Pediatric Rheumatology

RESEARCH ARTICLE Open Access

Effect of additional intravenous immunoglobulin for infliximab-refractory Kawasaki disease: a cohort study

Satoki Hatano[1,2], Hiro Nakao[1,2*], Hiroshi Masuda[2], Hiroshi Ono[3], Mitsuru Kubota[2] and Akira Ishiguro[1]

Abstract

Background Infliximab (IFX) is a reliable choice of treatment for intravenous immunoglobulin (IVIG)-resistant Kawasaki disease (KD) patients. Nationwide surveys in Japan demonstrated that additional treatment was still required for 20–30% of patients after IFX infusion. Additional IVIG was selected for 70% as the treatment for KD refractory to IFX. This study aimed to describe the therapeutic effect of IVIG after IFX for patients with KD refractory to IFX.

Methods A cohort study was conducted at a single center involving patients treated with additional IVIG for KD refractory to IFX between January 2016 and March 2023 (IVIG-after-IFX group). Additionally, KD patients resistant to the initial IVIG and who received a second IVIG in 2016 were included as a comparison group (second-IVIG group). We employed descriptive statistics and survival analysis to describe their clinical course information, including the time from initiation of the treatment to resolution of fever and the appearance of coronary artery lesions (CALs).

Results The analysis included 27 cases in the IVIG-after-IFX group. The additional IVIG-after-IFX was initiated on a median 11 days of illness (range 8–29). The median time until fever resolution was 1.0 day in the IVIG-after-IFX group and 1.0 day in the second-IVIG group ($P=0.783$, HR 1.00; 95% CI 0.58–1.70). The fever resolved within 2.0 days after the initiation of the therapy in 78% (21/27) in the IVIG-after-IFX group and 68% (26/38) in the second-IVIG group. CALs were identified in 26% (7/27) before initiating IVIG-after-IFX, and 7% (2/27) showed new CALs after IVIG after IFX. Persistent CALs were observed in 19% (5/27) after 12 months after diagnosis.

Conclusions Additional IVIG for IFX-refractory KD may have a therapeutic effect comparable to that of the second IVIG for IVIG-resistant KD and be a hopeful therapeutic option for IFX-refractory KD. Treatment of IFX-refractory KD remains a challenge for us and requires further exploration, particularly regarding CAL prevention.

Keywords Kawasaki disease, Infliximab, Intravenous Immunoglobulin, Coronary artery lesions

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Background

Refractory Kawasaki disease (KD) remains a challenge for pediatricians, even after 40 years of intravenous immunoglobulin (IVIG) treatment and 20 years of infliximab (IFX) therapy. KD is an acute, self-limited febrile illness of unknown cause that most commonly affects children [1]. According to the published guidelines, IVIG and aspirin are recommended for the initial treatment of KD [2, 3]. However, there are approximately 10-20% of KD patients who experience persistent and recurrent fever after initial IVIG therapy [4, 5]. IVIG-resistant patients are thought to have higher risks of developing coronary artery lesions (CALs) [6, 7]. Achieving early fever resolution is, therefore, crucial for the treatment of KD.

Although a second infusion of IVIG is the most common treatment for such IVIG-resistant KD patients, IFX, a chimeric anti-tumor necrosis factor (TNF)-α monoclonal antibody, is also a reasonable choice of treatment for IVIG-resistant KD patients [2, 3].

A recent randomized, multicenter comparative effectiveness trial, the KIDCARE study, suggested that IFX provides a shorter duration of fever compared to the second IVIG infusion when it is used for patients resistant to the initial IVIG treatment, indicating that the use of IFX would become a more prominent option for IVIG-resistant KD [8]. Another systematic review evaluating the effectiveness of second IVIG infusion, methylprednisolone, and IFX showed that IFX is more effective in fever resolution than second IVIG infusion and methylprednisolone in patients with refractory KD [9].

Although IFX is effective in refractory KD [8, 10–13], two nationwide surveys conducted in Japan demonstrated that additional treatment was still required for 27% and 30% of patients in each study after IFX infusion for IVIG-resistant KD [10, 11]. Despite a certain proportion of patients exhibiting resistance to IFX, the subsequent treatment after IFX has not been investigated sufficiently. The same nationwide surveys suggested that additional IVIG infusions were often selected for IFX-refractory KD patients; 60–70% of the patients were refractory to IFX treatment [10, 11]. However, we could not find any reports on the effect of the additional IVIG after IFX for KD treatment.

This study aimed to assess the therapeutic effect of additional IVIG treatment for IFX-refractory KD.

Methods

Patients and data collection

This cohort study of KD patients using electronic medical records was conducted at the National Center for Child Health and Development (NCCHD) in Japan. NCCHD is a children's hospital in Japan with approximately 400 pediatric beds and is one of the largest KD centers, with more than 100 KD hospitalizations per year. The diagnosis of KD was made using the Diagnostic Manual for Kawasaki Disease compiled by the Kawasaki Disease Research Team of the Ministry of Health, Labor, and Welfare [14, 15]. In Japan, IFX was approved for insurance coverage in December 2015, and we have encountered a certain number of IFX-refractory KD patients. We reviewed the medical records of patients treated with additional IVIG for IFX-refractory KD as described below between January 2016 and March 2023 (IVIG-after-IFX group), as well as those of KD patients who received the second IVIG due to resistance to the initial IVIG during 2016 (second-IVIG group).

