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Treatment Intensification in Patients With Kawasaki Disease and Coronary Aneurysm at Diagnosis

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abstract

BACKGROUND: Coronary artery aneurysms (CAA) are a serious complication of Kawasaki disease. Treatment with intravenous immunoglobulin (IVIg) within 10 days of fever onset reduces the risk of CAA from 25% to <5%. Corticosteroids and infliximab are often used in high-risk patients or those with CAA at diagnosis, but there are no data on their longer-term impact on CAA.

METHODS: Retrospective multicenter study including children who had CAA with a *z* score ≥2.5 and <10 at time of diagnosis and who received primary therapy with IVIg alone or in combination with either corticosteroids or infliximab within 10 days of onset of fever.

RESULTS: Of 121 children, with a median age of 2.8 (range 0.1–15.5) years, 30 (25%) received primary therapy with corticosteroids and IVIg, 58 (48%) received primary therapy with infliximab and IVIg, and 33 (27%) received primary therapy with IVIg only. Median coronary *z* scores at the time of diagnosis did not differ among treatment groups (P = .39). Primary treatment intensification with either corticosteroids or infliximab were independent protective factors against progression of coronary size on follow-up (coefficient: −1.31 [95% confidence interval: −2.33 to −0.29]; coefficient: −1.07 [95% confidence interval: −1.95 to −0.19], respectively).

CONCLUSIONS: Among a high-risk group of patients with Kawasaki disease with CAA on baseline echocardiography, those treated with corticosteroids or infliximab in addition to IVIg had less progression in CAA size compared with those treated with IVIg alone. Prospective randomized trials are needed to determine the best adjunctive treatment of patients who present with CAA.

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Dr Dionne conceptualized and designed the study, collected the data, interpreted the data, drafted the initial manuscript, and reviewed and revised the manuscript; Drs Burns, Dahdah, Tremoulet, and Fournier were responsible for acquisition and interpretation of the data and critically reviewed the manuscript for important intellectual content; Drs deFerranti, Son, and Newburger interpreted the data and critically reviewed the manuscript for important intellectual content; Mr Gould and Dr Baker were responsible for acquisition of data and critically reviewed the manuscript for important intellectual content; Ms Gauvreau was responsible for analysis of the data and critically reviewed the manuscript for important intellectual content; Dr Friedman conceptualized and designed the study, interpreted the data, and critically reviewed the manuscript for important intellectual content; and all authors approved the final manuscript as submitted.

WHAT'S KNOWN ON THIS SUBJECT: Treatment of Kawasaki disease with intravenous immunoglobulin within 10 days of fever reduces the risk of coronary aneurysm from 25% to <5%.

WHAT THIS STUDY ADDS: In high-risk patients with Kawasaki disease who have coronary aneurysm on baseline echocardiography, treatment intensification with corticosteroids or infliximab is associated with less progression of coronary aneurysm size compared with treatment with intravenous immunoglobulin alone.

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Kawasaki disease (KD) is an acute self-limited vasculitis that primarily affects infants and young children.[1] Coronary artery aneurysms (CAAs) are a serious complication of KD, placing patients at risk for coronary thrombosis or stenosis, myocardial infarction, and cardiac death.[1–3] Intravenous immunoglobulin (IVIg) is the mainstay of treatment and has been shown to reduce the risk of CAA from 25% to <5%.[4] Adjunctive therapies beyond IVIg have been sought to further reduce the incidence of CAA.[5–14] In the absence of an evidence base, centers have varied widely in their treatment practices, including in the use of corticosteroids, infliximab, and other adjunctive anti-inflammatory medications for either intensification of primary therapy in high-risk patients or rescue treatment of IVIg-resistant patients.

In Japan, clinical risk scores have been established and are used in clinical practice to identify patients at high risk of developing IVIg resistance and CAA.[15–17] In these patients, adjunctive therapy with corticosteroids at time of diagnosis has been shown to improve coronary outcome.[8] In the North American population, the Japanese clinical risk stratification scores lack both sensitivity and specificity for identifying high-risk patients and thus are not used in clinical practice.[18,19] However, the coronary artery *z* score at the time of diagnosis has proven to be a strong predictor for future adverse coronary outcome in North America,[20–23] providing a means of selecting patients with KD at highest risk for adverse coronary outcome.

