	18.2		
Anakinra treatment duration (month)			3	1-4

IQR: Interquartile range; SoJIA: Systemic-onset juvenile idiopathic arthritis; CAPS: Cryopyrin-associated periodic syndrome; MAS: Macrophage activation syndrome; NAPS12: NLRP12-associated periodic fever syndrome; SAID: Systemic autoinflammatory disease.

with this treatment. Also, a serious adverse event (SAE) was defined as any untoward medical occurrence that at any dose results in death; life-threatening; requiring inpatient hospitalization or prolongation of existing hospitalization; producing persistent or significant disability/incapacity, or a congenital anomaly/birth defect.[16] All TAESs and SAEs were also collected and evaluated.

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 23.0 software (IBM Corp., Armonk, NY, USA). Descriptive data were expressed in mean ± standard deviation (SD), median (min-max) or number and frequency, where applicable. The normality of the distribution of the variables was assessed by

Table 2. Comparison of outcome parameters between patients with SoJIA and SAID before and after treatment

	Patients with SoJIA			Patients with SAID		
	Pre-treatment	After treatment		Pre-treatment	After treatment	
	Mean±SD	Mean±SD	*p*	Mean±SD	Mean±SD	*p*
AIDAI	NA	NA	-	14.8±9.5	1.3±2	<0.001
C-reactive protein (mg/L)	91.3±32.8	13.5±21.7	0.003	99.3±40.2	4.5±3.3	<0.001
Erythrocyte sedimentation rate (mm/h)	33.6±9.6	18.9±12.5	0.03	52.4±16.8	14.3±6	<0.001
Platelet count* (/mm^3)	240,272±102,791	340,545±83,820	0.06	418,636±69,084	290,227±52,887	<0.001
Ferritin* (mg/dL)	4,910±599	234±203	0.003	NA	NA	-

SoJIA: Systemic-onset juvenile idiopathic arthritis; SAID: Systemic autoinflammatory disease; SD: Standard deviation; AIDAI: Autoinflammatory diseases activity index; NA: Not available.

Table 3. Comparison of outcome parameters between responsive and non-responsive patients

	SoJIA group						SAID group				
	Patients with complete response (n=7)			Patients with partial or non-response (n=4)			Patients with complete response (n=14)			Patients with partial or non-response (n=8)		
	n	%	Mean±SD	n	%	Mean±SD	p	n	%	Mean±SD	n	%	Mean±SD	p
AIDAI*			NA			NA	-			13.2±10.4			17.6±7.3	0.29
CRP* (mg/L)			84±37.8			104.2±19.4	0.32			86.5±33.7			121.7±42.9	0.04
ESR* (mm/h)			35.4±11.5			30.5±11.4	0.41			52.4±19.3			52.5±12.3	0.99
Platelet count* (x10^3) (/mm^3)			266±103			195±98	0.26			423±71			409±68	0.65
Ferritin* (mg/dL)			4,547±6111			5,547±3817	0.75			NA			NA	-
Presence of arthritis	0	0		2	50		0.1	NA	NA		NA	NA		-

SoJIA: Systemic-onset juvenile idiopathic arthritis; SAID: Systemic autoinflammatory disease; SD: Standard deviation; AIDAI: Autoinflammatory diseases activity index; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; NA: Not available.

visual (histogram, probability plots) and analytic methods (Kolmogorov-Smirnov/Shapiro-Wilk test). The Wilcoxon test was used to analyze differences between the non-parametric dependent variables. A p value of <0.05 was considered statistically significant.

RESULTS

There were 33 patients treated with anakinra for the different pediatric rheumatic diseases, in the study group. The diagnoses of these patients were as follows: 11 were sJIA complicated by MAS, six were HIDS, five were CAPS, five were FMF, four were IRP, one was NLRP12-associated periodic fever syndrome (NAPS12) and the other one was unclassified SAID. The median age at the time of diagnosis was six (range, 4 to 13) years. The median follow-up duration of the patients was 14 (range, 3.7 to 28) months. Twenty-two of the patients were on treatment with colchicine, 11 with methylprednisolone, four of them with methotrexate, and six of them with cyclosporine before the initiation of anakinra. Demographic and clinical characteristics of the patients are shown in Table 1.

