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Effective infliximab therapy for the early regression of coronary artery aneurysm in Kawasaki disease

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ABSTRACT

Background: There is limited information available regarding the role of infliximab (IFX) following the acute phase of Kawasaki disease (KD). We aimed to evaluate whether IFX is associated with coronary artery aneurysm (CAA) regression.
Methods: Between 2005 and 2016, we identified 971 consecutive patients with KD from 3 tertiary institutions, and 49 (5%) with CAAs were enrolled in our study. Patients were divided into 2 groups: 27 who received IFX and 22 who did not. The persistence rate of CAAs was compared between the groups.
Results: Age, sex, and duration of the febrile period did not significantly differ between the groups. The maximum value of C-reactive protein was higher in the IFX- than in the non-IFX group. The maximum z-score of CAAs did not differ between the groups. The 2-, 4- and 6-year cumulative persistence rate of CAA was 24%, 24% and 24% in IFX-group, whereas 67%, 52% and 33% in non-IFX group, respectively ($P = 0.03$). The median duration of CAA regression was 1.1 vs. 4.6 years. Among those who developed medium- or large-sized CAAs, the 2-, 4- and 6-year cumulative persistence rate of CAA was 33%, 33% and 33% in IFX group, whereas 77%, 51% and 48% in non-IFX group, respectively ($P = 0.047$). Multivariate logistic regression analysis indicated that the maximum z-score (hazard ratio 0.72, $p < 0.001$) and response to IFX (hazard ratio 4.56, $p = 0.017$) were independently related to regression.
Conclusion: IFX therapy was observed to be effective for the early improvement of CAAs in patients with intravenous immunoglobulin-resistant KD.

1. Introduction

Kawasaki disease (KD) is an acute systemic vasculitis syndrome primarily affecting small- and medium-sized arteries, particularly the coronary arteries [1]. Therapy using intravenous immunoglobulin (IVIG) infusion and administration of high-dose aspirin has reduced the risk of development of coronary artery aneurysms (CAAs) from 25 to 3–5% [2–4]. However, 10–20% of patients with KD show persistent fever after first-line IVIG therapy, and demonstrate a higher risk of development of CAA [5–7]. CAAs dynamically change over time owing to intimal thickening and vascular remodeling. Kato et al. [8] reported CAA regression 1–2 years after the onset of KD in 72 of 146 (49.3%) patients. In contrast, 28 (19.2%) patients demonstrated stenosis associated with CAAs, and 11 among these developed myocardial infarctions. Therefore, the most critical issue in the treatment of KD is effective control of acute vasculitis and its remodeling to prevent the occurrence of ischemic heart disease in KD patients presenting with CAAs. Tumor necrosis factor alpha (TNF-α) plays a key role in the development of CAAs during the acute phase of KD [9,10]. Recently, infliximab (IFX), a TNF-α blocker, has been used as an effective and safe drug in patients with KD who are refractory to IVIG therapy. A growing body of evidence indicates that a single dose of IFX effectively controls acute inflammation in IVIG-resistant KD [11,12]. In contrast, the clinical effect of IFX on defervescence as an initial treatment of KD did not overcome that of IVIG [13,14]. Tremoulet et al. noted a greater reduction in the z-score for the left anterior descending (LAD) artery in IFX-treated patients, although it was a secondary endpoint of the study [13]. There is limited information available regarding the effect of IFX therapy on the development and regression of CAAs in patients with KD. The anti-inflammatory effects of IFX may control the acute vasculitis

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associated with KD, as well as the subsequent vascular remodeling of CAAs, and lead to improved outcomes in patients with refractory KD.

We investigated the long-term effects of IFX therapy on CAAs observed in KD patients. We compared the persistence of CAAs beyond a month of illness between patients who received alternative IFX therapy and those who did not. Additionally, we describe the biological effects of TNF blockers on the resilience of coronary arteries in children.