Patients enrolled in this study included KD patients who received treatment at NCCHD from the beginning and those who received initial treatment at another hospital and transferred to NCCHD during the course of the treatment. All the patients with diagnosed KD were initially treated with IVIG (2 g/kg) and aspirin (30 mg/kg/day) according to the treatment guidelines. Infliximab was infused as 5 mg/kg in a single infusion during the course of the treatment. Other therapeutic approaches, including the use of corticosteroids, varied depending on the individual cases. As the use of corticosteroids for KD has recently been revived and varies among facilities [16–18], we also compared the treatment effects between KD patients who received corticosteroids and those who did not.

Data

We mainly analyzed the IVIG-after-IFX group. Demographic data included the age at KD onset, sex, whether the diagnosis was complete KD or incomplete KD, the timing and the date of the focused treatment, and the use of corticosteroids. Complete KD was diagnosed when a patient exhibited at least five out of six typical clinical signs of KD (fever, bilateral conjunctival congestion, changes in the lips and oral cavity, polymorphous exanthema, changes in the peripheral extremities, and nonpurulent cervical lymphadenopathy). Incomplete KD was diagnosed when patients had less than five of the typical clinical findings but exhibited other laboratory or echocardiographic findings suggestive of KD.

The following laboratory data was collected at the time of KD diagnosis, on the day of or the day before IVIG-after-IFX, and 1–3 days after IVIG-after-IFX: white blood cell (WBC) count, percentage of neutrophils, platelet count, total bilirubin, albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), sodium, C-reactive protein (CRP), and IgG.

Coronary arteries were assessed by two-dimensional echocardiography. CALs were defined as the maximum coronary artery branch (right coronary artery, left main trunk, left anterior descending artery, left circumflex artery) diameter exceeding 3 mm for individuals under

5 years of age and exceeding 4 mm for those 5 years and older, or a Z score ≥ 2.5 according to the guidelines in Japan and the USA [2, 14]. We evaluated the presence of CALs at the time of diagnosis, before initiating IVIG-after-IFX, and at 1, 3, 6, and 12 months after the diagnosis.

Analysis

We mainly employed descriptive statistics and survival analysis methods to describe clinical course information, including the appearance of CALs and the time from initiation of the treatment to resolution of fever.

Continuous variables were presented as the median (range) or mean (standard deviation), whereas categorical data were represented by number (%). We compared the treatment effects as fever resolution time utilizing the Kaplan-Meier method, adjunctively using the log-rank test and Cox regression analysis. We tested the paired continuous variables utilizing the Wilcoxon signed-rank test. The reported *P* values were two-sided, values < 0.05 were considered statistically significant, and multiple testing correction was performed by Bonferroni's method. We conducted all analyses using EZR version 1.61, which is based on R and R commander [19].

Ethical considerations

The Ethics Committee of the NCCHD approved the study (review No. 2023 – 124), and we adopted an opt-out procedure. Data were anonymized, and all personal information was removed.

Results

Characteristics of the IVIG-after-IFX group

As shown in Figs. 1 and 27 patients with IFX-refractory KD received additional IVIG (IVIG-after-IFX group) throughout the study period.

Table 1 describes the characteristics of patients enrolled in this study. In the IVIG-after-IFX group,

