

Infliximab versus second intravenous immunoglobulin for treatment of resistant Kawasaki disease in the USA (KIDCARE): a randomised, multicentre comparative effectiveness trial

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Summary

Background Although intravenous immunoglobulin (IVIG) is effective therapy for Kawasaki disease, 10–20% of patients have recrudescent fever as a sign of persistent inflammation and require additional treatment. We aimed to compare infliximab with a second infusion of IVIG for treatment of resistant Kawasaki disease.

Methods In this multicentre comparative effectiveness trial, patients (aged 4 weeks to 17 years) with IVIG resistant Kawasaki disease and fever at least 36 h after completion of their first IVIG infusion were recruited from 30 hospitals across the USA. Patients were randomly assigned (1:1) to second IVIG (2 g/kg over 8–12 h) or intravenous infliximab (10 mg/kg over 2 h without premedication), by using a randomly permuted block randomisation design with block size of two or four. Patients with fever 24 h to 7 days following completion of first study treatment crossed over to receive the other study treatment. The primary outcome measure was resolution of fever at 24 h after initiation of study treatment with no recurrence of fever attributed to Kawasaki disease within 7 days post-discharge. Secondary outcome measures included duration of fever from enrolment, duration of hospitalisation after randomisation, and changes in markers of inflammation and coronary artery Z score. Efficacy was analysed in participants who received treatment and had available outcome values. Safety was analysed in all randomised patients who did not withdraw consent. This clinical trial is registered with ClinicalTrials.gov, NCT03065244.

Findings Between March 1, 2017, and Aug 31, 2020, 105 patients were randomly assigned to treatment and 103 were included in the intention-to-treat population (54 in the infliximab group, 49 in the second IVIG group). Two patients randomised to infliximab did not receive allocated treatment. The primary outcome was met by 40 (77%) of 52 patients in the infliximab group and 25 (51%) of 49 patients in the second IVIG infusion group (odds ratio 0·31, 95% CI 0·13–0·73, $p=0\cdot0076$). 31 patients with fever beyond 24 h received crossover treatment: nine (17%) in the infliximab group received second IVIG and 22 (45%) in second IVIG group received infliximab ($p=0\cdot0024$). Three patients randomly assigned to infliximab and two to second IVIG with fever beyond 24 h did not receive crossover treatment. Mean fever days from enrolment was 1·5 (SD 1·4) for the infliximab group and 2·5 (2·5) for the second IVIG group ($p=0\cdot014$). Mean hospital stay was 3·2 days (2·1) for the infliximab group and 4·5 days (2·5) for the second IVIG group ($p<0\cdot001$). There was no difference between treatment groups for markers of inflammation or coronary artery outcome. 24 (44%) of 54 patients in the infliximab group and 33 (67%) of 49 in the second IVIG group had at least one adverse event. A drop in haemoglobin concentration of at least 2g/dL was seen in 19 (33%) of 58 patients who received IVIG as either their first or second study treatment (three of whom required transfusion) and in three (7%) of 43 who received only infliximab (none required transfusion; $p=0\cdot0028$). Haemolytic anaemia was the only serious adverse events deemed definitely or probably related to study treatment, and was reported in nine (15%) of 58 patients who received IVIG as either their first or second study treatment and none who received infliximab only.

Interpretation Infliximab is a safe, well tolerated, and effective treatment for patients with IVIG resistant Kawasaki disease, and results in shorter duration of fever, reduced need for additional therapy, less severe anaemia, and shorter hospitalisation compared with second IVIG infusion.

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Introduction

Kawasaki disease is a self-limited vasculitis of unknown cause that is the most common cause of acquired heart disease in children in developed countries.¹ Treatment with intravenous immunoglobulin (IVIG) reduces the

incidence of coronary artery aneurysms from 25% to approximately 5%.² However, for the 10–20% of IVIG resistant patients (defined as having an oral or rectal temperature $\geq 38\cdot0^{\circ}\text{C}$ at least 36 h following the end of the initial IVIG infusion), there is no robust evidence to guide

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Research in context

Evidence before this study

Intravenous immunoglobulin (IVIG) is an effective therapy to reduce inflammation and prevent coronary artery damage in Kawasaki disease. 10–20% of children have recurrence of fever after initial therapy and are at increased risk of coronary artery aneurysms. A second infusion of IVIG, infliximab, and corticosteroids have all been advocated for treatment of IVIG resistant Kawasaki disease. We searched PubMed for research articles from database inception to Dec 31, 2020, using the terms “Kawasaki disease”, “intravenous immunoglobulin resistance”, “infliximab”, and “clinical trials”. We identified three randomised controlled trials that compared second infusion of IVIG and infliximab for IVIG resistant patients with Kawasaki disease. All three studies (one done in the USA with 24 patients, one in Japan with 31 patients, and one in Korea with 43 patients) found a higher rate of fever resolution and shorter duration of hospitalisation in patients who received infliximab. A 2018 Cochrane review of these studies concluded that there was insufficient evidence that infliximab had a beneficial effect on IVIG treatment resistance due to the small number of underpowered randomised controlled trials.

