

BMJ Open Study protocol for a phase III multicentre, randomised, open-label, blinded-end point trial to evaluate the efficacy and safety of immunoglobulin plus cyclosporin A in patients with severe Kawasaki disease (KAICA Trial)

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ABSTRACT

Introduction: Kawasaki disease (KD) is an acute, self-limited vasculitis of unknown aetiology that predominantly affects infants and young children. We hypothesise that cyclosporin A (CsA) may be effective in treating KD by regulating the Ca²⁺/NFAT signalling pathway. This trial compares the current standard therapy of intravenous immunoglobulin (IVIG) and the combined IVIG+CsA therapy in paediatric patients with severe KD.

Methods and analysis: This trial is a phase III, multicentre, randomised, open-label, blinded-end point trial that evaluates the efficacy and safety of IVIG+CsA therapy. Patients with severe KD who satisfy the eligibility criteria are randomised (1:1) to receive either CsA (5 mg/kg/day for 5 days; Neoral) plus high-dose IVIG (2 g/kg for 24 h and aspirin 30 mg/kg/day), or high-dose IVIG alone (2 g/kg for 24 h and aspirin 30 mg/kg/day). The primary end point is the frequency of occurrence of coronary artery abnormalities during the trial period. An independent end point review committee will be in charge of the trial assessment.

Ethics and dissemination: The protocol was approved by the Institutional Review Board of each institution. The trial was notified and registered at the Pharmaceutical and Medical Devices Agency, in Japan. The trial is currently on-going and is scheduled to finish in April 2017. The findings will be disseminated through peer-reviewed publications and conference presentations.

Trial registration number: JMA-IIA00174; Pre-results.

INTRODUCTION

Kawasaki disease (KD) is an acute systemic vasculitis of unknown aetiology that affects

Strengths and limitations of this study

- This study is the first randomised control trial to assess the efficacy and safety of intravenous immunoglobulin+cyclosporin A (CsA) combination treatment in patients with severe Kawasaki disease.
- The study has been designed to meet the criteria for high-quality randomised clinical trials by performing central randomisation, and ensuring multicentre participation and blinded assessment and analysis.
- In order to reduce the bias associated with the open-label design, we use a remote central randomisation system after collection of baseline data, a hard outcome as primary end point, and blinded investigators.
- Potential limitations of the trial include the fact that the optimal dosing of CsA has not been appropriately determined, and a short follow-up period.

mainly paediatric patients.^{1 2} The incidence of KD has been increasing since the mid-1990s and, currently, there are more than 10 000 new cases per year in Japan.³ The standard therapy, high-dose intravenous immunoglobulin (IVIG) plus aspirin, usually resolves the inflammation and reduces the occurrence of coronary artery abnormalities (CAAs).⁴⁻⁶ However, about 20% of patients are refractory to the standard therapy. These patients present a particularly high risk of developing CAAs.³ According to new findings from the RAISE study, initial IVIG plus prednisolone combination therapy

proved to be superior to the standard treatment for patients with severe KD (risk score ≥ 5 points).⁷ However, the current treatment for refractory patients is often additional IVIG, sometimes in combination with other treatment methods,⁸ but before making a therapeutic decision, physicians should consider the benefits of the treatment versus the risk of developing CAAs.⁹

In our previous studies, we identified functional single nucleotide polymorphisms (SNPs) related to KD susceptibility within the inositol 1,4,5-trisphosphate 3-kinase C (*ITPKC*) and the caspase 3 (*CASP3*) genes located on chromosome 19 and chromosome 4, respectively.^{10 11} These findings suggest that *ITPKC* and *CASP3* may play a role in suppressing immune hyper-reactivity by negatively regulating signal transduction of the Ca^{2+} /NFAT pathway.¹⁰ Further genetic analysis also indicated a cooperative association of the two SNPs with risks for unresponsiveness to IVIG treatment and CAA formation in patients with KD.¹² Thus cyclosporin A (CsA), an immunosuppressant targeting the Ca^{2+} /NFAT signalling pathway, may represent a promising agent for the treatment of KD. Furthermore, in a phase II trial that we conducted testing the use of CsA on refractory patients with KD, no major adverse events (AE) were reported, including CAAs. Moreover, 79% of paediatric patients treated showed defervescence, which demonstrated CsA efficacy.¹³

In light of these results, we have now designed the KAICA Trial, a phase III multicentre, randomised, open-

label, blinded-end point trial that aims to assess the efficacy and safety of IVIG+CsA combination therapy compared to the IVIG standard therapy in patients with severe KD (risk score ≥ 5 points).