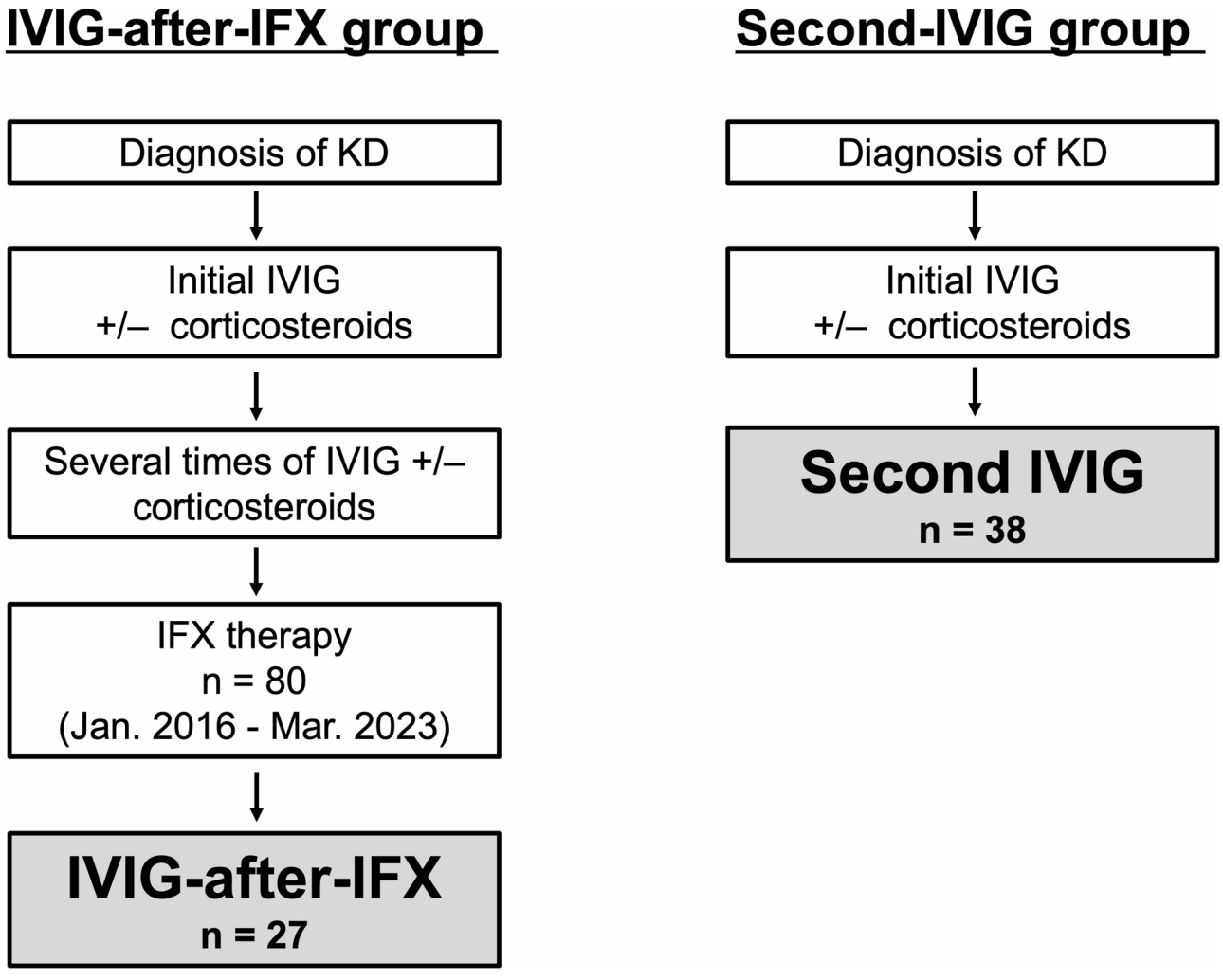

Fig. 1 Study flow. In 80 KD patients who received IFX therapy from January 2016 to March 2023, 53 achieved fever resolution, and 27 required additional IVIG-after-IFX therapy

Table 1 Patient characteristics

	IVIG-after-IFX group (*n* = 27)	Second-IVIG group (*n* = 38)
Age, median months (range)	29 (2–88)	22.5 (3–77)
Fever duration prior to diagnosis, days (range)	4 (2–6)	5 (2–7)
Male sex, number (%)	22 (81)	25 (66)
Complete KD, number (%)	26 (96)	37 (97)
Timing of IFX, number (%)	2nd line, 1 (4)† 3rd line, 21 (78)‡ 4th line, 5 (18)§	NA
Date of IVIG-after-IFX, day (range)	11 (8–29)	NA
Corticosteroid use, number (%)	13 (48)	5 (13)

IVIG, intravenous immunoglobulin; IFX, infliximab; KD, Kawasaki disease; NA, not applicable

Patients received the following treatments before IFX administration:

† Initial IVIG with prednisolone

‡ Initial IVIG followed by a second dose of IVIG, with some patients also receiving prednisolone concurrently

§ Three courses of IVIG (*n* = 1) or two courses of IVIG and methylprednisolone pulse (*n* = 4)

the median age at KD diagnosis was 29 months (range 2–88). The median fever duration was 4 days (range 2–6) before the diagnosis of KD was established. There were 22 (81%) male patients and five (19%) female patients. Complete KD was diagnosed in all patients except one. IFX was administered as the third-line treatment in 21 cases (78%), with one case in the second line and five in the fourth line. The additional IVIG after IFX was initiated on a median 11 days of illness (range 8–29). Among the 27 cases in the IVIG-after-IFX group, corticosteroids were used in 13 cases (48%) during the course.

In addition to IVIG-after-IFX, 5/27 cases (17%) received further treatment, including cases both without fever resolution and with fever resolution but with sustained elevated CRP levels. Although there was a case in which cyclosporine was used after IVIG after IFX, the other three cases achieved fever resolution with one to three rounds of additional IVIG and did not require other interventions, including plasma exchange.

Treatment effect

Besides 27 patients in the IVIG-after-IFX group, we extracted information from 38 patients in the second-IVIG group consisting of KD patients who underwent a second IVIG because of resistance to the initial IVIG in 2016. We depicted the time until fever resolution following IVIG-after-IFX or second-IVIG by Kaplan-Meier curves using half a day as a unit (Fig. 2), and no apparent difference was shown between the two curves ($P = 0.783$ by log-rank test, hazard ratio 1.00; 95% CI 0.58–1.70 by Cox regression analysis). The median time until fever resolution was 1.0 day (95% CI 0.5–2.0) in the IVIG-after-IFX group and 1.0 day (95% CI 0.5–1.5) in the second-IVIG group. The fever resolved within 2.0 days after the initiation of the therapy in 78% (21/27 cases) in the IVIG-after-IFX group and 68% (26/38 cases) in the second-IVIG group.

The total duration of fever from initial treatment to resolution was a median of 8.0 days (range 6.0–30) in the IVIG-after-IFX group, which was longer than in the second-IVIG group, with a median of 4.5 days (range 2.5–19).

