The use of interleukin 1 receptor antagonist (anakinra) in Kawasaki disease: A retrospective cases series

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Conflicts of interest

MP has no conflict of interest related to this study
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Key words: Kawasaki disease; vasculitis; pediatric; interleukin-1; anakinra, coronary artery aneurysms; pediatrics; autoinflammatory disease.

Abstract

Objectives

To identify the clinical characteristics, reasons for use and response to treatment with anakinra in a series of patients with Kawasaki Disease (KD).

Study design

A retrospective chart review of patients treated with anakinra for KD diagnosed according to the AHA criteria. We compared clinical, biological and echocardiographic characteristics of KD before and after anakinra use. We analysed reasons for use of anakinra, and compared treatment regimens used in 7 European KD referral centres.

Results

Eight boys and 3 girls with treatment-refractory KD, aged 4 months to 9 years old, received at least 2 different KD treatments prior to anakinra, which was given on mean at 25 days after disease onset (8 to 87 days). The main reasons for use of anakinra were clinical and biological inflammation, progression of coronary dilatations, and severe myocarditis with cardiac failure. Doses of anakinra ranged from 2 to 8 mg/kg and duration varied from 6 to 81 days. Efficacy of anakinra was judged in terms of fever resolution (100%), decrease of CRP (100%), and in terms of its effect on coronary artery dilatation Z scores, which decreased in 10/11 patients and increased in one who died suddenly of pericardial hemorrhage.

Conclusion

Anakinra used late in the disease course led to a rapid and sustained improvement in clinical and biological inflammation. Our retrospective analysis did show neither a striking nor a rapid decrease of coronary dilatations and we cannot determine if anakinra itself had an effect on coronary artery dimensions.

Introduction

Kawasaki disease (KD) is the most frequent vasculitis of children aged less than 5 years, and the main cause of acquired heart disease in developed countries. KD has also been seldom reported in young adults at a mean age of 30 years [1]. Epidemiologic data strongly suggest an infectious aetiology, although the causative agent has yet to be identified. Genetic factors also increase susceptibility to KD, as indicated by its strikingly high incidence in children of Asian ethnicity, both in and outside the Far East, and by an increased incidence in first-degree family members [2, 3]. KD is a self-limited illness that results in coronary artery aneurysms in up to 25% of untreated children. Giant aneurysms, myocardial infarction and myocarditis are present in a minority of KD cases, and rarely lead to early death [4]. Administration of high-dose intravenous immunoglobulin (IVIG) in combination with aspirin results in dramatic clinical improvement and reduced incidence of coronary artery aneurysms in the majority of patients with KD [5,6]. A subset (20%) of patients has persistence or recrudescence of fever following IVIG treatment, and are at increased risk for coronary vasculitis. The American heart association (AHA) has recommended administering a second dose of IVIG (2 g/kg) to patients who fail to become afebrile within 48 hours after completion of the first infusion, even though the benefits of this approach may be limited, especially in terms of efficacy on coronary abnormalities [7]. Identifying patients at risk for IVIG resistance is difficult outside the Asian population, and there remains a critical unmet need to identify an anti-inflammatory treatment that is efficacious in all KD patients. Some clinical features of KD are similar to those observed in systemic autoinflammatory diseases (SAID), including systemic-onset juvenile idiopathic arthritis (SoJIA): abrupt and seemingly unprovoked onset of fever at a young age, skin rash, eye and mouth inflammation, cervical adenitis, and pericarditis. Marked elevation of acute phase reactants: e.g. CRP and neutrophils, elevated platelets, hypoalbuminemia without evidence of autoantibodies are also very concordant with soJIA. Intriguingly, transient coronary abnormalities have also been noticed in patients with soJIA [8]. Recent evidence from studies in animals and humans suggest a critical role for interleukin-1 (IL-1) α and β in the pathogenesis of KD. For example, IL-1 polymorphisms could be associated either to response or resistance to IVIG treatment. Interestingly elevated transcripts have been shown in IVIG-resistant KD patients, those carrying the highest risk for coronary aneurysms [9, 10]. Of particular note, only