OBJECTIVES

To assess whether IVIG+CsA combination therapy as the primary treatment is superior to the standard IVIG treatment in preventing the development of CAAs in paediatric patients with severe KD.

METHODS

Trial design

The KAICA Trial is a multicentre, prospective, randomised, open-label, blinded-end point trial (PROBE) designed to assess the efficacy of IVIG+CsA for the primary treatment of KD. The participants are diagnosed with KD using the Kawasaki Disease Diagnostic Criteria (the 5th revised edition).¹⁴ Patients who meet the eligibility criteria are randomly assigned (1:1) to a group receiving either CsA (5 mg/kg/day for 5 consecutive days; Neoral) plus IVIG (2 g/kg for 24 h and aspirin 30 mg/kg/day) or IVIG alone (2 g/kg for 24 h and aspirin 30 mg/kg/day). The primary end point is defined as the frequency of CAAs during the study period. A schematic depiction of the trial design can be found in figure 1.

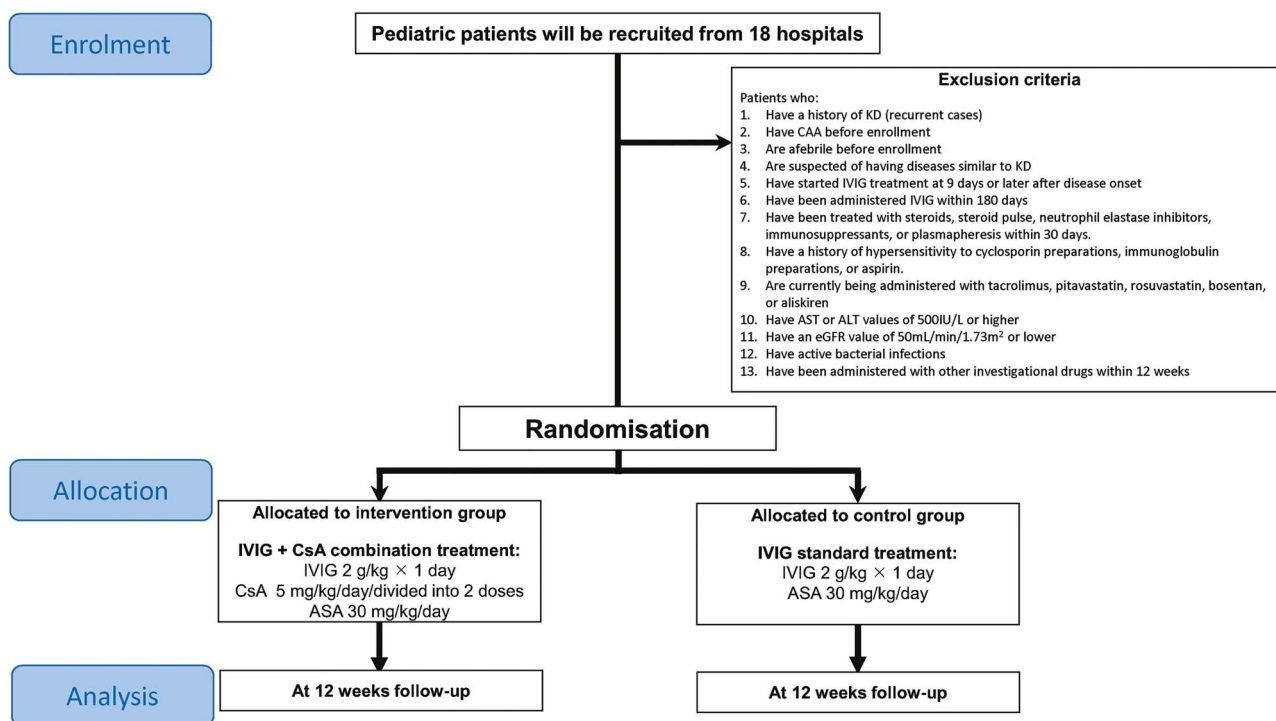


Figure 1 KAICA study flow. ALT, alanine aminotransferase; ASA, aminosalicic acid; AST, aspartate aminotransferase; CAA, coronary artery abnormalities; CsA, cyclosporin A; eGFR, estimated glomerular filtration rate; IVIG, intravenous immunoglobulin; KD, Kawasaki disease.