Frequency of CALs

The frequency of CALs in the IVIG-after-IFX group at each phase of the treatment is detailed in Fig. 3. CALs were identified in seven cases (26%) before initiating IVIG-after-IFX, and two cases (7%) showed new CALs after IVIG-after-IFX. CALs improved in some cases within the observation period, and five cases (19%) showed persistent CALs after 12 months after diagnosis. In some cases, the size of CALs also exhibited improvement after treatment, but CALs larger than 6 mm did not improve after 3 months after diagnosis. One case exhibited CALs on the RCA one month after diagnosis, which improved three months after diagnosis. However, the dilation of the distal part of the LAD artery became more prominent after 6 months following the diagnosis.

Five patients were prescribed antiplatelet drugs, such as clopidogrel or cilostazol. Four patients were prescribed warfarin. All of them showed CALs larger than 6 mm during the course of treatment, though only one patient showed giant CALs. Additionally, two patients were advised to avoid strenuous activities such as contact sports or marathons after discharge.

CALs were not identified in any case at diagnosis in the second-IVIG group. Two cases (5%) developed CALs before initiating the second IVIG, and these did not improve within one month after diagnosis. One patient showed no CALs 12 months after diagnosis, while the other was referred to a local hospital and could not be followed up at our institution.

Laboratory data

Table 2 presents the laboratory data at the time of KD diagnosis, before and after IVIG-after-IFX. IgG data at diagnosis was missing in four patients. IgG data after IVIG-after-IFX was missing in one patient. The "percentage of neutrophils" data at diagnosis was missing in one patient. Significant decreases were seen in laboratory measures, such as the WBC count, percentage of neutrophils, and CRP after IVIG-after-IFX administration, compared to those before IVIG-after-IFX ($P < 0.001$). The mean level of IgG was 7.64 g/L at KD diagnosis,