blockade of IL-1, but not of tumour necrosis factor (TNF) α, reduced the myocarditis in the LCWE (Lactobacillus casei cell wall extract)-injected mice and TNFα blockade as adjunctive therapy to IVIG gave success regarding fever and inflammatory parameters but with no differences in coronary artery evolution in a controlled trial in humans [11-14]. Anakinra has been reported to successfully treat KD in 3 patients not responding to standard treatment with IVIG [15-18].

Due to its availability and its safety of use, anakinra is increasingly used off label to treat patients with other IL-1 related diseases [19, 20]. Here, we present further experience of anakinra use in order to identify the clinical characteristics, reasons for use and response to treatment with anakinra in a retrospective series of patients with KD.

Patients and methods

We collected retrospective data from KD patients treated with anakinra using a dedicated questionnaire. Patients were recruited in France through the SOFREMIP (SOciété Francophone de Rhumatologie Et de Médecine Interne Pédiatriques) network, and other European countries (Italy, Spain, United Kingdom) through an established international network on KD. Inclusion criteria were a diagnosis of KD according to the American Heart association (AHA) criteria for complete or incomplete KD, treatment with anakinra for KD, and sufficient available data for analyses. Recorded data included demographics, clinical, biological and echocardiographic characteristics of KD, and timing of treatments, history before and after anakinra. Data collected regarding anakinra treatment were: reasons for use, doses applied, and duration of treatment, concomitant treatments and any adverse event. Cardiologic findings were recorded before and after anakinra treatment, and at the last follow-up. Efficacy of anakinra was assessed by clinical (fever and symptoms of KD), biological (blood cell count, C-reactive protein: CRP), and cardiologic findings. As we performed a retrospective chart review, there was institutional approval for collection of the data as part of an audit, without individual patient consent

Results

Clinical, biological and cardiologic characteristics

Eleven patients, 8 boys and 3 girls, were included. Age at symptom onset ranged from 4 months to 9 years [median 22 months], and included 4 patients under 6 months. Nine patients fulfilled AHA criteria for complete KD and two for incomplete KD. The median delay to diagnosis was 8 days [mean 13 days; 3 to 50 days]. The mean disease follow-up from diagnosis was 8 months [1 to 31 months]. In addition to major AHA criteria, 90% of patients (9/10) were irritable, 70% had hepatomegaly (7/10), 3/11had digestive manifestations (pain, diarrhea), 22% hydrocholecystis (2/9), 3/11 had neck pain, and two were hypotonic (Table 1). Two patients presented with acute cardiac failure (Kawasaki shock syndrome) and were admitted to intensive care units. The initial blood cell count was performed at a mean timing of 9 days (0 to 37 days) from the first symptom of KD (19 days before diagnosis to 4 days after diagnosis). Laboratory values at several time-points are presented in table 2. The first echocardiography was performed at a mean of 10.6 days (3 to 37 days) from the first symptom. Seven patients had coronary abnormalities at evaluation between day 3 to day 12 of disease, and three others presented them subsequently. One patient had no cardiac complications. Z scores before anakinra were available in 10/11 patients and ranged from +2.5 to 12.4 (Table 3). Two patients had myocarditis, and one valvar dysfunction.

Treatments

The number of treatment modalities used was 3 in 3 patients, 4 in 2 patients, 5 in 3 patients, and ≥6 in 3 patients (Table 3). The first line was IVIG at the dosage of 2g/kg in all patients, which was administered at a delay of 3 to 50 days (mean: 13 days, median: 8 days) after the first symptom of KD. The second line was a second infusion of IVIG in 5 patients, infliximab in 3 patients, and intravenous methylprednisolone in 3 patients given at 0.8 to 30 mg/kg/infusion. The third line was intravenous methylprednisolone in 6 patients (0.8 to 30 mg/kg/infusion), oral corticosteroids in 1 patient (1mg/kg/day), and IVIG in one patient. Anakinra was the third line in 3 patients. Others treatments were cyclosporine and methotrexate (n= 1 and 1). All patients were treated with aspirin (50 mg/kg/d); four received anticoagulants.