2. Methods

2.1. Study patients

A total of 971 patients diagnosed with KD were treated in tertiary institutions of Kyushu University ($n = 210$), Yamaguchi University ($n = 317$), and the Japan Community Healthcare Organization (JCHO) Kyushu Hospital ($n = 444$) between 2005 and 2016 (Fig. 1). We excluded 50 patients who were diagnosed as having non-KD ($n = 40$) or were diagnosed with any other underlying disease ($n = 10$). We observed that 4 patients developed recurrent KD. There was no KD-related mortality. Among 921 patients, 122 (13%) failed to respond to initial IVIG therapy and thereafter received IFX (a single intravenous infusion at a dose of 5 mg/kg) as the second- or third-line therapy during the acute phase of KD. IVIG resistance was defined as the persistence of fever 24 h after completion of IVIG infusion. In this study, the rescue treatments for KD including IFX were performed according to the decision of the doctors in charge of the patients. In the 3 tertiary institutions, IFX therapy was indicated for patients with sustainable fever due to KD, who were refractory to the preceding therapy. On the other hand, patients considered to have intense inflammation after 10 days of illness underwent urgent plasma exchange without IFX therapy. IFX was administered for patients without a history of tuberculosis or hepatitis, or BCG vaccination within 6 months. CAAs persisted beyond a month of illness in 49 patients—in 27 patients who received IFX and in 22 patients who did not receive IFX. Detailed information pertaining to the treatment choices and responses of 49 patients has been presented in Supplementary Fig. 1. We retrospectively investigated and compared the treatment course and coronary outcomes in 49 patients (Kyushu University $n = 13$, Yamaguchi University $n = 6$, JCHO Kyushu Hospital $n = 30$) between the IFX-treated and non-IFX-treated group. We also compared the coronary outcomes between the IFX-responders and the IFX-non-responders. Patients who showed a prompt defervescence after administration of IFX was defined as IFX responders. Patients who showed sustained fever after IFX or received no administration of IFX were defined as IFX-non-responders. This observational, retrospective, and multicenter study was approved by the Institutional Review Board of the 3 aforementioned institutions.

KD was diagnosed based on the Japanese guideline for the diagnosis of KD [15]. We calculated the Gunma risk score for each patient. The Gunma risk score ranges between 0 and 11, with higher scores predicting unresponsiveness of Japanese children to IVIG therapy. The score comprises age (1 point if ≤12 months), days of illness at the time of diagnosis (2 points if ≤4 days), platelet counts (1 point if $\leq 30 \times 10^4/\mu L$), percentage of neutrophil count (2 points if ≥80%), and serum sodium concentration (2 points if ≤133 mmol/L), asparate aminotransferase (2 points if ≥100 IU/L), and C-reactive protein (1 point if ≥100 mg/L) [16]. Echocardiography based on standard protocols was regularly performed during the acute phase of KD, including measurements of the luminal diameter of the right and the left main coronary artery, the LAD and the left circumflex artery. CAA was defined as the presence of dilatation or aneurysm formation of the coronary arteries a month after the onset of KD. Transient coronary artery lesions within a month of illness were excluded from this study. The largest segment of these vessels in their course was defined as the maximum size of CAAs. The coronary artery sizes were assessed using the converted values to z-scores adjusted for the body surface area, based on the standards established for Japanese children [17]. The severity of CAA was classified into 3 categories: small CAAs showing a z-score of <5, medium CAAs showing a z-score of ≥5 but <10, and large CAAs showing a z-score of ≥10 [18]. During the convalescent phase, we performed coronary angiography within 3 months after the disease onset in all patients with CAA, and subsequently every year until CAA regression. CAA regression was confirmed using coronary angiography in all but 1 patient who underwent contrast-enhanced computed tomography in adolescence to confirm CAA regression. CAAs were considered to have regressed when the enlarged coronary arteries demonstrated a normal internal diameter without any irregularities. The persistence interval of CAA was defined as the time interval between the onset of KD and CAA regression.

2.2. Statistical analysis

Clinical data were compared between the IFX- and the non-IFX group using the independent sample *t*-test, and the Mann–Whitney *U* test. Sequential persistence curves were calculated using the Kaplan–Meier method and were compared using the log-rank test. Independent prognostic factors associated with CAA regression were studied using Cox regression analysis. For all statistical analysis, *p* values of <0.05 were considered statistically significant. All statistical analyses were performed using the JMP Pro software (ver. 11.0.0. SAS Institute, 2001, Cary, NC).