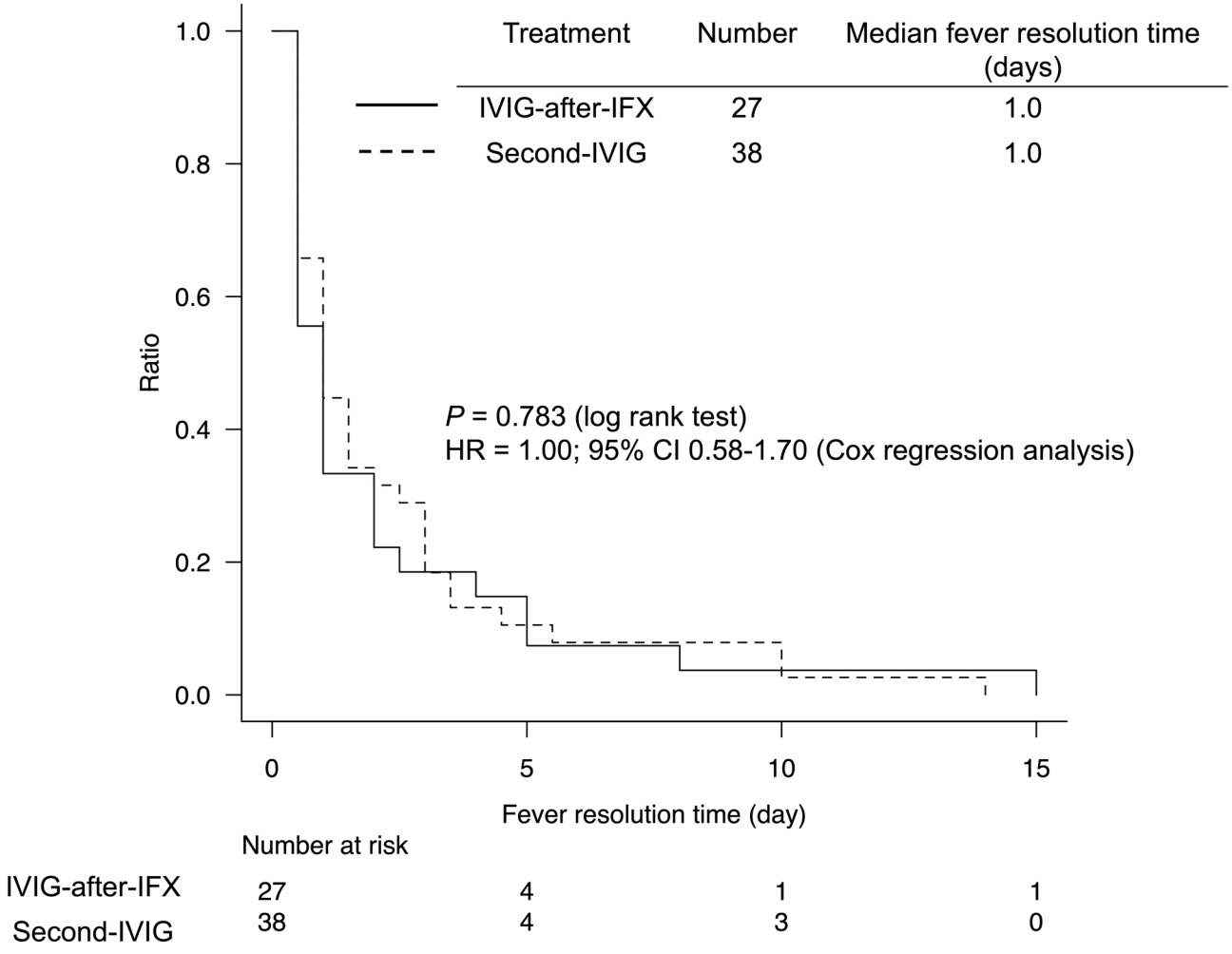

Fig. 2 Time from the initiation of the treatment to fever resolution. The black line represents the Kaplan-Meier plot of febrile duration until fever resolution following IVIG-after-IFX ($n=27$), and the dotted line represents that following the second IVIG ($n=38$). The median fever resolution times were 1.0 day in the IVIG-after-IFX and the second-IVIG groups. These two resolution curves appeared similar ($P=0.783$, HR = 1.00)

which increased to 27.66 g/L before IVIG-after-IFX and 40.31 g/L after IVIG-after-IFX.

Corticosteroid use

Among the 27 cases of the IVIG-after-IFX group, all received IVIG, IFX, and aspirin; 13 cases received corticosteroids during the treatment and 14 did not. As we were concerned about whether the corticosteroids could affect the IVIG-after-IFX effect, we compared the Kaplan-Meier curve illustrating the time until fever resolution following IVIG-after-IFX with and without the use of corticosteroids (Fig. 4). The median time to fever resolution of the corticosteroid group was longer (2.0 days) than the non-corticosteroid group (0.75 days), but we could not obtain a significant difference ($P=0.323$ by log-rank test; hazard ratio 0.76; 95% CI 0.31–1.86 by Cox regression analysis).

Discussion

The present study demonstrated that additional IVIG for IFX-refractory KD had a therapeutic effect comparable to that of the second IVIG treatment for IVIG-resistant KD. Fever resolution within 2.0 days after the initiation of IVIG-after-IFX was confirmed in 78% of the cases, as well as decreases in inflammatory markers, such as WBC and CRP, were also observed. CALs were detected in 26% of the cases before initiating IVIG-after-IFX, and 7% of the patients exhibited new CALs after IVIG-after-IFX. The fevers seemed to resolve sooner without the use of corticosteroids during the course of the treatment, but there was no significant difference in the median time until fever resolution.

Although IVIG has been frequently used to treat IFX-refractory KD patients [10, 11], its effect has not yet been sufficiently investigated. As for the treatment effect of IVIG, there have been reports on only IVIG as the initial or the second-line therapy [2, 3]. In the present study,