All patients were treated with anakinra with a dosage ranging from 2mg/kg/d to 8 mg/Kg/d (Table 3). Anakinra was initiated on average at 25 days after disease onset (median 15 days, ranging from 8 to 87 days). It was associated with oral prednisone at 2mg/kg in 5 patients, cyclosporin at 3mg/kg in one and infliximab 5 mg/kg in another one. The main reasons for

use of anakinra were persistent fever (8/11); progressive coronary dilatation (7/11), persistent clinical symptoms (2/11), persistent blood inflammation (6/11), and Kawasaki-related shock syndrome (severe myocarditis) in one case. On anakinra treatment, fever disappeared within hours (<24 h) in 3 patients, and within 2 and 6 days in two patients respectively. Six others patients were not febrile at onset of anakinra. In addition, CRP levels fell two to three fold within 48 hours in 7/9 evaluable patients. At the last echography, coronary abnormalities improved or normalized in 10/11 patients. One patient never had coronary abnormalities. Total clinical and cardiac recovery was obtained in 6/11 patients; most of them received anakinra at a maximum of 15 days after disease onset. Patient 11 had aneurysms and thrombosis of legs arteries and bowel ischemia. One patient had sudden death probably due to massive pericardial effusion secondary to giant aneurysm rupture under anticoagulants (no autopsy performed). The duration of treatment was highly variable from 6 to 81 days, and is still ongoing in two patients.

Discussion

We have presented the largest published case-series so far of patients with KD treated with anakinra. Common characteristics of these patients were IVIG resistance, cardiac complications (with cardiogenic shock in 2 cases), and at least two lines of other treatment before anakinra. It is well known that IVIG resistance is associated with coronary vasculitis and genetic studies have identified the inositol 1,4,5-trisphosphate 3-kinase C, (ITPKC) as a susceptibility factor for both KD and coronary aneurysm across diverse populations [3]. Polymorphisms in the ITPKC gene induce increased Ca++ flux into the mononuclear cell, NLRP3 inflammasome activation and increased secretion of IL-1β and IL-1α [21, 22]. In addition, it is known that IVIG decrease the level of proinflammatory cytokines (IL-1β, IL-6 and TNFα) in responsive patients and that IVIG-resistant KD patients, have decreased expression of IL-1 receptor antagonist (IL1-Ra) [21-23]. Anakinra is an analog of the IL-1-Ra, which blocks both the IL-1 β and the IL1α [24]. In IL-1 mediated autoinflammatory diseases; i.e. cryopoyrin-associated periodic syndrome and SoJIA, anakinra has shown rapid efficacy on inflammatory symptoms at doses ranging from 2 to 10mg/kg, with a very good safety profile due to its very short serum half-life (6 hours) [20, 25]. Similarly, in our retrospective study, in all febrile patients, fever disappeared rapidly, within a few hours to a maximum of six days in one case. The effect on other symptoms of KD could not be evaluated

retrospectively due to missing information. Of interest, persistent inflammation with or without fever was another reason to use anakinra, which induced a decrease of 2 to 3 fold of the CRP levels within 48h. The efficacy on cardiac abnormalities was difficult to assess, because anakinra dosing and timing of cardiac measurements were not standardized. However, and contrary to what one might have thought by referring to the murine model, the effect of anakinra on patients' coronaries was neither fast nor striking [11]. Overall and after various regimens of anakinra treatment, coronary dilatations decreased or disappeared at last echography in all but one patient. Our results are consistent with three published patients with catastrophic KD, involving severe myocarditis and cardiac aneurysm in one and cardiac aneurysm and macrophage activation syndrome in another [15-17]. Both were finally successfully treated with anakinra at 8mg/kg and 2mg/kg respectively but required treatment duration of 2 and 5 months, respectively, to achieve complete cardiac recovery.