3. Results

3.1. Clinical profiles of patients who were administered infliximab therapy

IFX was administered to 122 initial IVIG-resistant patients at median 9 days as the second-line therapy in 1 (1%), as third-line therapy in 102 (83%) and fourth-line therapy in 19 (16%) patients (Supplementary Table 1). All patients who received IFX had shown sustainable fever refractory to the preceding therapy. At the time of diagnosis of KD,

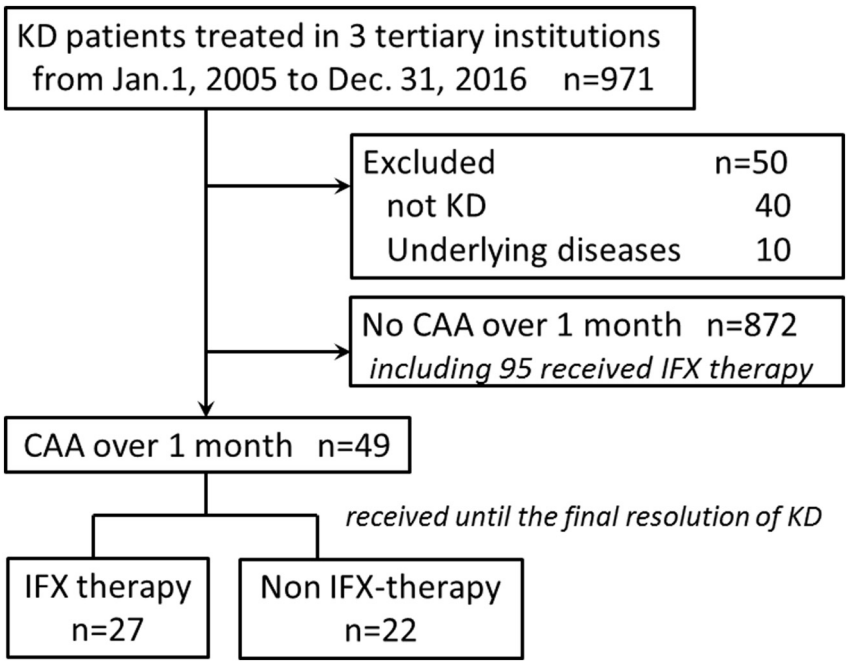

Fig. 1. Flowchart of the selection of 49 patients who had coronary artery aneurysm (CAA) over one month after the onset of Kawasaki disease (KD). The CAA-developed patients had not responded to initial intravenous immunoglobulin and then received infliximab (IFX) therapy ($n = 27$) or not ($n = 22$). The diagnosis and treatment of 971 patients were conducted in 3 tertiary institutions in Japan between 2005 and 2016.

the maximum level of C-reactive protein (CRP) was a median of 16.2 mg/dL, and the IVIG-refractory risk score (Gunma score) showed a median score of 7. CRP levels and the Gunma score in 122 patients administered IFX therapy were higher than those observed in patients who responded to initial IVIG therapy (data not shown). Complete resolution of KD was observed in 70 of 122 (57%) patients after a single infusion of IFX. Four of 5 patients who were observed to experience adverse events had received full-dose IFX therapy (5 mg/kg). In 122 patients who were administered IFX therapy, CAAs were noted beyond a month after onset in 27 (22%) and at the time of their last follow-up in 7 (6%) patients. Among those 27 patients who received IFX therapy, 17 (63%) did not require further treatment for KD. Five patients showed a remarkable reduction in fever after IFX therapy and achieved complete defervescence after additional IVIG therapy. The remaining 5 patients required plasma exchange after IFX therapy.

3.2. Occurrence of coronary artery aneurysms in patients who received infliximab and those who did not

Among 49 KD patients who developed CAAs, 27 (55%) received IFX therapy in the acute phase and 22 (45%) did not receive it. The clinical profiles of patients in both groups are shown in Table 1. The maximum values of CRP during the acute phase were higher in the IFX- than those in the non-IFX group (16.2 vs. 9.8 mg/dL, respectively median, $P = 0.04$). Total doses of IVIG required for the resolution of KD were higher in the IFX- than those required in the non-IFX group (median 4.0 vs. 3.0 g/kg, respectively, $P = 0.005$). The baseline CA size measured on admission to the 3 tertiary institutions did not differ significantly between the groups. No statistically significant difference was observed with regard to the other clinical variables, treatments, or observation periods indicating that the disease severity at the time of diagnosis was greater in the IFX- than that observed in the non-IFX group.

The severity and treatment outcomes of CAAs in KD patients with and without IFX therapy are shown in Table 1. No statistically significant difference was observed in the maximum z-scores of CAAs, or in the distribution of the size of CAAs between the IFX- and the non-IFX group. During the observation period, all but one patient(s) were free from cardiac intervention in both groups. The only one patient required percutaneous coronary angioplasty due to coronary stenosis in the non-IFX group. No patient reported cardiovascular events. The regression rate at the time of their last follow-up (median 4.1 years in the IFX- and 6.5 years in the non-IFX group) did not significantly differ between the IFX- and the non-IFX group (74% vs. 55%, respectively, $P = 0.26$).