The standard dosage of 2 mg/kg/day for anakinra (maximum daily dose was 100 mg in children above 50 kg) was started in all the patients. The patient's median anakinra treatment duration was three (range, 1 to 4) months. Fever and CRP normalized within median two (range, 1 to 3) and five (range, 5 to 7) days, respectively. The median physician's and PGA scores were found to be seven (range, 6 to 8) and eight (range, 7 to 9) at the time of anakinra initiation. The mean CRP, ESR, ferritin, and platelet counts in the sJIA and SAID patient groups before treatment are presented in Table 2. The mean AIDAI score in patients with SAID is also shown in Table 2.

Third-month outcomes

Until the third month of treatment, 23 patients (69.7%) achieved a complete remission (no attack was seen or MAS was improved). While 21 of these patients (63.6%) were in remission on medication, anakinra was ceased in two (6.1%) of them (remission off medication). Also, the frequency of attacks was decreased by more

than 50% (partial response) in eight patients (24.2%) and less than 50% (non-response) in two (6.1%). Anakinra treatment was switched to canakinumab due to local reaction or daily use difficulties in one patient from remission on medication group and in three patients from the partial responder group. One patient with sJIA developed persistent arthritis and, in another with resistant MAS, anakinra treatment was switched to tocilizumab due to unresponsiveness. Of these two non-responders, the patient with resistant MAS died due to being unresponsive to biological and immunosuppressive treatments. Three- and 12-month efficacy outcomes of anakinra treatment are shown in Table 4.

First-year outcomes

At 12-month assessment after the initiation of treatment, 63.6% of patients were achieved complete remission. Inactive disease status was achieved in 45.5% of patients with remission on medication and 18.2% of patients with remission off medication (anakinra ceased between one to 12 months after initiation). The median physician's and PGA scores were found to be 1 (range, 0 to 3) and 1 (range, 0 to 2) at the last admission. While a statistically significant improvement was observed in all parameters in the SAID group after treatment ($p<0.001$), it was found in CRP and ferritin values in the sJIA group ($p=0.003$) (Table 2).

Treatment-responsive and non-responsive patients were compared by clinical and laboratory manifestations on admission, within the sJIA/MAS and SAID groups (Table 3). In the sJIA/MAS group, there was no parameter predicting treatment unresponsiveness, except for the presence of arthritis. Half of the patients with arthritis on admission did not achieve a complete or partial response to the treatment within a year. In the SAID group, baseline CRP was significantly higher in patients that were non-responsive/partially responsive to treatment ($p=0.04$). Conversely, no statistically significant difference was observed between baseline AIDAI scores among SAID patients.

In 51.5% of patients, anakinra was switched to other biological treatments for different reasons (36.3% partial response or non-response, 6.1% injection site reactions and 9.1% daily injection difficulty), at the end of a year. Biological drug switch to canakinumab and tocilizumab was observed in 70.6% and 29.4% of these patients, respectively (Table 4). No adverse events were observed, except for local reactions (n=2).

Table 4. Efficacy and safety outcomes of anakinra treatment

Characteristics	n	%	Median	IQR	n	%	Median	IQR
Complete responders	23	69.7			21	63.6		
Remission on medication	21	63.6			15	45.5		
Remission off medication	2	6.1			6	18.2		
Partial responders	8	24.2			10	30.3		
Non- responders	2	6.1			2	6.1		
Physician's global assessment score (0-10)			7 (at baseline)	6-8			1 (at last administration)	0-3
Patient's global assessment score (0-10)			8 (at baseline)	7-9			1 (at last administration)	0-2
The patients whose treatment switched or ceased due to lack of efficacy	2	6.1			12	36.3		
The patients whose treatment switched or ceased due to other reasons*	4	12.1			5	15.1		
The patients switched to canakinumab	4				12			
The patients switched to tocilizumab	2				5			

IQR: Interquartile range; * Injection site reactions and daily injection difficulties.

Table 5. Treatment responses and switch outcomes at 12 months with respect to patient groups

		Remission on medication		Remission off medication		Partial responders		Non-responders		Biologic switch		The patients switched to canakinumab		The patients switched to tocilizumab	
	n*	n	%	n	%	n	%	n	%	n	%	n	%	n	%
SoJIA	11	3	27	4	36	2	18	2	18	4	36	-	-	4	36
FMF	5	2	40	2	40	1	20	-	-	3	60	3	60	-	-
HIDS	6	2	33	-	-	4	66	-	-	4	66	4	66	-	-
CAPS	5	4	80	-	-	1	20	-	-	4	80	4	80	-	-
IRP	4	3	75	-	-	1	25	-	-	1	25	-	-	1	25
NAPS12	1	1	-	-	-	-	-	-	-	-	-	-	-	-	-
uSAIO	1	-	-	-	-	1	100	-	-	1	100	1	100	-	-

* Number of patients for each disease. SoJIA: Systemic-onset juvenile idiopathic arthritis; FMF: Familial Mediterranean fever; HIDS: Hyperimmunoglobulin-D syndrome; CAPS: Cryopyrin-associated periodic syndrome; IRP: Idiopathic recurrent pericarditis; NAPS12: NLRP12-associated periodic fever syndrome, uSAID: Unclassified systemic autoinflammatory disease.