Anakinra was given late in the course of KD, at an average of 25 days after the onset of symptoms and in association with other treatments in 7/11 patients. With small case numbers, it is not possible to separate the role of anakinra from the other agents used alongside, or from the natural history of waxing and waning inflammation and aneurysmal dilatation in KD. All but two patients had severe coronary dilatations. In the LCWE(Lactobacillus casei cell wall extract)-induced mouse vasculitis model, anakinra was able to prevent aortic aneurysms and to improve cardiac ejection fraction by controlling myocarditis, suggesting that early use of anakinra might better prevent or treat early coronary lesions [11]. Patient 11, with KD-related shock syndrome due to severe myocarditis had dramatic response on treatment by anakinra at 6mg/kg. One patient (4) with rapid increase of coronary aneurysms died of massive pericardial hemorrhage probably due to aneurysm rupture. This case is questioning and similar observation of rapidly increasing coronary aneurysms was recently reported in two on four patients with IVIG resistant KD treated with anti -IL-6 receptor (tocilizumab) [26]. As these are isolated observations and that the natural history of KD can produce the same effects, it is impossible to conclude in an inductive effect of these biotherapies on endothelial inflammation. Similar cases under glucocorticoid therapy have led to discontinuation of this treatment for years and in the obvious absence of controlled studies.

In conclusion, our retrospective study supports further investigation of the role for IL1 blockade in the treatment of KD, especially in patients with persistent clinical and biological inflammation. Indeed, all but one patient (who died early) reported herein with difficult to treat KD, had rapid response to anakinra at various doses both on inflammatory symptoms and on biological inflammation, even two of them were already afebrile. Unfortunately, the heterogeneity of our data collected retrospectively does not allow concluding on efficacy of anakinra alone on coronary dilatations. More robust data will be available soon from the two Phase II ongoing trials, KAWAKINRA using anakinra treatment early after one failure of IVIG treatment (European Clinical Trials no. 2014-002715-41) and ANAKID (ClinicalTrials.gov identifier: NCT02179853), focused on patients with coronary giant aneurysms [27, 28].

List of abbreviations and acronyms

KD: Kawasaki disease

IVIG: intravenous immunoglobulin

SoJIA: Systemic onset juvenile idiopathic arthritis

IL-1: Interleukin 1

AHA: American Heart association

CRP: C-reactive protein

ESR: Erythrocyte sedimentation rate

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Table 1. The main clinical symptoms of 11 KD patients treated with anakinra. M= Male F= Female,

Patients	gender	Age at disease onset (years)	Diagnosis delay (days)	Length of fever (days)	Cervical adenitis > 1.5 cm	Bilateral non purulent conjunctivitis	Modifications of oral mucosae	Diffuse exanthema	Modifications of extremities	Irritability	Other clinical signs	Delay to first echocardiography (days)	Coronary abnormalities at first echocardiography
1	M	5	4	12	Yes	Yes	Yes	Yes	Yes	Yes	Hepatomegaly	4	Yes
2	M	4.2	3	15	Yes	Yes	Yes	Yes	Yes	Yes	Hepatomegaly, Splenomegaly Neck pain	3	Yes
3	M	1.9	6	13	Yes	Yes	Yes	Yes	Yes	Yes	Hepatomegaly	12	No
4	M	0.4	8	11	No	Yes	Yes	Yes	Yes	Yes	Seat erythema, Hepatomegaly, Splenomegaly Hypotonia	8	Yes
5	M	0.3	4	20	Yes	Yes	Yes	Yes	Yes	Yes	Hepatomegaly, Seat erythema, Arthritis	4	Yes
6	F	0.7	26	41	Yes	Yes	No	Yes	Yes	Unknown	Abdominal pain	10	No
7	M	2.8	4	10	Yes	Yes	Yes	Yes	No	Yes	diarrhea	8	Yes
8	F	0.4	50	15	No	Yes	No	Yes	Yes	Yes	Perineal desquamation Kawasaki shock syndrome, Hepatomegaly High blood pressure	37	No
9	M	1.9	8	10	No	Yes	Yes	Yes	Yes	Yes	Neck pain	12	Yes
10	M	9.0	9	11	Yes	Yes	Yes	No	Yes	No	Neck pain	9	Yes
11	F	0.3	19	31	No	Yes	No	Yes	Yes	Yes	Diarrhea, Hepatomegaly, hypotonia Kawasaki shock syndrome,	10	No