3.3. Time-dependent change in coronary artery aneurysms in patients with and without infliximab therapy

The changes in CAAs over time were studied in patients with and without IFX therapy. The Kaplan–Meier curves for the cumulative persistence rates of CAAs are shown in Fig. 2a. The 2-year, 4-year and 6-year cumulative persistence rate of CAA was 24%, 24% and 24% in IFX group, whereas 67%, 52% and 37% in non-IFX group, respectively (log-rank, $P = 0.03$). The median duration of CAA regression in the IFX- vs. the non-IFX group was 1.1 vs 4.6 years, respectively. Furthermore, as shown in Fig. 2b, even in patients who developed medium- or large-sized CAAs, the 2-year, 4-year and 6-year cumulative persistence rate of CAA was 33%, 33% and 33% in the IFX group, whereas 77%, 51% and 48% in non-IFX group, respectively (log-rank, $P = 0.047$). The changes in CAAs were compared between IFX responders and non-responders. The persistence rates of CAAs are shown in Supplementary Fig. 2. In IFX responders, this rate was observed to have remained the same (16%) at 2, 4, and 6 years, whereas in IFX non-responders it was observed to be 66%, 53%, and 38%, respectively (log-rank, $P = 0.005$). Univariate logistic regression analyses indicated that the maximum z-score of CAAs (hazard ratio [HR] 0.73, $P < 0.001$), responder to IFX therapy (HR 2.68, $P = 0.008$), and the use of IFX (HR 2.16, $P = 0.036$) were factors associated with CAA regression (Table 2). Multivariate logistic regression analysis indicated that the maximum z-score of CAAs (HR 0.72, $P < 0.001$) and IFX-responder status (HR 4.56, $P = 0.017$) were independently related to CAA regression. No other variables showed a statistically significant association with CAA regression during the observation period.

Table 1
Clinical profiles and outcomes of coronary artery aneurysm-developed patients with or without IFX.

	IFX group (n = 27)	Non-IFX group (n = 22)	*P*-value
Clinical profiles of coronary artery aneurysm-developed patients			
Age at onset, months	24.0, 3–118	36.0, 1–167	0.29
No. (%) of Infants, <6 months	3 (11)	6 (27)	0.16
No. (%) of Male	23 (89)	14 (64)	0.08
Gunma's risk score	6.5, 1.0–9.0	6.0, 3.0–10.0	0.85
Maximum CRP, mg/dl	16.2, 3.0–34.5	9.8, 6.4–32.0	0.042
Day of illness at initial IVIG	4.0, 2–11	4.0, 3–10	0.34
Day of illness on admission	8.5, 3–19	8.0, 4–13	0.96
Baseline z-score[a]	3.7, 0.1–7.7	4.7, 0.1–7.1	0.21
Duration of fever, days	11.0, 9.0–22.0	12.0, 6.0–27.0	0.11
Follow up period, years	4.1, 1.1–10.6	6.5, 0.6–11.0	0.21
Other treatments			
No. (%) of IVIG	27 (100)	21 (95)	0.20
Total doses of IVIG, g/kg	4.0, 3.0–8.0	3.0, 0.0–10.0	0.01
No. (%) of IVMP	7 (26)	10 (45)	0.15
No. (%) of Plasma exchange	5 (19)	3 (14)	0.64
Outcomes of coronary artery aneurysm			
Maximum z-score	5.9, 3.9–13.4	7.5, 3.5–15.3	0.072
Affected sizes according to z-score			
Small: <5	7 (26%)	4 (18%)	0.95
Medium: 5≤, <10	16 (59%)	12 (55%)	
Large: 10≤	4 (15%)	6 (27%)	
Required cardiac intervention	0	1, PTCA	
Cardiovascular event	0	0	
Regression at			
2 years after onset	14/19 (74%)	6/19 (32%)	0.02
4 years after onset	10/13 (77%)	8/15 (54%)	0.36
6 years after onset	8/10 (80%)	8/12 (67%)	0.48

Each represent the number of patients, or the median and ranges of continuous variables. CAA: coronary artery aneurysm, IFX: infliximab, IVIG: intravenous immunoglobulin, IVMP: intravenous methylprednisolone, KD: Kawasaki disease, PTCA: percutaneous transluminal coronary angioplasty.

[a] Data were collected on admission to the 3 tertiary institutions.