The treatment responses and switch outcomes of the patients in the 12-month period with respect to patient groups are shown in Table 5. While remission off medication was achieved in four patients with SoJIA, it was not provided in any of the other patients with SAID, since a flare was emerged in the interval widening period (Table 5).

DISCUSSION

Interleukin-1 is the prototypical pro-inflammatory cytokine that modulates the inflammatory cascade in many diseases. In this study, we evaluated the efficacy and safety of anakinra treatment, as an IL-1Ra, in our pediatric patients with varying autoinflammatory diseases. In the majority of our patients, partial or complete responses were achieved and no significant side effects occurred. During the 12-month follow-up period, complete response with anakinra was achieved in 21 (63.6%) of 33 patients and partial response in 10 (30.3%) of them. Seventeen patients required to switch to another biological drug due to inadequate response (n=12, 36.3%) and adverse events or non-compliance with treatment (n=5, 15.1%). Previous studies have reported varying rates of treatment response with anakinra in sJIA ranging from 31 to 85%.[17-19] Saccomanno et al.[19] evaluated the potential predictors for the effectiveness of anakinra treatment in sJIA patients and they showed that the shorter disease duration, lower active joint count, higher ferritin level, and systemic manifestations were associated with the achievement of complete remission. It was also demonstrated that intravenous anakinra therapy can be also used effectively in the treatment of MAS.[20] Another recent study showed that administration of methotrexate from baseline in patients with sJIA, regardless of the presence of MAS, might be beneficial in maintaining inactive disease status.[21] In a MAS cohort of 80 patients, corticosteroid and intravenous immunoglobulin treatments were used as the first-line treatment options, and 12.5% of the patients required biological therapy. This study also showed that tocilizumab and infliximab were effective in controlling sJIA complicated by MAS.[22] Seven of our 11 patients (63.7%) with sJIA complicated by MAS achieved complete remission, while two had a partial response and two were

unresponsive in our cohort. We observed that the anakinra was usually effective in breaking the MAS course in sJIA patients. The short half-life of anakinra provided an important advantage in these patients thanks to its rapid impact. Even, frequent disease flares and tocilizumab switch while taking anakinra therapy were observed in patients with persistent arthritis. Half of our sJIA patients with partial or non-response to anakinra consisted of patients with arthritis. Correspondingly, one non-responsive sJIA patient presented with chronic arthritis and reached remission after switching to tocilizumab. Additionally, there may be conditions in which the IL-1-based inflammation cascade cannot be treated, despite maximum anti-IL-1 treatment dosages. Also, one patient with sJIA complicated by MAS died, despite the maximum dosage of anakinra and tocilizumab treatments.

The inflammasomopathies constitute the prototype of SAIDs, resulting in mutations in NLRP3, NLRP1, NLRC4, and pyrin inflammasomes. Previous studies have shown the effectiveness of anakinra among patients with inflammasomopathies.[3,4,7,23,24] In the present study, a total of 21 patients with inflammasomopathy were treated with anakinra. Among them, two patients with HIDS, four with CAPS, four with FMF, three with IRP and one with NAPS12 achieved remission. Anakinra was switched to canakinumab in seven patients due to inadequate response and in five due to injection site reactions or daily injection difficulties. In our cohort, inadequate response or disease flare under anakinra treatment was usually observed during the interval widening of treatment in patients with SAIDs. Close monitoring of these patients is important during the interval widening of treatment. This group of patients (CAPS, HIDS or IRP) appears to be anti-IL-1 treatment-dependent, due to the short effectiveness of anakinra. We consider that the development of drug modifications with a longer half-life such as canakinumab may be beneficial to provide treatment alternatives in this group of patients. However, the existing data about the predictors for the effectiveness of anakinra in SAIDs are still limited.