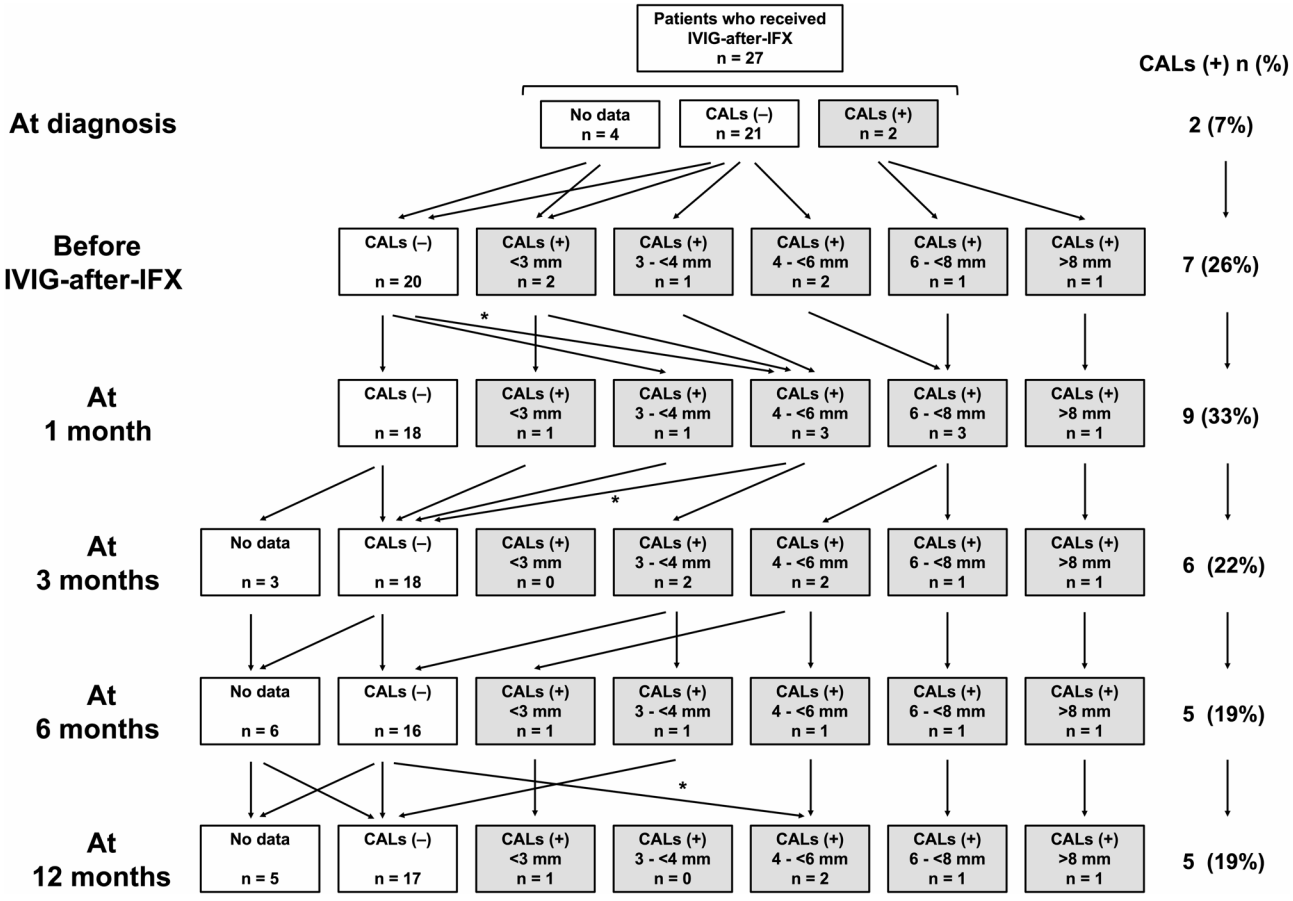

Fig. 3 Coronary artery lesions (CALs) in the IVIG-after-IFX group. CALs were identified in seven cases (26%) before initiating IVIG-after-IFX, and two cases (7%) showed new CALs after IVIG-after-IFX. At 3 months after diagnosis, three cases of CALs improved. Eventually, five cases showed persistent CALs after 12 months after diagnosis. The size of CALs also improved over time, but CALs larger than 6 mm did not improve after 3 months after diagnosis. There was no data available in four cases at the time of diagnosis, three cases at 3 months after diagnosis, six cases at 6 months after diagnosis, and five cases at 12 months after diagnosis

*This case did not exhibit CALs before IVIG-after-IFX. New CALs were detected on the RCA after treatment that improved within the observation period. However, the dilation of the distal part of the LAD artery, which had not been clearly depicted before 6 months, became more prominent after 6 months following the diagnosis. Therefore, this was not considered as a new CAL after 6 months

fever resolved in more than 80% of patients in the IVIG-after-IFX group. According to the past literature, about 80–90% of patients with KD acquired fever resolution with initial IVIG [4, 20, 21], which is similar to the percentages observed in this study. The IVIG effect seemed to be restored to the same level even after a certain number of ineffective IVIG treatments. This result might have some implications for the pathogenesis of KD and its treatment. For example, the administration of IFX might enhance the IVIG effect or IFX might change the type of KD inflammation from IVIG-refractory to IVIG-responsive type. In addition, the frequency of side effects with IVIG is considered to be no higher compared to aspirin, IFX, or prednisolone [22], so IVIG can be regarded as a more readily chosen treatment option for IFX-refractory KD compared to other therapies.

There is an institutional difference in the use of corticosteroids in the treatment of KD because the effectiveness and risk of its use are still controversial [17, 22, 23]. Therefore, we do not routinely use corticosteroids in the initial treatment of KD. All patients who received corticosteroids in this study were referral cases from surrounding medical facilities, as our hospital serves as a tertiary referral center for treatment-resistant KD in our region. These patients had Kobayashi scores of 5 or higher, indicating a predicted risk of IVIG resistance as specified in the Japanese guidelines for KD treatment [3], which recommends corticosteroids as a therapeutic option for such high-risk cases. Based on the results of the present study, we could not conclude whether the effect of IVIG-after-IFX is equivalent regardless of the use or non-use of corticosteroids. Although there was no significant difference in the median time until fever resolution following IVIG-after-IFX, the Kaplan-Meier curve implied that the time until fever resolution appeared to be longer with the use of corticosteroids than without. The small sample

Table 2 Laboratory data at diagnosis of KD, before and after IVIG-after-IFX

	At diagnosis	Before IVIG-after-IFX	After IVIG-after-IFX	*P* value†
WBC count ($\times 10^3$/L)	13.7 ± 6.3	22.5 ± 25.8	13.5 ± 8.5	< 0.001‡
Percentage of neutrophils	83 ± 11	64 ± 10	54 ± 14	< 0.001‡
Platelet count ($\times 10^9$/L)	333 ± 131	587 ± 196	681 ± 205	0.007
Total bilirubin (mg/L)	19.0 ± 16.0	4.4 ± 2.5	4.2 ± 2.5	0.509
Albumin (g/L)	33 ± 4	24 ± 5	24 ± 4	0.554
AST (IU/L)	158 ± 167	50 ± 81	42 ± 44	0.731
ALT (IU/L)	173 ± 170	39 ± 42	32 ± 34	0.001
Sodium (mmol/L)	133 ± 3	135 ± 3	134 ± 3	0.020
CRP (mg/L)	122 ± 47	80 ± 50	45 ± 36	< 0.001‡
IgG (g/L)	7.64 ± 6.11	27.66 ± 6.26	40.31 ± 7.28	< 0.001‡

*IgG data at diagnosis were missing in four patients

*IgG data after IVIG-after-IFX were missing in one patient

*Percentage of neutrophil data at diagnosis was missing in one patient

†Wilcoxon ranked-sum test to compare the data before and after IVIG-after-IFX

‡Statistically significant at Bonferroni's multiple correction level.