In this retrospective multicenter study, we evaluated the effect of infliximab and corticosteroids in patients with KD and a coronary *z* score ≥2.5 but <10.0 at the time of diagnosis. We hypothesized that primary treatment with an adjunctive anti-inflammatory therapy such as corticosteroids or infliximab together with IVIg, compared with IVIg alone, would improve coronary outcomes in the high-risk population of children whose coronary arteries were already enlarged at the time of first presentation. Because 3 centers with large KD populations in North America differed in their treatment practices, we were able to retrospectively test our hypothesis.

METHODS

Population

This retrospective study included children with a diagnosis of KD between 2008 and 2017 treated at Boston Children's Hospital (Boston, MA), Rady Children's Hospital (San Diego, CA), or Sainte-Justine's University Hospital Center (Montreal, Canada) with CAA at the time of diagnosis. We included all patients with nongiant CAA on their initial echocardiogram, defined as a *z* score ≥2.5 and <10 in the right coronary artery (RCA) or left anterior descending coronary artery (LAD). Exclusion criteria included the following: (1) delayed IVIg treatment (>10 days after fever onset) and (2) coexisting congenital heart disease (except for bicommissural aortic valve without stenosis or regurgitation), mitral valve prolapse, and hemodynamically insignificant ventricular septal defects.

Consistent, protocol-driven practice variation across centers in the treatment of patients with CAA at the time of diagnosis allowed us to group patients on the basis of their primary treatment. Patients were classified according to the primary therapy received within the first 48 hours after diagnosis into the following groups: (1) IVIg (2 g/kg) and corticosteroids (center 1), (2) IVIg (2 g/kg) and infliximab (center 2), or (3) IVIg (2 g/kg) alone (center 3). Within each center, all patients presenting with CAA received the same treatment. All patients received aspirin during the acute phase. High-dose aspirin (80–100 mg/kg per day) was initially used in all 3 centers; center 2 switched to moderate-dose aspirin (30–50 mg/kg per day) in 2013, and center 1 switched in 2016. For patients who received corticosteroids, dosing and duration of treatment varied. Most commonly, intravenous methylprednisolone at 2 mg/kg per day was started at the time of diagnosis and continued for 48 hours or until the patient was afebrile. Intravenous methylprednisolone was then changed to oral prednisolone at 2 mg/kg per day and tapered over ~2 weeks at the time of outpatient follow-up if inflammatory markers remained low. Notably, during a portion of the study period, a second dose of IVIg was routinely administered in patients with CAA in addition to corticosteroids, irrespective of clinical response to first IVIg treatment. For patients who received infliximab, the dose varied over time with 5 mg/kg administered until 2014 and 10 mg/kg administered from 2014 to 2017. Treatments were considered secondary if given >48 hours after KD diagnosis and given because of persistent fever after primary therapy (treatment resistance) or for additional treatment of CAA.

Data Collection and Definitions

We reviewed medical records for demographic characteristics, clinical course, laboratory values, and treatment received in the acute phase. Children were classified as having had complete or incomplete KD on the basis of the 2017 American Heart Association case definitions.[1] Specifically, incomplete clinical presentation was defined as the presence of fever and ≤3 clinical criteria. We also classified patients according to whether they received treatment with corticosteroids, infliximab, or IVIg alone in the first 48 hours after diagnosis. IVIg resistance was defined as persistent or recrudescent fever (>38°C orally or rectally) at least 36 hours after the

end of the first IVIg infusion. Echocardiographic coronary dimensions were reviewed at the time of diagnosis and during the first year of follow-up after diagnosis of KD. Coronary artery *z* scores were calculated for the RCA and LAD by using the Boston formula.[22] Measurements of the left main coronary artery were not used for inclusion because of the significant normal variability described in previous studies.[1] Aneurysms were considered small if *z* scores were ≥2.5 to <5, medium if *z* scores were ≥5 to <10, and large or giant if *z* scores were ≥10 or >8 mm in diameter.[1] Regression of CAA was defined as a *z* score <2 for all coronary artery segments.

Outcomes

The primary outcome was change in coronary *z* score (worst *z* score − baseline *z* score) for the RCA or the LAD over the first year of follow-up. Secondary outcomes included increase in coronary *z* score by more than 1 SD unit, worst-ever coronary *z* score, bilateral coronary involvement, time to normalization of internal lumen diameter (coronary *z* scores <2 for both the RCA and LAD), and resistance to initial treatment.