Eligibility criteria

Eligible patients are those who meet all of the inclusion criteria mentioned below and none of the listed exclusion criteria:

Inclusion criteria

1. A diagnosis of KD according to the Kawasaki Disease Diagnostic Criteria (the 5th revised edition)¹⁴
2. A score of five points or higher on the Kobayashi risk score scale (table 1)¹⁵
3. Age of 4 months or more at the time of signing the informed consent form
4. Inclusion in the study within 7 days of disease onset (considering day 1 to be the day when the fever develops)
5. Informed consent form signed by the patient or a legal guardian

Exclusion criteria

1. A history of KD recurrence
2. CAAs prior to enrolment
3. No presence of fever prior to enrolment
4. Suspicion that the symptoms may correspond to a disease other than KD (haemolytic streptococcal infection, EB virus infection, Yersinia infection, measles or Stevens-Johnson syndrome)
5. Initiation of IVIG treatment later than 9 days after disease onset
6. Administration of IVIG within 180 days prior to obtaining informed consent
7. Treatment with steroids (except external preparations), steroid pulse, neutrophil elastase inhibitors, immunosuppressants, or plasmapheresis within 30 days
8. History of hypersensitivity to CsA preparations, immunoglobulin preparations, or aspirin
9. Having had treatment with tacrolimus, pitavastatin, rosuvastatin, bosentan or aliskiren
10. Aspartate aminotransferase or, alanine aminotransferase values of 500 IU/L or higher
11. An estimated glomerular filtration rate of 50 mL/min/1.73 m² or lower
12. Presence of an active bacterial infection: septicaemia, meningitis purulenta, peritonitis or bacterial pneumonia
13. Treatment with other investigational drugs within 12 weeks of study commencement

Recruitment

This trial was declared and registered at the Pharmaceuticals and Medical Devices Agency (PMDA) in May 2013. Recruitment started in May 2014 and will end in April 2017, or until a total of 172 participants have been recruited. This study is being conducted at 18 tertiary hospitals in Japan.

Sample size calculation

The target sample size for this randomised trial is 172. This number was based on results from previous

Table 1 Risk-scoring system for KD, described by Kobayashi *et al*¹⁵

Score component	Point assignment
AST \geq 100	2
Sodium $<$ 133 mmol/L	2
Fever days \leq 4	2
% Neutrophils \geq 80	2
C reactive protein \geq 10 mg/dL	1
Age \leq 1 year	1
Platelets \leq 30 \times 10 ⁴ /mm ³	1

AST, aspartate aminotransferase; KD, Kawasaki disease.

randomised controlled trials.^{6 7 13} The estimated proportions of CAAs are 5% after the IVIG+CsA combination treatment, and 20% after IVIG standard treatment. Assuming a group difference of 15% during the study period, 82 patients per arm would provide a power over 80%, enough to detect a difference in the proportion of CAAs between the IVIG+CsA and the IVIG-alone treatment, using a two-sided, χ^2 test at a 5% level of significance. A dropout rate of 10% was allowed; thus, with 86 patients required per group, a total sample size of 172 patients was required for the trial.

Allocation

A registration form for each eligible patient will be sent electronically by the investigators to the Data Management Centre at Chiba Clinical Research Centre (CCRC). Registration and group allocation will be implemented at the Data Management Centre. Eligible patients with appropriately signed informed consent will be randomised to either the IVIG+CsA or IVIG-alone group at a ratio of 1:1, by employing a minimisation method with biased coin assignment balancing for sex (male or female), age (\geq 12 months or $<$ 12 months), and the risk score (\geq 7 or $<$ 7) at the time of screening.^{16 17} Investigators will prescribe the investigational drug according to the number allocated at the data management centre.

Blinding

Participants and study investigators are unblinded to IVIG+CsA or IVIG treatments. The primary end point, a CAA, will be strictly adjudicated by an Independent Endpoint Evaluation Review Committee blinded to the assigned treatment group.