Non-steroidal anti-inflammatory drugs and colchicine are the first-line treatments of acute pericarditis. Nevertheless, corticosteroids and immunosuppressant drugs are required in persistent or relapsing cases. According to the European Society of Cardiology (ESC) guidelines, anti-IL-1 therapy is recommended in patients requiring prolonged steroid treatment.[25,26] Up to date, a restricted number of pediatric patients with IRP receiving anakinra was reported and all of them achieved rapid maintained response.[27,28] Similarly, three of our four patients with IRP achieved complete remission within a short period and were still in remission with anakinra during the 12-month follow-up period.

The most frequent adverse event in patients receiving anakinra is an injection site reaction which is usually mild, dose-dependent, and transient resolving spontaneously within a few weeks.[29] The rate of injection site reactions was 6.1% in our study. Furthermore, patients may refuse daily injections due to its painful effect and restriction of daily activities. Anakinra was switched to canakinumab in 9.1% of patients due to daily injection difficulty.

The single-center, retrospective design with a relatively small and heterogeneous sample size are the main limitations of this study.

In conclusion, our study results show that anakinra is an effective and safe treatment option in patients with MAS or refractory autoinflammatory diseases. Mortal conditions such as MAS can be quickly improved with anakinra. In sJIA patients with a monocyclic course, the attack or MAS course can be controlled with short-term hit-and-run treatment of anakinra, while the SAIDs group seems to be more dependent on anti-IL-1 treatment.

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Ethics Committee Approval: The study protocol was approved by the Ümraniye Training and Research Hospital Ethics Committee (no: B10.1TKH.4.34.H.G.P.0.01). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from the parents and/or legal guardians of the patients.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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REFERENCES

1. Dinarello CA. Immunological and inflammatory functions of the interleukin-1 family. Annu Rev Immunol 2009;27:519-50.
2. Goldbach-Mansky R, Kastner DL. Autoinflammation: The prominent role of IL-1 in monogenic autoinflammatory diseases and implications for common illnesses. J Allergy Clin Immunol 2009;124:1141-9.
3. Jesus AA, Goldbach-Mansky R. IL-1 blockade in autoinflammatory syndromes. Annu Rev Med 2014;65:223-44.
4. Ben-Zvi I, Kukuy O, Giat E, Pras E, Feld O, Kivity S, et al. Anakinra for colchicine-resistant familial mediterranean fever: A randomized, double-blind, placebo-controlled trial. Arthritis Rheumatol 2017;69:854-62.
5. Sag E, Akal F, Atalay E, Akca UK, Demir S, Demirel D, et al. Anti-IL1 treatment in colchicine-resistant paediatric FMF patients: Real life data from the HELIOS registry. Rheumatology (Oxford) 2020;59:3324-9.
6. Sönmez HE, Demir S, Bilginer Y, Özen S. Anakinra treatment in macrophage activation syndrome: A single center experience and systemic review of literature. Clin Rheumatol 2018;37:3329-35.
7. Kuemmerle-Deschner JB, Tyrrell PN, Koetter I, Wittkowski H, Bialkowski A, Tzaribachev N, et al. Efficacy and safety of anakinra therapy in pediatric and adult patients with the autoinflammatory Muckle-Wells syndrome. Arthritis Rheum 2011;63:840-9.
8. Garg S, Wynne K, Omoyinmi E, Eleftheriou D, Brogan P. Efficacy and safety of anakinra for undifferentiated autoinflammatory diseases in children: A retrospective case review. Rheumatol Adv Pract 2019;3:rkz004.
9. Ravelli A, Minoia F, Davì S, Horne A, Bovis F, Pistorio A, 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 Collaborative Initiative. Ann Rheum Dis 2016;75:481-9.
10. Yalçinkaya F, Ozen S, Ozçakar ZB, Aktay N, Cakar N, Düzova A, et al. A new set of criteria for the diagnosis of familial Mediterranean fever in childhood. Rheumatology (Oxford) 2009;48:395-8.
11. Gattorno M, Hofer M, Federici S, Vanoni F, Bovis F, Aksentijevich I, et al. Classification criteria for autoinflammatory recurrent fevers. Ann Rheum Dis 2019;78:1025-32.
12. Shinar Y, Ceccherini I, Rowczenio D, Aksentijevich I, Arostegui J, Ben-Chétrit E, et al. ISSAID/EMQN best practice guidelines for the genetic diagnosis of monogenic autoinflammatory diseases in the next-generation sequencing era. Clin Chem 2020;66:525-36.
13. Demir F, Doğan ÖA, Demirkol YK, Tekkuş KE, Canbek S, Karadağ ŞG, et al. Genetic panel screening in patients with clinically unclassified systemic autoinflammatory diseases. Clin Rheumatol 2020;39:3733-45.
14. Wallace CA, Giannini EH, Huang B, Itert L, Ruperto N; Childhood Arthritis Rheumatology Research Alliance; Pediatric Rheumatology Collaborative Study Group; Paediatric Rheumatology International Trials Organisation. American College of Rheumatology provisional criteria for defining clinical inactive disease in select categories of juvenile idiopathic arthritis. Arthritis Care Res (Hoboken) 2011;63:929-36.
15. Piram M, Koné-Paut I, Lachmann HJ, Frenkel J, Ozen S, Kuemmerle-Deschner J, et al. Validation of the auto-inflammatory diseases activity index (AIDAI) for hereditary recurrent fever syndromes. Ann Rheum Dis 2014;73:2168-73.
16. International Conference on Harmonisation. Clinical Safety Data Management: definitions and standards for expedited reporting E2A. Available at: https://database.ich.org/sites/default/files/E2A_Guideline.pdf [Accessed: June, 2016].
17. Quartier P, Allantaz F, Cimaz R, Pillet P, Messiaen C, Bardin C, et al. A multicentre, randomised, double-blind, placebo-controlled trial with the interleukin-1 receptor antagonist anakinra in patients with systemic-onset juvenile idiopathic arthritis (ANAJIS trial). Ann Rheum Dis 2011;70:747-54.
18. Nigrovic PA, Beukelman T, Tomlinson G, Feldman BM, Schanberg LE, Kimura Y; Childhood Arthritis and Rheumatology Research Alliance Systemic Juvenile Idiopathic Arthritis Consensus Treatment Plan Workgroup. Bayesian comparative effectiveness study of four consensus treatment plans for initial management of systemic juvenile idiopathic arthritis: FiRst-Line Options for Systemic juvenile idiopathic arthritis Treatment (FROST). Clin Trials 2018;15:268-77.
19. Saccomanno B, Tibaldi J, Minoia F, Bagnasco F, Pistorio A, Guariento A, et al. Predictors of effectiveness of anakinra in systemic juvenile idiopathic arthritis. J Rheumatol 2019;46:416-21.
20. Phadke O, Rouster-Stevens K, Giannopoulos H, Chandrakasan S, Prahalad S. Intravenous administration of anakinra in children with

