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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,

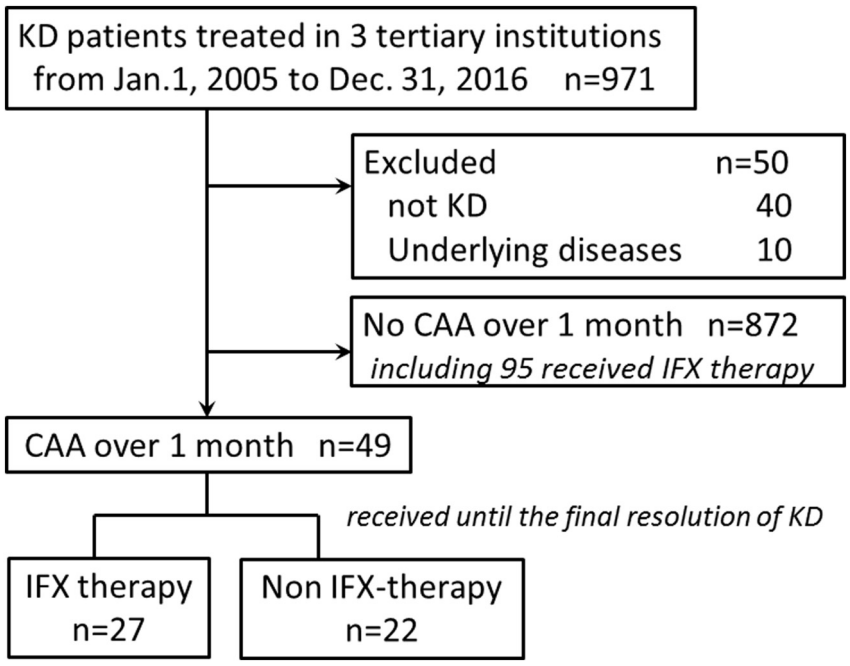

Fig. 1. Flowchart of the selection of 49 patients who had coronary artery aneurysm (CAA) over one month after the onset of Kawasaki disease (KD). The CAA-developed patients had not responded to initial intravenous immunoglobulin and then received infliximab (IFX) therapy ($n = 27$) or not ($n = 22$).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

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