Interventions

IVIG+CsA combination treatment and IVIG standard treatment will both be administered for 5 days. Patients will return for follow-up at week 12 (day 85). The IVIG standard treatment group will receive 2 g/kg of IVIG administered over 24 h and 30 mg/kg of aspirin per day until they are afebrile, followed by 5 mg/kg of aspirin per day for at least 6 weeks after fever onset. The IVIG +CsA combination treatment group will receive the same

IVIg regimen as the control group plus 5 mg/kg CsA per day in two separate oral doses for 5 days. All patients are treated with Neoral, because Neoral has better bio-availability than other forms of oral cyclosporine. In the event of occurrence of AEs, dosing of IVIG+CsA or IVIG may be reduced and eventually discontinued during the study period if investigators consider it appropriate. The schedule for the study visits and data collection is summarised in [table 2](#).

Outcomes

The primary end point of the study is to determine the frequency of CAAs during the study period. Two-dimensional echocardiography will be performed in order to identify such alterations in the coronary arteries. In a similar way as in the RAISE study, the two-dimensional echocardiograms obtained will be digitally recorded at the clinical institutions and interpreted at a core laboratory by three paediatric cardiologists blinded to patient identity and group allocation.⁷ For the purpose of this study, CAAs are defined as follows: (1) in children younger than 5 years old, the largest luminal diameter of a coronary artery is more than 3.0 mm or 1.5 times longer than the diameter of a neighbouring artery; (2) in children aged 5 years or above, the largest luminal diameter of a coronary artery is more than 4.0 mm or 1.5 times longer than the diameter of a neighbouring artery, (3) the internal diameter of a segment is 1.5 times longer than its baseline and (4) the luminal contour is clearly irregular.^{7 18}

The secondary end points include the frequency of CAAs at week 4, the frequency of treatment resistance (initial treatment unresponsiveness or relapse during the 12 weeks), Z scores for the right coronary artery, and the left main coronary trunk and anterior descending artery, fever duration period, change in body temperature, frequency of defervescence, change in serum concentration of C reactive protein (CRP), genotype frequency of *ITPKC* and *CASP3* SNPs, additional treatment and follow-up treatment, and frequency of AEs.

Data management, monitoring, safety and auditing

The investigators will maintain individual records for each patient as source data, which include a log of informed consent forms, medical history, laboratory data and other records, as appropriate. All entries in the electronic case report forms (eCRF) will be backed up by the relevant source data. In addition, all source data will be kept according to good clinical practice (GCP) and eCRFs will be completed in a timely manner.

All data will be collected by the Data Management Centre at CCRC. There will be no direct communication between investigators and data managers. The clinical data entry, coding, data management and reporting will be performed using the data management system Medidata RAVE (Medidata Solutions, Inc, NY, USA). Moreover, data management will be conducted according to the standard operating procedures of the trial.

Monitors will ensure that the investigational team is complying with the study protocol and GCP standards, that the data and AEs are accurately and appropriately recorded in the eCRFs, that severe AEs (SAEs) are forwarded to the trial coordinator and the investigational drug provider, and that those meeting reporting criteria are forwarded to the institutional review board (IRB).

AEs will be classified in accordance with the Medical Dictionary for Regulatory Activities, Japanese translation MedDRA/J V.16.1 (MedDRA Japanese Maintenance Organization, Tokyo, Japan). All AEs are to be followed up during their course and until their resolution, or for 4 weeks after the end of the trial. All SAEs will be reported to all investigators, discussed through a web-based AE reporting system, and will be reported to the PMDA, if necessary.

The study will be regularly audited during the trial duration, and will finally be inspected by the investigational drug provider and PMDA.

STATISTICAL METHODS

The analyses of the primary and secondary end points will be performed in a full analysis set, which includes all patients who: took at least one dose of treatment during the study; do not present any serious violation of the study protocol; have data collected after treatment commencement. For the baseline characteristics, summary statistics will comprise frequencies and proportions for categorical variables, and means and SDs for continuous variables. The patient characteristics will be compared using a χ^2 test for categorical variables, and a t test or Wilcoxon rank sum test for continuous variables.

For the primary analysis, aimed at comparing treatment effects, the adjusted risk ratio and its 95% CI will be estimated using the Mantel-Haenszel method.¹⁹ To test for significant association of the primary end point, the Mantel-Haenszel test will be applied adjusting for sex (male or female), age (≥ 12 months or < 12 months) and the baseline risk score (≥ 7 or < 7).