KD, Kawasaki disease; IVIG, intravenous immunoglobulin; IFX, infliximab; WBC, white blood cell; AST, aspartate aminotransferase; ALT, alanine aminotransferase; CRP, C-reactive protein

size may have contributed to the lack of statistical significance. If there were actually a significant difference in the effectiveness of IVIG-after-IFX between steroid users and non-users, several explanations are possible. First, the use of corticosteroids may indicate the inclusion of more severe cases, as the Japanese guidelines for KD treatment recommend corticosteroid use in anticipated IVIG non-responders [3]. Second, referral bias is possible because all cases using corticosteroids came from hospitals other than the NCCHD. Moreover, some cases showed fever relapses during the tapering of corticosteroid dose, suggesting that the KD inflammation might have been masked by corticosteroids, leading to a longer time for fever resolution after IVIG-after-IFX administration. In any case, a larger sample size and adjustment for confounding by KD severity are necessary to clarify the association between corticosteroid use and IVIG effect.

The frequency of CALs in the IVIG-after-IFX group was 26% before IVIG-after-IFX and 33% at 1 month after diagnosis. The previous nationwide survey in Japan stated that about 30% of KD patients treated with IFX showed CALs before IFX therapy and that 38% of them exhibited CALs after IFX [11]. The frequency of CALs in the present study seems lower than in that report; this might be due to the timing of IFX being administered at an earlier stage of therapy year by year compared to the previous study. In the KIDCARE study, where IFX was administered as a second-line treatment, the median day of illness at randomization was 8.0, and 13% of patients who received IFX therapy developed CALs at study completion [8]. The timing of IFX therapy might be earlier than in the present study (median 11 days), which might be one reason for the fewer CALs in the KIDCARE study.

In this study, 33% of the IVIG-after-IFX group had CALs at one month after diagnosis. Furthermore, although about half of CALs at one month after diagnosis (14% of all cases) showed improvement, CALs larger than 6 mm did not show improvement after 3 months after diagnosis. This finding is consistent with a previous report suggesting that CALs larger than 6 mm are less likely to regress [24]. Early fever resolution is considered critical to prevent CALs from progressing beyond 6 mm and prevent irreversible coronary artery dilation.

We set the second-IVIG group as the comparison group to verify the effectiveness of IVIG-after-IFX. We were aware that another treatment after IFX would be the ideal comparison group for IVIG-after-IFX. However, there were no promising candidates for another treatment after IFX other than plasma exchange, which has been excluded from our options due to its high invasiveness and frequent adverse events [25]. Therefore, we gave up comparing some treatment-after-IFX to IVIG-after-IFX and instead selected second IVIG, that is, IVIG-after-IVIG, as a comparison group.

Certainly, IVIG-after-IFX could be considered as an additional treatment for cases that did not improve after second IVIG. In other words, the effect of IVIG-after-IFX could be the cumulative effect of all the treatments that have been administered to the patients rather than the effect of the last IVIG alone. Therefore, we understand that we should not simply compare the IVIG-after-IFX group with the second IVIG group, but it is noteworthy that the effectiveness of IVIG-after-IFX in such refractory cases is equivalent to the common second IVIG.

Limitations include this being a single-center study with a small sample size as not many patients with KD require fourth-line or fifth-line treatment and the difficulties in randomizing treatment, as noted above. On the other hand, a single-center study at one of the largest KD centers in Japan enabled reliable data collection with precise clinical course information, very little missing data, and long echocardiography follow-up. This strength contributed to a detailed description of treatment for refractory KD. Another limitation lies in comparability, particularly of the CAL incidence. A direct comparison of the frequency of CALs, the long-term outcome of KD treatment, was avoided, because there were apparent differences in disease severities between groups. The IVIG-after-IFX group included patients who had already failed at least one dose of IVIG and IFX, representing a more