macrophage activation syndrome. Pediatr Rheumatol Online J 2021;19:98.
21. Adiguzel Dundar H, Acari C, Turkucar S, Unsal E. Treatment of systemic JIA: When do we need a biologic? Real world data of a single center. Mod Rheumatol 2021;31:684-90.
22. Zou LX, Zhu Y, Sun L, Ma HH, Yang SR, Zeng HS, et al. Clinical and laboratory features, treatment, and outcomes of macrophage activation syndrome in 80 children: A multi-center study in China. World J Pediatr 2020;16:89-98.
23. Sönmez HE, Özen S. A clinical update on inflammasomopathies. Int Immunol 2017;29:393-400.
24. Soriano A, Soriano M, Espinosa G, Manna R, Emmi G, Cantarini L, et al. Current therapeutic options for the main monogenic autoinflammatory diseases and PFAPA syndrome: Evidence-based approach and proposal of a practical guide. Front Immunol 2020;11:865.
25. Adler Y, Charron P, Imazio M, Badano L, Barón-Esquivias G, Bogaert J, et al. 2015 ESC Guidelines for the diagnosis and management of pericardial diseases: The Task Force for the Diagnosis and Management of Pericardial Diseases of the European Society of Cardiology (ESC): Endorsed by: The European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J 2015;36:2921-64.
26. Brucato A, Imazio M, Gattorno M, Lazaros G, Maestroni S, Carraro M, et al. Effect of anakinra on recurrent pericarditis among patients with colchicine resistance and corticosteroid dependence: The AIRTRIP randomized clinical trial. JAMA 2016;316:1906-12.
27. Imazio M, Brucato A, Pluymaekers N, Breda L, Calabri G, Cantarini L, et al. Recurrent pericarditis in children and adolescents: A multicentre cohort study. J Cardiovasc Med (Hagerstown) 2016;17:707-12.
28. Rodriguez-Gonzalez M, Ruiz-Gonzalez E, Castellano-Martinez A. Anakinra as rescue therapy for steroid-dependent idiopathic recurrent pericarditis in children: Case report and literature review. Cardiol Young 2019;29:241-3.
29. Cvetkovic RS, Keating G. Anakinra. BioDrugs 2002;16:303-11.