Statistical Analysis

Continuous variables were summarized as mean ± SD or median (interquartile range [IQR], 25th–75th percentile), and categorical variables were summarized as frequencies and percentages. Nonnormal distribution of continuous variables was suggested in the Shapiro-Wilk test. Comparison of clinical characteristics across the 3 treatment groups was performed by using the nonparametric median test. The Fisher exact test was used for comparison of categorical variables. Median and logistic regressions were used to examine the association between primary treatment received and increase in coronary *z* score during follow-up, controlling for potential confounder variables. Nonparametric median regression was used because of the significantly skewed distribution of the data, even after log transformation. An increase in coronary artery *z* score by more than 1 SD unit during follow-up was arbitrarily chosen as the cutoff value for logistic regression. All analyses were performed with SPSS Statistics version 23 (IBM SPSS Statistics, IBM Corporation, Chicago, IL). A 2-tailed *P* value of <.05 was deemed statistically significant.

RESULTS

The study included 121 patients (88 boys, 73%), with a median age of 2.8 (range: 0.1–15.5) years; 26 (22%) were younger than age 6 months at time of KD diagnosis. Incomplete clinical criteria were present in 44 (36%) of the children. Diagnosis was made at a median of 6 (IQR: 4–8) days from fever onset. All patients received IVIg (2 g/kg) at the time of diagnosis. Primary therapy was corticosteroids plus IVIg in 30 patients (25%), infliximab plus IVIg in 58 patients (48%), and IVIg alone in 33 patients (27%) (Table 1). There was no significant difference in coronary artery *z* score at the time of diagnosis among the groups (Table 2). At the time of diagnosis, 42 (35%) patients had bilateral coronary involvement with no difference between treatment groups.

Overall, secondary treatment was administered in 50 (41%) patients, for the indication of persistent fever after primary treatment in 15 (12%) patients and for coronary abnormalities in 35 (29%) patients. Additional therapies consisted of a second dose of IVIg in 38 (31%) patients, corticosteroids in 12 patients (10%), cyclosporine in 10 patients (8%), anakinra in 6 patients (5%), and cyclophosphamide in 2 patients (2%). Patients who were initially treated with IVIg only or IVIg and infliximab were more likely to require additional therapies because of persistent fever, compared with those who received IVIg and corticosteroids (7 [21%] vs 8 [14%] vs 0 [0%], *P* = .03). Additional treatments for coronary abnormalities were administered more frequently in patients who

TABLE 1 Patients' Characteristics Stratified by Initial Therapy Received

Baseline Characteristics	IVIg Only, *n* = 33	IVIg and Infliximab, *n* = 58	IVIg and Corticosteroids, *n* = 30	*P*[a]
Age in y, median (IQR)	2.0 (1.2 to 5.6)	1.1 (0.5 to 3.0)	2.6 (0.9 to 4.5)	.04
Infant <6 mo, *n* (%)	9 (27)	16 (28)	5 (17)	.29
Boy, *n* (%)	19 (58)	44 (77)	25 (83)	<.001
Length of fever in d, median (IQR)	6 (4 to 7)	5 (3 to 6)	6 (4 to 7)	.28
Complete clinical criteria, *n* (%)	20 (61)	46 (79)	11 (37)	<.001
Persistence of fever after IVIg treatment, *n* (%)	7 (21)	8 (14)	0 (0)	.02
Additional therapies, *n* (%)	14 (42)	19 (33)	17 (57)	.10
Second dose of IVIg[b], *n* (%)	11 (33)	10 (17)	17 (57)	.001
Other immunosuppressive therapies, *n* (%)	11 (33)	12 (21)	3 (10)	.084

[a] Nonparametric test for median for continuous values; Fisher exact test for qualitative values.

[b] A second dose of IVIg was routinely administered in patients with CAAs at the center using corticosteroids, irrespective of clinical response to first IVIg treatment.