4. Discussion

A significant finding of this present study was that the CAA regression rates among IVIG-resistant KD were higher in patients who received IFX than those who did not receive IFX therapy. The final outcomes of CAAs did not significantly differ between the IFX- and the non-IFX group; however, IFX resistance and maximum size of CAAs were an independent predictor for long-term CAA occurrence. It is well known that patients with a lower maximum z-score are more likely to demonstrate regression. In our present study, those belonging to the IFX group showed a strong trend toward lower maximum z-scores. However, even in patients limited to those who developed medium- to large-sized CAAs, the IFX group showed early CAA regression suggesting that IFX therapy was effective not only to achieve defervescence during the acute phase of KD but also for early CAA regression in the initially IVIG-resistant patients.

IFX is widely used as adjuvant therapy for IVIG-resistant patients who are at high risk of developing CAAs. Serum concentrations of TNF-α are elevated in patients during the acute phase of KD and the levels are higher in those who develop CAAs [9]. In the mouse model, TNF-α was observed to be a significant inducer of inflammation in the coronary arteries and the development of CAAs [19]. In human studies [13,14], IVIG-resistant patients who subsequently received IFX

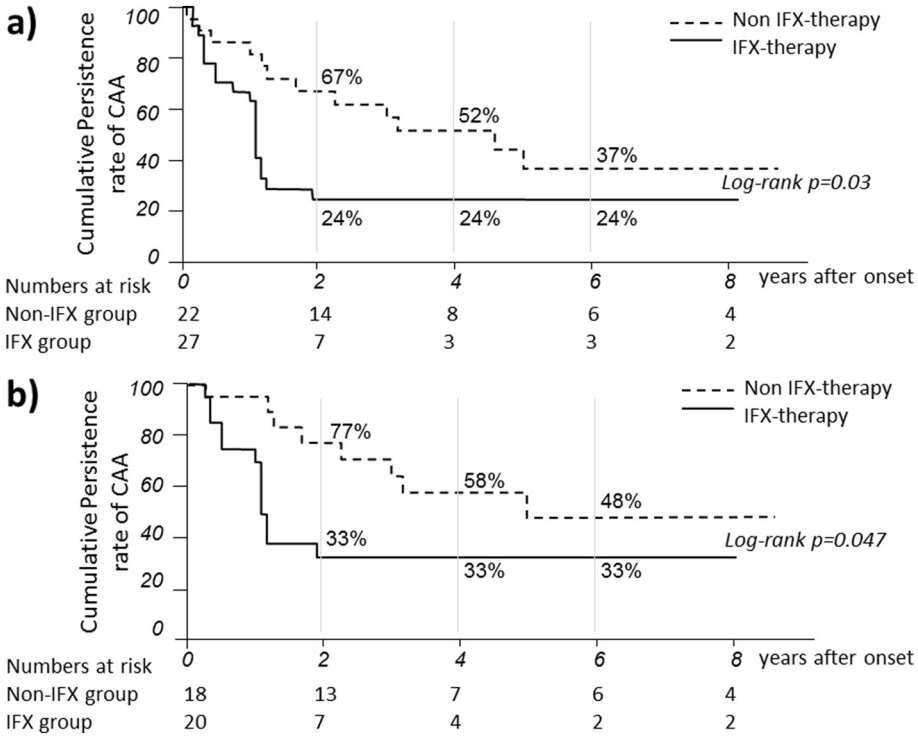

Fig. 2. a) Kaplan-Meier analyses for the cumulative persistence rate of CAA. The persistence interval of CAA was defined as the time from the onset of KD to the regression of CAA. The CAA persistence rate was significantly higher in non-IFX-group (dotted line) than seen in IFX-group patients (solid line). b) Kaplan-Meier analyses for the cumulative persistence rate of CAA in patients who developed medium or large CAA. The persistence interval of CAA was defined as the time from the onset of KD to the regression of CAA. The CAA persistence rate was significantly higher in non-IFX-group (dotted line) than seen in IFX-group patients (solid line). CAA: coronary artery aneurysm, IFX: infliximab.

demonstrated a significantly shorter duration of fever and hospitalization than that observed in those who received additional IVIG. However, these studies failed to prove the efficacy of IFX in reducing the development of CAAs during the acute phase of KD. A prospective study in Japan [20] showed that 15 of 76 patients who were resistant to initial IVIG administration who were subsequently treated with IFX, showed the development of CAAs a month after the onset of KD. CAA regression was noted in 80% of patients (12/15) during long-term follow-up. Similarly, the regression rate 6 years after onset was 80% (8/10) in the present study, and the cumulative persistence rate of CAAs was lower in the IFX- than that observed in the non-IFX group. These findings strongly suggest that IFX therapy could accelerate/facilitate rapid CAA regression in KD patients.