For the secondary analysis, the frequency of CAAs at week 4 after enrolment, that of defervescence, and level of treatment resistance, will be compared using the Mantel-Haenszel method. The adjusted risk ratio and its 95% CIs will be estimated. For Z scores, change in body temperature, and serum concentration of CRP, the adjusted difference of treatment mean and its 95% CIs, will be estimated using a mixed effects model, for repeated measures. The model includes treatment, visit, treatment-by-visit interaction, sex, age and the baseline risk score as fixed effects, with unstructured covariance structure. The fever duration period will be evaluated as time-to-event data and the median duration of the fever and its 95% CI will be estimated by the Kaplan-Meier method. The adjusted HR and its 95% CIs will be estimated using a Cox regression model, adjusting for sex, age and the baseline risk score. The genotype frequency

Table 2 Schedule of study data collection

Item	Screening period	Treatment period					Post-treatment observation period				Discontinuation
	Registration	Day 1	Day 2	Day 3	Day 4	Day 5	Day 8 (1 weeks)	Day 15 (2 weeks)	Day 29 (4 weeks)	Day 85 (12 weeks)	
Informed consent	○										
Baseline characteristics	○										
Adverse event assessment*		←————→					←-----→				
Temperature	○	●	●	●	●	●	●	●	●	●	●
Signs and symptoms†	○		●	●	●	●	●	●	●	●	●
Vital signs‡	○	●	●	●	●	●	●		●	●	●
Weight	○	●				●				●	●
Haematological test§	○	●		●		●	●		●	●	●
Blood biochemical test¶	○	●		●		●	●		●	●	●
ECG	○										
Echocardiogram	○			●	(●)	(●)	●	●	●	●	●
Coronary angiography**							←-----→				
Blood concentration††				●		●					●
<i>ITPKC</i> and <i>CASP3</i> SNPs		●									
Concomitant drug		←————→									

○: To be performed before starting the treatment; ●: to be performed after starting the treatment; preinformed consent data may also be used.

*Adverse event refers to any and all untoward events, including adverse reactions, regardless of causal relationship with the study drug.

†Assessment of major symptoms of Kawasaki disease, not including fever.

‡Blood pressure, and pulse and respiratory rate (SpO₂ as necessary).

§WCC, differential leucocyte count, neutrophil (%), RBC, haemoglobin, haematocrit, platelet count.

¶Total bilirubin, Alb, eGFR, BUN, AST, ALT, amylase, CRP, potassium, creatinine, Cl, Na, LDH, total cholesterol, blood glucose, total protein.

**Coronary angiography to be performed 12 weeks after the treatment in patients with coronary aneurysm identified by echocardiogram.

††Blood concentration will be measured only in the study treatment group (IVIG+CsA) after the first dose on day 3 and at the end of treatment or when the treatment is discontinued.

Alb, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; *CASP3*, caspase 3; CRP, C reactive protein; CsA, cyclosporin A; eGFR, estimated glomerular filtration rate; *ITPKC*, inositol 1,4,5-trisphosphate 3-kinase C; IVIG, intravenous immunoglobulin; LDH, lactate dehydrogenase; RBC, red blood cell; SNPs, single nucleotide polymorphisms WCC, white cell count.

of *ITPKC* and *CASP3* SNPs will be summarised by proportions and percentage, and the association between the primary end point and SNPs will be evaluated by a logistic regression model. This model includes treatment, genotype, a treatment-by-genotype interaction, sex, age and the baseline risk score as fixed effects. The adjusted odds ratio and its 95% CIs will be estimated. The additional and follow-up treatments as well as the frequency of AEs will be compared using the Fisher's exact test.

All comparisons are planned and all p values will be two sided. p Values <0.05 will be considered statistically significant. All statistical analyses will be performed using the SAS software, V.9.4 (SAS Institute, Cary, NC, USA). The statistical analysis plan will be developed by the principal investigator and the biostatistician before completion of patient recruitment and fixing of data.

ETHICS AND DISSEMINATION

Research ethics approval and protocol amendments

The trial was approved by the IRB at each of the participating institutions and will be conducted in accordance with GCP standards and the Declaration of Helsinki. The trial was notified and registered at PMDA, at the UMIN clinical registry (UMIN000017585) and at the JMACCT registry (JMA-IIA00174).