TABLE 2 Coronary Artery Outcome Stratified by Treatment Group

Coronary Outcome	IVIg Only, *n* = 33	IVIg and Infliximab, *n* = 58	IVIg and Corticosteroids, *n* = 30	*P*[a]
Baseline, median (IQR)				
RCA *z* score	2.8 (1.2 to 3.5)	2.6 (1.6 to 3.8)	2.6 (1.6 to 3.3)	.46
LAD *z* score	2.5 (0.9 to 3.5)	3.1 (2.7 to 3.9)	3.2 (2.8 to 4.4)	.12
Maximum coronary *z* score	3.2 (2.8 to 4.2)	3.6 (2.9 to 4.3)	3.5 (3.0 to 4.5)	.39
At 12 mo postonset				
Maximum coronary *z* score, median (IQR)	0.6 (−0.3 to 1.5)	1.3 (0.6 to 2.2)	1.0 (0.5 to 1.8)	.21
Regression aneurysm[b], *n* (%)	26 (79)	43 (74)	24 (80)	.82
Maximum coronary *z* score within first 12 mo, median (IQR)	3.5 (2.9 to 6.3)	4.0 (3.0 to 5.0)	3.6 (3.2 to 5.3)	.85
Giant aneurysms, *n* (%)	4 (12)	5 (9)	1 (3)	.49
Increase in coronary dimensions during follow-up				
Maximum ↑ in *z* score[c], median (IQR)	1.5 (0.0 to 3.2)	0.3 (0.0 to 1.0)	0.3 (0.0 to 1.0)	.057
↑ in *z* score >1 SD unit, *n* (%)	19 (58)	14 (24)	7 (23)	.003
↑ in *z* score >2 SD unit, *n* (%)	8 (24)	6 (10)	5 (17)	.058

↑, increase.

[a] Nonparametric test for median for continuous values; Fisher exact test for qualitative values.

[b] Regression defined as a *z* score <2 for all coronary artery segments.

[c] Worst coronary artery *z* score − baseline coronary artery *z* score.

initially received IVIg and corticosteroids, followed by those who received IVIg only and IVIg and infliximab (17 [57%] vs 7 [21%] vs 11 [19%], $P = .001$).

During follow-up, the maximal coronary artery *z* score increased by a median of 0.4 SD units (IQR: 0–1.8) (Fig 1). Primary treatment intensification with corticosteroids or infliximab, compared with IVIg alone, was associated with less progression in coronary artery size on follow-up (unadjusted $P = .004$, $P = .001$, respectively). Use of corticosteroids or infliximab remained independently associated with less progression in coronary size on multivariable analysis (Table 3). A higher proportion of patients who received IVIg only had an increase in coronary artery *z* score by more than 1 SD unit, compared with patients whose primary therapy included infliximab or corticosteroids (19 [58%] vs 14 [24%] vs 7 [23%] patients, $P = .003$; Table 4). In a multivariable logistic regression analysis, primary treatment with corticosteroids or infliximab was associated with a lower likelihood of increase in coronary artery *z* score by >1 ($P = .02$, $P = .002$, respectively; Table 4).

The worst-ever coronary artery *z* score was similar between the 3 treatment groups (3.5 [IQR: 2.9–6.3] for IVIg only versus 4.0 [IQR: 3.0–5.0] for IVIg and infliximab versus 3.6 [IQR: 3.2–5.3] for IVIg and corticosteroids, $P = .85$). A similar proportion of patients in each treatment group developed giant aneurysms during follow-up (4 [12%] patients who received IVIg only versus 5 [9%] patients who received IVIg and infliximab versus 1 [3%] patient who received IVIg and corticosteroids, $P = .49$). CAA regressed to normal internal lumen diameter (*z* score <2.0) during the first year of follow-up in 91 (75%) patients, with no difference among groups in regression rate (26 [79%] vs 43 [74%] vs 24 [80%] for patients who received IVIg only, IVIg and infliximab, or IVIg and corticosteroids, respectively, $P = .85$).