Figure 1: Levels of CRP before and after Anakinra in the 11 patients .

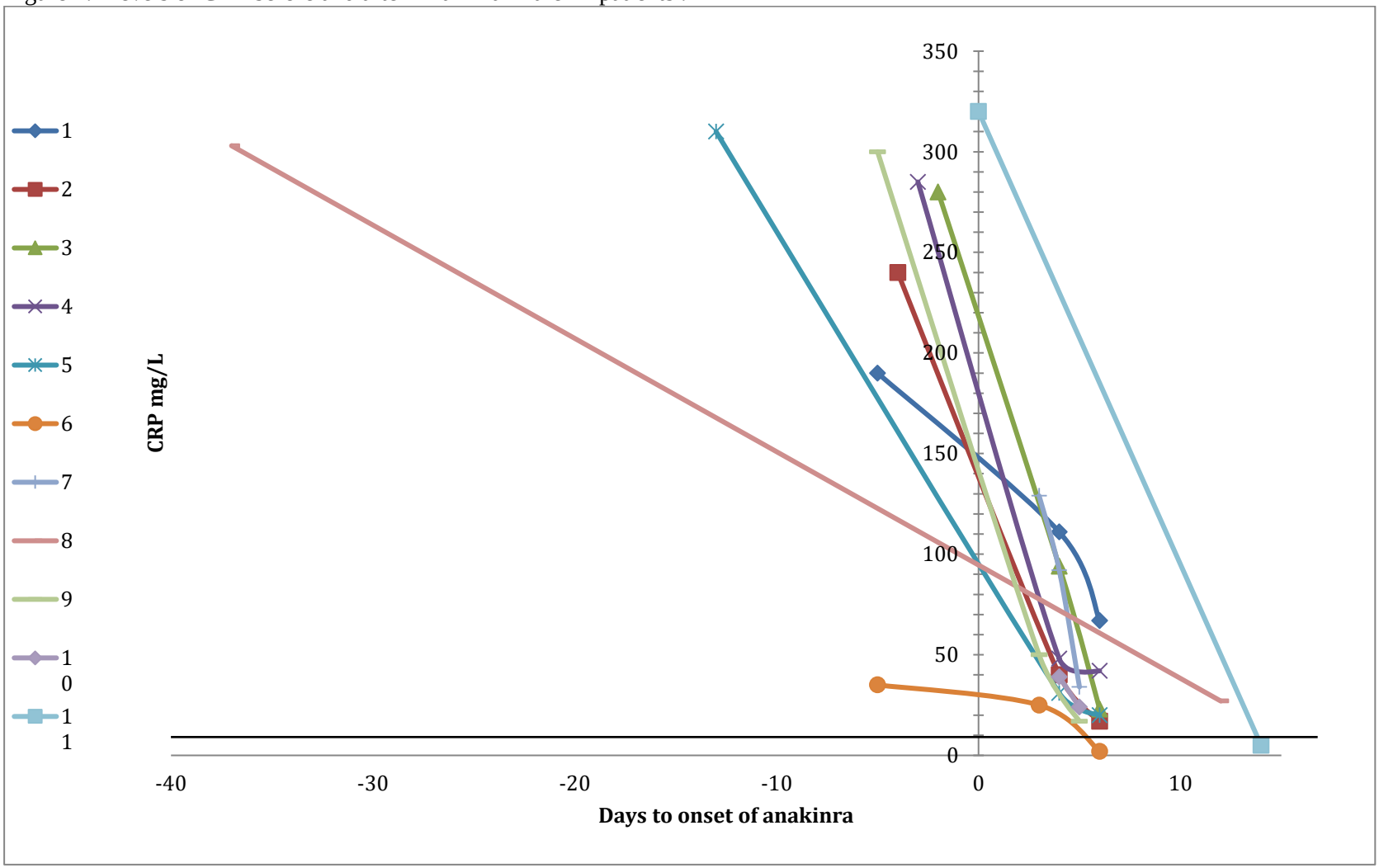

Table 2. Main initial biological results and peak of leucocytes and platelets in our 11 patients with Kawasaki disease.

Patients	Delay between initial blood test and disease onset (days)	Leucocytes /mm^3	Neutrophils /mm^3	Lymphocytes /mm^3	Platelets / mm^3	Hemoglobin g/dl	CRP mg/L	Peak of leucocytes (days from disease onset)	Peak of leucocytes /mm^3	Peak of platelets /mm3
1	3	20 000	15 430	2460	306 000	13	190	3	20 000	.
2	3	26 790	23 360	2060	313 000	11,2	162	10	51 410	2 287 000
3	5	9 100	6 470	1380	289 000	10,4	280	12	14 000	1 320 000
4	1	16 000	12 300	2300	402 000	11	82	12	73 120	941 000
5	1	22 300	14 670	5750	160 000	9,3	98	6	30 070	1 600 000
6	26	5 430	2 540	2100	423 000	9	35	36	17 720	453 000
7	7	20 400	13 600	5200	446 000	11,4	129	7	20 400	736 000
8	37	26 900	.	.	349 000	9,1	110	46	43 000	1 175 000
9	5	16 300	13 400	1800	447 000	9,6	273	17	24 400	934 000
10	13	6 400	2 300	3200	114 000	11,5	38,8	13	6 400	506 000
11	0	28 000	23 000	2500	388 000	9,5	116	.	.	700 000
Median	5	20 000	13 500	2380	349 000	10,4	116	12	22 400	937 500
Mean	9,2	17 965	12 707	2875	330 636	10,5	138	16	30 052	1 065 200

Table 3. Anakinra and evolution on fever, CRP and cardiac complications for our 11 KD patients.