Informed consent

All participants or their legal guardians will receive adequate information about the nature, purpose, possible risks and benefits of the trial, and about alternative therapeutic choices, using an informed consent form approved by the IRB. The participants will be given ample time and opportunity to ask questions and to consider participation in the trial. The informed consent form, signed by the participant or a legal guardian, is required for enrolment in the trial. The investigators will maintain the original and a copy of the signed consent form with the trial records.

Confidentiality

To assure confidentiality, trial participants will be allocated a unique trial identification number throughout the trial.

DISCUSSION

Patients with severe KD who have persistent fever and lasting inflammation even after standard treatment with IVIG have an increased risk of developing CAAs.^{5 20–22} Unfortunately, there is no current alternative to effectively treat refractory KD despite the need for it and efforts made to identify it. Previous attempts to treat severe KD include: (1) additional IVIG, (2) methylprednisolone pulse, (3) prednisolone, (4) biological preparations, (5) ulinastatin, (6) serum exchange and (7) CsA, which is the approach used in this trial. However, from a safety standpoint, the following issues remain: treatments

(1) and (4) carrying an increased risk of infection; treatments (2) and (3) pose the risks of KD recurrence at the time of steroid reduction, as well as the development of giant aneurysms, hyperthermia and thrombosis;²³ treatment (4) has the risk of infection;²⁴ and treatment (5) can cause leucopenia or shock;²⁵ treatment (6), additionally, is invasive and expensive.

In the eligibility criteria, the enrolment of this study is limited to patients 4 months and above. Based on previous reports, the incidence of KD in patients ≤ 6 months of age in relation to patients with KD is approximately 10%,^{26 27} which is similar to the 11.2% in Japan²⁸ and 7.7% in Korea.²⁹ Additionally, the incidence of patients with KD ≤ 3 months of age was 1.7% in Japan³⁰ and 2.2% in Korea. Lee *et al*³¹ reported that there was no significantly higher prevalence of CAAs (3.4% vs 2.6%, respectively) found in patients with KD ≤ 3 months of age and patients with KD > 3 months of age; therefore those patients with KD ≤ 3 months of age are not at elevated risk of severe KD. In the previous clinical trial,¹³ the included patients with KD were between 4 and 94 months old, and no SAEs occurred. We did not have safety data of patients with severe KD ≤ 3 months of age who were treated with CsA. For reasons of safety, young patients with KD (even those as young as 1 or 2 months of age) are excluded from the trial. We consider CsA to be a valuable and promising alternative for the treatment of severe KD. CsA, which can be taken orally, has been widely used in paediatric patients with nephrosis and after organ transplantation, and there is cumulative evidence about its safety in this age group. This new treatment for severe KD has the advantage of oral, safe and inexpensive administration compared to some other options.^{13 22}

This trial will investigate the superiority of combination therapy of IVIG+CsA compared to standard IVIG therapy, for preventing CAA complications, in a prospective randomised, open-label, blinded-end point study. To avoid biases associated with open label studies, the primary end points were set as hard end points, and the adjudication of primary end points was strictly conducted by the independent end point evaluation review committee. A study to determine the most suitable dosage of CsA for the treatment of severe KD has not yet been conducted, but the CsA dosage was set at 5 mg/kg/day, a dose administered to steroid-resistant paediatric patients with nephrosis. In our previous study,¹³ the CsA dosage was set at 4 mg/kg/day as the initial dosage and increased, appropriately, to 5–8 mg/kg/day, targeting the CsA blood concentration monitoring at 60–200 ng/mL. As a result, for most patients, fever subsided within 5 days after the administration of CsA. Therefore, based on the efficacy and safety of the previous study, we have set the initial dosage as 5 mg/kg/day and made it possible to change the dosage by blood level monitoring, which is set between 60 and 200 ng/mL, and set a treatment course of 5 days. The follow-up period of this trial has been set at 12 weeks. The AHA guidelines stated that echocardiographic

evaluation should be performed at 2 weeks, and then at 6–8 weeks, after the onset of the disease.³² Previous reports have shown that, if it has not been acquired by them earlier, it is rare for patients with KD to develop a CAA after 4–8 weeks.^{33 34} There are several randomised controlled trials for the treatment of KD,^{7 35 36} and they suggest a 4 or 5 week period for observation. Considering all these facts, we set 12 weeks as the follow-up period.

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Competing interests None.

Patient consent Obtained.

Ethics approval The protocol was approved by the Institutional Review Board of each participating institution.

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