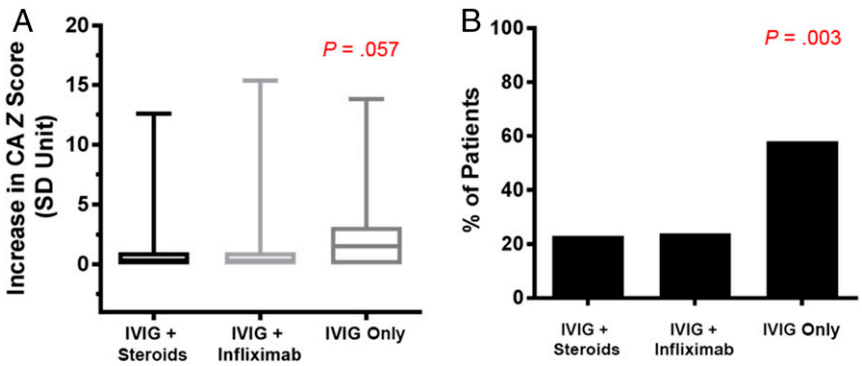

FIGURE 1

A, Increase in coronary artery *z* score during the first year of follow-up (worst coronary artery *z* score − baseline coronary artery *z* score) based on treatment received. B, Percentage of patients with increase in coronary artery *z* score by more than 1 SD unit during follow-up based on initial treatment received. CA, coronary artery.

DISCUSSION

In this retrospective series, adjunctive primary treatment with

TABLE 3 Multivariable Median Linear Regression for Increase in Coronary Artery *Z* Score During Follow-up

Predictors	Coefficients	95% CI	*P*
Boy	0.01	−0.81 to 0.83	.98
Age at time of diagnosis in y	0.07	−0.04 to 0.18	.23
Length of fever in d at time of diagnosis	−0.03	−0.20 to 0.15	.75
Corticosteroids	−1.31	−2.33 to −0.29	.012
Infliximab	−1.07	−1.95 to −0.19	.018
Second dose of IVIg	0.27	−0.55 to 1.08	.52
Other immunosuppressive therapies	−0.31	−1.22 to 0.61	.51
Baseline coronary *z* score	0.43	0.20 to 0.66]	<.001

CI, confidence interval.

corticosteroids or infliximab may be beneficial in preventing CAA progression. Patients who received primary treatment intensification with either corticosteroids or infliximab had less increase in coronary artery *z* score during follow-up compared with those who received IVIg alone. However, there was no significant difference in maximal coronary artery *z* score or the CAA regression rate. With these findings, it is suggested that primary adjunctive treatment with corticosteroids or infliximab may be beneficial in patients with CAA at the time of diagnosis.

The 2017 American Heart Association guidelines recommend primary adjunctive therapy for patients considered to be at high risk for CAA. However, the definition of high risk in the non-Japanese population is not standardized, and the optimal treatment of primary adjunctive therapy is not well established. In a study by Kobayashi et al,[8] researchers provide convincing evidence for the use of corticosteroids in Japanese patients who are high risk for IVIg resistance by clinical scoring systems, but there are limitations in generalizability because clinical risk scores are problematic outside of Japan and the study excluded patients with CAA at presentation (based on Japanese Ministry of Health criteria). The current study is the first to evaluate primary treatment intensification with corticosteroids in patients presenting with CAA and, similar to the study by Kobayashi et al,[8] shows corticosteroids to be beneficial for coronary arteries and clinical outcomes. The data for infliximab in children presenting with CAA are limited to a single retrospective, single-site experience[14] and were used to show that infliximab as initial therapy reduced the need for additional treatments; however, there was no significant difference in length of stay, improvement in coronary *z* scores at 2 to 6 weeks, or rate of decrease in C-reactive protein. Although it is suggested in our observational study that adjunctive primary therapy with corticosteroids or infliximab may improve coronary outcomes in those who present with a coronary *z* score ≥2.5, prospective, randomized studies are needed to identify optimal therapy in this patient population.

In addition to improved coronary outcomes, the rate of primary treatment resistance was lower in patients who received corticosteroids compared with those who received infliximab or IVIg only. Duration of fever and resistance to IVIg treatment are well-established risk factors for

TABLE 4 Univariate and Multivariable Logistic Regression for Increase in Coronary Artery *Z* Score During Follow-up