Patients	Age at disease onset (years)	Delay to 1st treatment (days)	Delay to Anakinra (days)	Indication	Number of treatment performed before anakinra	Initial dosage (mg/kg)	Maximal dosage (mg/kg)	CRP before anakinra (days before)	CRP after anakinra (days after)	Echocardiography before anakinra mm (z-score) (days before)	Echocardiography after anakinra (days after)	Last echocardiography (days after anakinra)	Length of treatment with anakinra (days)	Efficacy on fever and inflammation	Coronary changes after anakinra
1	5	4	12	PF, PD	2	2	2	111 (0)	67 (2)	RCA 5 mm (+10) LAD 5.5 mm (+8) (0)	RCA 6.5 mm(+12.4) LAD 7.6 mm (+15.6) (5)	RCA 4 mm (+6) LAD 7 mm(+14) (139)	81	Yes	Decrease
2	4.2	3	15	PF, PI	4	2	2	40 (0)	17 (2)	RCA 2.5mm (+0.9) LAD 2 mm (+0.6) LMCA 3.5 mm(+2.7) (0)	RCA 2.7 mm (+1.4) LAD 1.8 mm (-0.2) LMCA 3.2 mm (+2.0) (5)	RCA 2.1mm(-0.2) LAD 2,1 mm(-0,2) LMCA 2 mm(-0,1) (185)	25	Yes	Decrease
3	1.9	6	13	PF, PI	3	2	2	94 (0)	23 (2)	RCA 2.5 mm(+2.5) LMCA 2.6 mm (+1.2) (-1)	Normal coronary artery (10)	Normal (108)	13	Yes	Decrease
4	0.4	9	15	PD, PI,	2	4	6	48 (0)	42 (2)	RCA 5.8 mm (+12.3) LAD 5.3 mm (+12.4) LMCA 5.3 mm (+10.4) (-1)	RCA 7.3 mm (+16.8) LAD 6 mm (+14.7) LMCA 5.5 mm(+11.1) (1)	RCA 9mm (+21.4) LMCA 9mm (+21.7) Pericarditis (6)	6	No	Increase Death
5	0.3	4	24	PF, PD	5	2	2	31 (0)	20 (2)	RCA 2.6 mm (+3.8) LAD 2.6 mm (+4.6) LMCA 3.2 mm (+5.0) (0)	RCA 3.8 mm (+7.3) LAD 4 mm (+9.2) LMCA 2.4 mm (+2.6) (12)	RCA 3.0 mm (+5.0) LAD 3.2 mm (+6.5) LMCA 2.4 mm (+2.6) (20)	ongoing	Yes	Decrease
6	0.7	26	35	PD, PI	3	4	4	25 (-1)	2 (0)	RCA 3.5 mm (+5.9) LAD 3 mm (+5.4) LMCA 3.6 mm (+5.6) (-2)	RCA 3.5 mm (+5.9) LAD 3 mm (+5.4) LMCA 3.6 mm (+5.6) (2)	RCA: normal LAD 2.9 (+2.9) LMCA 4.0 (+3.1) (24)	ongoing	Yes	Decrease
7	2.8	4	8	PF, PI, PC	3	6	6	92 (0)	34 (1)	RCA 3.2 mm (+3.8) LAD 4.5 mm (+5.2) LMCA 4.5 mm (+5.8) (0)	.	RCA 2.4 mm (+1.4) LAD 1.5 mm (-1.5) LMCA 2.5 mm (+0.9) (161)	41	Yes	Decrease
8	0.4	50	87	PF, PD	5	4	4	.	27 (12)	RCA 6 mm (+12.3) LAD 4.6 mm LMCA 3mm (-12)	RCA 5.7 mm LAD 3.2 mm LMCA 3.2mm (1)	RCA 4.8 mm LMCA 3.9mm (28) Normal coronary arteries at cardiac catheter (245)	50	Yes	Decrease
9	1.9	8	14	PF, PD,	4	7.5	7.5	50 (-1)	17 (1)	RCA 4mm (+6.6) LAD 4.2 mm (+7.7) LMCA 2.2 mm (+0.4) (-2)	RCA 5.4 mm (+10.3) LAD 5 mm (+10) LMCA 3 mm (+2.0) (6)	RCA 2.7 mm (+0.6) LAD 2.4 mm (+1.6) LMCA 2.5 mm (+0.0) (420)	42	Yes	Decrease
10	9.0	9	13	PD	2	4	4	39 (0)	24 (1)	RCA 6.6 mm (+10.9) LAD 5mm (+9.1) LMCA 6mm (+7.2) (-1)	RCA 6.7 mm LAD 5.8mm LMCA 6.6 mm (2)	RCA 6.7 mm (+11) LAD 2.2mm (-0.3) LMCA 6.7 mm (+8.5) (78)	43	No	Stable /Decrease
11	0.3	19	35	PF, KCS, PI, PC	3	6	8	320 (-4)	5 (10)	RCA 3.2 mm LMCA 4.2 mm LAD 3.4 mm (-12)	RCA 3.2 mm LMCA 4.2 mm LAD 3.4 mm (7)	RCA 2.8 mm LMCA 2.5 mm LAD 2.5 mm (95)	73	Yes	Decrease

PF: persistant fever; KCS : Kawasaki shock syndrome, PD: progressive coronary dilatation, PI: Persistant blood inflammation, PC: persistant clinical symptoms