Table 2
Logistic regression analysis for the regression of CAA in 49 patients with KD.

	Univariate			Multivariate		
	Hazard ratio	95%CI	P-value	Hazard ratio	95%CI	P-value
Maximum z-score	0.73	0.60–0.87	<0.001	0.72	0.59–0.87	<0.001
Response to IFX	2.68	1.31–5.63	0.008	4.56	1.27–29.2	0.017
Use of IFX	2.16	1.05–4.64	0.036	1.96	0.52–12.74	0.35
Age at onset	0.88	0.75–1.02	0.11			
Use of IVMP	0.60	0.26–1.17	0.18			
Max CRP	1.01	0.96–1.06	0.68			
Duration of fever	0.81	0.17–3.39	0.78			
Total doses of IVIG	0.87	0.13–4.68	0.88			
Male	1.04	0.50–2.38	0.91			

CAA: coronary artery aneurysm, CI: confidence interval, IFX: infliximab, IVMP: intravenous methylprednisolone, CRP: C-reactive protein, IVIG: intravenous immunoglobulin.

The pathophysiological processes involved in CAA formation are: [1] necrotizing arteritis, [2] subacute/chronic vasculitis, and [3] luminal myofibroblastic proliferation [21]. Histopathologically, necrotizing arteritis is characterized by progressive inflammation with neutrophilic infiltrates within 2 weeks of fever onset. In contrast, subacute vasculitis shows lymphocytic infiltration that begins during the first 2 weeks of fever onset and continues for months to years. Luminal myofibroblastic proliferation represents the final process of chronic inflammation. "Regression" implies normalization of the vascular lumen of a CAA which had been narrowed due to proliferative myointimal thickening [22–24]. A localized inflammatory response persists in coronary arteries during the convalescent phase of KD in patients who develop CAAs [25,26]. In the mouse model of KD [19], the production of TNF-α was observed to be elevated in the coronary vessel wall at day 60 following KD onset. In this setting, we hypothesized that the administration of IFX led to sustained TNF-α blockade in coronary artery tissues and was associated with the subsequent control of subacute/chronic vasculitis, thereby contributing to CAA regression. IFX might effectively control not only the acute systemic inflammation observed in patients with IVIG-refractory KD, but also the local remodeling of CAAs after defervescence.

CAA regression occurs in a significant number of KD patients. In the pre-IVIG era, the number of patients who showed CAA regression (assessed by coronary angiography) until 1–2 years and 10–21 years after the onset of KD was 49.3% and 54.8%, respectively [8]. Marked intimal thickening causes local stenosis, stiffness of the vessel wall, and endothelial cell dysfunction in patients with regressed CAAs [27–29]. Although TNF-α exacerbates vascular calcification and endothelial dysfunction, TNF-blockade/blockers improve endothelial function to thereby reduce the cardiovascular risk among patients with rheumatoid arthritis [30–36]. In this study, although no statistically significant difference was observed in the final regression rate between the IFX- and the non-IFX group, the IFX group showed earlier CAA regression (median 1.1 vs. 4.6 years, respectively). This observation could be related to the pathophysiology of CAAs based on the phases of KD.

Alternatively, there may be certain genetic factors vulnerable to the remodeling of vascular injury in a group of patients.

Limitations of our retrospective study: 1) The choice of IFX used as a drug to treat IVIG-resistant patients was not subject to any randomization, which introduced a selection bias in the study population. However, the IFX-group patients showed higher levels of maximum CRP and required higher total doses of IVIG than that observed in the non-IFX group, which indicated the severity of disease in the IFX group. 2) The median observation period was 4.4 years, and long-term observation over decades after onset of KD could not be performed. Several case reports have described the recurrence of CAAs several years after regression [24]. Although Kato et al. reported that regressed CAAs did not show subsequent changes, careful observation with longer-term follow-up is warranted.

In conclusion, IFX therapy was associated with significant early regression of CAAs in patients presenting with refractory KD. The early regression was more evident in patients who responded to IFX therapy. IFX not only suppresses inflammatory responses that lead to the development of CAAs, but may additionally assist with/achieve vascular remodeling following early CAA regression. Further prospective studies are warranted to better understand the efficacy of IFX as a treatment option to manage CAAs during the acute phase of KD.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2018.04.062.

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Conflict of interest

The authors have no conflict of interests to disclose.

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