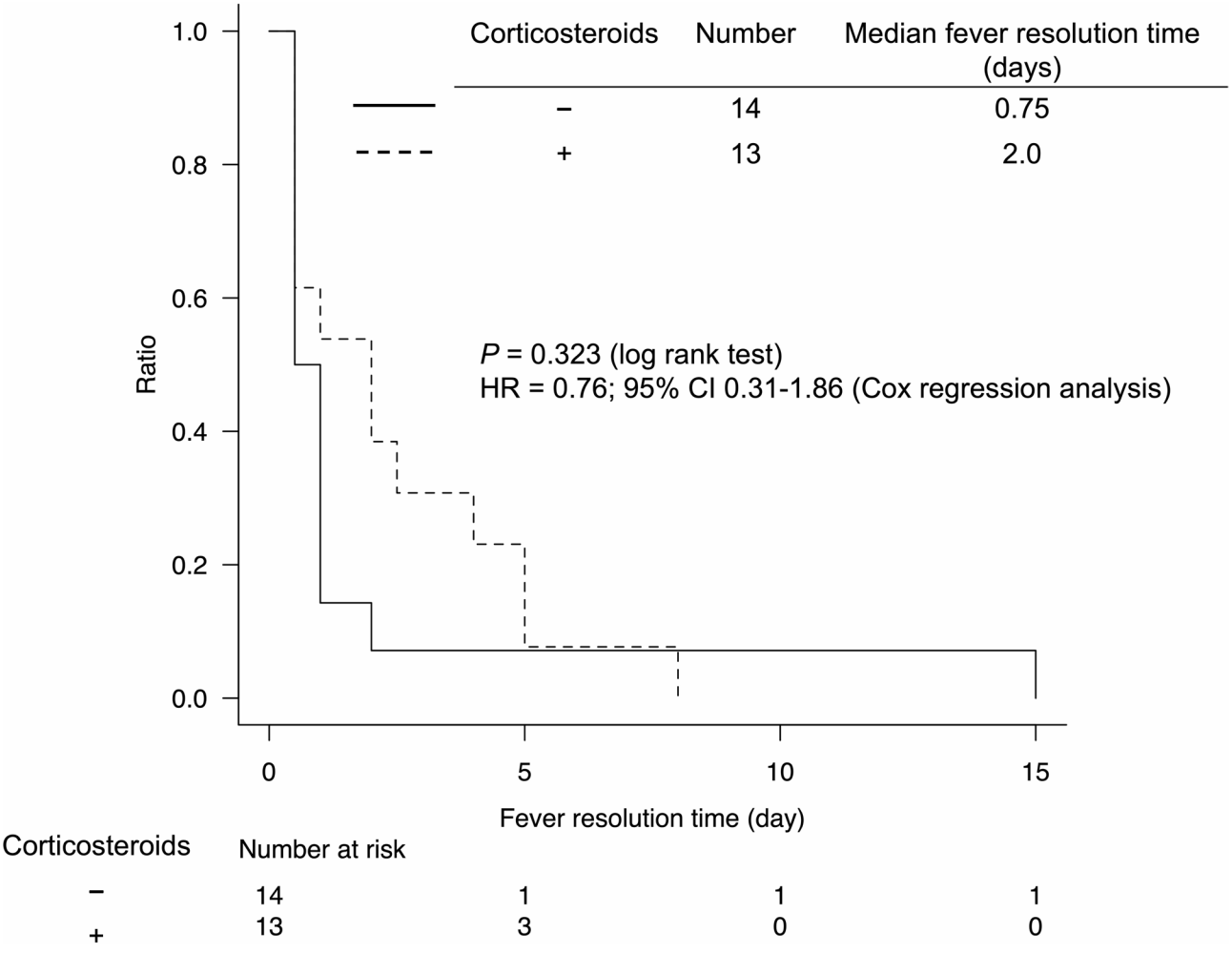

Fig. 4 Time from initiation of the treatment to fever resolution in the IVIG-after-IFX group. The black line represents the Kaplan-Meier plot of febrile duration until fever resolution following IVIG-after-IFX without the use of corticosteroids during the whole course of the treatment ($n = 14$) and the dotted line represents the use of corticosteroids ($n = 13$). The median fever resolution time was 0.75 days in the non-corticosteroids group and 2.0 days in the corticosteroids group. Although the curve appeared to indicate slower fever resolution in the corticosteroids group than in the non-corticosteroids group, there were no statistically significant differences ($P = 0.323$, HR = 0.76)

resistant population, whereas the second-IVIG group consisted of less refractory cases. Given this fundamental difference, any direct comparison of the frequency of CALs would cause significant confounding and may misrepresent the true effect of IVIG-after-IFX therapy. Therefore, the current study had to focus on the short-term therapeutic response, that is, time to defervescence after initiating the index IVIG, as a comparable outcome at this time.

We acknowledge the possibility that natural disease history could lead to fever resolution after a prolonged duration. Fever resolution as part of the natural disease course is always discussed in KD treatment. The ultimate goal of KD treatment should be to prevent the development of CALs through inflammation suppression. The power to detect CAL suppression in this study was insufficient due to the rarity of IFX-refractory KD and CALs.

Conclusions

Additional IVIG for IFX-refractory KD may have a therapeutic effect comparable to that of the second IVIG treatment for IVIG-resistant KD. IVIG would therefore be a hopeful therapeutic option for IFX-refractory KD. Treatment of IFX-refractory KD remains a challenge for us and requires further exploration, particularly regarding CAL prevention.

Abbreviations

CALs	Coronary artery lesions
CI	Confidence interval
CRP	C-reactive protein
IFX	Infliximab
IVIG	Intravenous immunoglobulin
KD	Kawasaki disease

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12969-025-01108-0.

Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Acknowledgements
We thank all our patients and their parents for their contribution to our research.

Author contributions
SH, HN, and HM conceptualized the investigation and designed methodology; SH and HM curated data; SH and HN analyzed data; HN acquired financial assistance; SH, HN, and HM wrote the original manuscript; HO, MK, and AI supervised the investigation and revised and edited the intellectual content of the manuscript; all authors approved the final manuscript.

Funding
This study was supported by a grant from the National Center for Child Health and Development in Japan (2023E-1).

Data Availability
Data supporting the findings of this study are available from the corresponding author on request.

Declarations

Ethics approval and consent to participate
The Ethics Committee of the NCCHD approved the study (review No. 2023 – 124), and we adopted an opt-out procedure.

Competing interests
The authors declare that they have no competing interests.

Consent for publication
Not applicable.

Received: 9 November 2024 / Accepted: 5 May 2025
Published online: 13 May 2025

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