Predictors	Univariate			Multivariable		
	No Increase in CA *Z* Scores >1, *n* = 81	Increase in CA *Z* Scores >1, *n* = 40	*P*	OR	95% CI	*P*
Male, *n* (%)	59 (73)	29 (73)	.23	1.72	0.60 to 4.88	.31
Age at time of diagnosis in y, median (IQR)	1.5 (0.6 to 3.4)	2.2 (0.7 to 4.1)	.16	1.08	0.94 to 1.24	.30
Length of fever in d at time of diagnosis, median (IQR)	6 (4.5 to 7)	7 (4 to 8)	.37	1.04	0.83 to 1.30	.73
Primary treatment, *n* (%)	—	—	.003	—	—	—
IVIg only, *n* = 33	14 (42)	19 (58)	—	1	—	—
IVIg and corticosteroids, *n* = 30	23 (77)	7 (23)	—	0.21	0.06 to 0.77	.02
IVIg and infliximab, *n* = 58	44 (76)	14 (24)	—	0.17	0.06 to 0.51	.002
IVIg resistance, *n* (%)	10 (12)	6 (15)	.78	4.31	0.70 to 26.37	.11
Second dose of IVIg, *n* (%)	24 (30)	14 (35)	.68	0.63	0.18 to 2.26	.48
Other immunosuppressive therapies, *n* (%)	15 (19)	11 (28)	.35	0.98	0.32 to 3.01	.97
Baseline bilateral CAAs, *n* (%)	26 (32)	16 (40)	.42	1.90	0.62 to 5.81	.26
Baseline coronary *z* score, median (IQR)	3.4 (2.9, 4.2)	3.5 (2.9, 4.6)	.90	1.25	0.91 to 1.71	.17

CA, coronary artery; CI, confidence interval; OR, odds ratio; —, not applicable.

the development of CAA.[1] In previous studies, it has been shown that corticosteroids at the time of KD diagnosis reduce the duration of fever and initial treatment failure rate compared with IVIg alone.[8,24,25] Corticosteroids are effective in a broad range of vasculitides and other inflammatory conditions. Corticosteroids suppress fever and inflammation through inhibition of prostaglandins and other inflammatory cytokines.[26] Although evidence is provided in the current study that corticosteroids decrease primary treatment failure, questions remain whether corticosteroids are only masking fever or fully suppressing inflammation. Infliximab, a monoclonal antibody, is a more selective anti-inflammatory treatment that works by blocking tumor necrosis factor α. The proinflammatory cytokine tumor necrosis factor α has been shown to be elevated in patients with KD, with the highest levels observed in patients with CAA.[27] In previous studies, primary adjunctive treatment with infliximab reduced duration of fever but was not associated with a decreased risk of treatment resistance.[13] Further randomized controlled trials are needed to determine if primary adjunctive therapy with corticosteroids leads to a lower rate of primary treatment resistance and if this results in improved clinical and coronary outcomes.

This study should be interpreted in light of its limitations. In this retrospective review, treatment administered was based on patients' characteristics and local center practice. The use of adjunctive therapies (second IVIg dose and other anti-inflammatory agents) was inconsistent among centers, with different indications for intensification of treatment based on coronary status. The center using corticosteroids routinely administered a second IVIg dose in patients with CAA at the time of diagnosis, irrespective of response to primary therapy. Although we were able to account for some of the variation in practice across centers in a multivariate model, there may have been other confounders that we could not account for. The majority of patients in this study had small CAA at diagnosis (102 patients, 86%). Compared with patients with larger CAA, those with small aneurysms are considerably more likely to have aneurysm regression regardless of treatment.[23] Thus, we had limited ability to identify the effects of treatment on progression to giant CAA and regression to normal internal lumen diameter. The treatment cohorts were relatively small, which limits our ability to perform subgroup analysis and the statistical power to show a significant difference, particularly in progression to giant CAA. Moreover, echocardiograms were interpreted in each center, and there was no centralized review of echocardiogram and coronary artery measurements.

CONCLUSIONS

In this series, adjunctive primary treatment with either corticosteroids or infliximab was superior to IVIg alone in preventing CAA progression. Patients who received primary treatment intensification with corticosteroids or infliximab had less progression of coronary dilation on follow-up. However, maximal coronary artery *z* score and the rate of CAA regression were similar among groups. Our data suggest that adjunctive treatment at the time of diagnosis may be beneficial in patients with CAA. Future adequately powered, prospective randomized trials are needed to determine the best adjunctive treatment of patients with KD who present with coronary changes.

ABBREVIATIONS

CAA: coronary artery aneurysm
IQR: interquartile range
IVIg: intravenous immunoglobulin
KD: Kawasaki disease
LAD: left anterior descending coronary artery
RCA: right coronary artery

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