Added value of this study

To our knowledge, we report results of the first adequately powered randomised controlled trial that compared a second IVIG infusion to infliximab in children with Kawasaki disease and IVIG resistance enrolled at 30 clinical sites across the USA. Children who received infliximab were more likely to become and remain afebrile, had less need for additional anti-inflammatory therapy, had shorter duration of hospitalisation, and fewer serious adverse events including haemolytic anaemia, compared with the group treated with second IVIG. There was no difference in laboratory markers of inflammation or coronary artery outcome at study completion between the two treatment groups.

Implications of all the available evidence

Children with Kawasaki disease and IVIG resistance can be safely treated with infliximab, which results in faster resolution of fever and less severe anaemia, whereas a second infusion of IVIG is less effective in achieving cessation of fever and can be associated with haemolytic anaemia, particularly in patients with non-O blood type. Future clinical research should investigate best clinical practice for patients presenting with early aneurysms.

treatment and this group has an increased risk of coronary artery aneurysms. In a study of 362 consecutive patients with Kawasaki disease, nine (15%) of 60 IVIG resistant patients developed coronary artery aneurysms.³ Data from Japan suggest that the rates of IVIG resistance have risen from 7% in 2003 to 23% in 2014, with a concomitant increase in coronary artery aneurysms.⁴ The problem of IVIG resistance was first noted in the original IVIG trials in the 1980s.⁵ Based on the apparent dose response to IVIG, administration of a second dose of IVIG became first-line therapy for IVIG resistant patients and is still widely used today.⁶ However, treatment with a second infusion of IVIG has never been studied in an adequately powered, randomised clinical trial.⁷ The high cost of IVIG and the recent emergence of haemolytic anaemia following a second dose due to anti-blood type A and B antibodies in the IVIG preparations were the motivation to do this trial.

There is clinical equipoise regarding the best treatment for IVIG resistant patients, and a second infusion of IVIG with or without corticosteroids, pulsed or longer course corticosteroids alone, or infliximab are the most common second treatments. Persistent or recrudescing fever after the first IVIG infusion rather than any laboratory measure of inflammation is considered a sign of continuing inflammation and there is consensus that the patients with this symptom should receive additional therapy. The American Heart Association (AHA) Kawasaki disease guidelines assign an evidence level of B (non-randomised studies) to retreatment with second IVIG or steroids and an evidence level of C (consensus of

experts) to infliximab.⁸ Thus, robust randomised clinical trial data to guide treatment are needed. The clinical need is high for this subgroup of patients with coronary artery aneurysms due to persistent inflammation, which might lead to permanent damage to the arterial wall with an associated risk of myocardial infarction, arrhythmias, or sudden cardiac death.⁹

The Kawasaki Disease Comparative Effectiveness (KIDCARE) trial was designed to determine best practice for patients with Kawasaki disease resistant to IVIG in a multiethnic population with broad geographical representation across the USA.

Methods

Study design and participants

In this randomised, multicentre comparative effectiveness trial, patients with IVIG resistant Kawasaki disease and fever at least 36 h after completion of their first IVIG infusion were recruited from 30 hospitals across the USA.

Patients were enrolled from March 1, 2017, to Aug 31, 2020. Enrolment was ended according to the funding agency's contract on Aug 31, 2020. Infants and children aged 4 weeks to 17 years who met AHA criteria for complete or incomplete Kawasaki disease and were initially treated for Kawasaki disease with IVIG (2 g/kg) within the first 10 days after fever onset were eligible for enrolment. Exclusion criteria included initial treatment with IVIG after the tenth day of fever and treatment with steroids or other medication for intensification of initial

therapy; patients with chronic disease, except asthma, atopic dermatitis, autism, or controlled seizure disorder; patients with known previous infection with tuberculosis, coccidioidomycosis, or histoplasmosis, or household contact with active tuberculosis; patients who had used tumour necrosis factor (TNF) α -blocker within 3 months before enrolment; and patients with a history of hypersensitivity to infliximab.

The study protocol (appendix) was reviewed and approved by the institutional review board at all participating sites. Written informed consent from the parents or legal guardians and assent from patients were obtained as appropriate.

Randomisation and masking

Patients were randomly assigned in a 1:1 ratio to infliximab or second IVIG according to a prespecified randomisation scheme stratified by site, sex (male vs female), and age (>12 months or \leq 12 months) by using a randomly permuted block randomisation design with block size of two or four, which was created by the Data Coordinating Center. Patient enrolment and randomisation through the REDCap database was done by the study site investigators who could not predict the next treatment assignment. This was an open-label trial and no masking took place.

Procedures

The study was designed with input from a Stakeholder Advisory Board that included parents whose children previously had Kawasaki disease and adults with a history of Kawasaki disease in childhood.¹⁰ In this pragmatic trial, all infliximab or IVIG products were permitted and the manufacturer's name was recorded. Infliximab was administered intravenously over 2 h without premedication. The dose of infliximab (10 mg/kg) was chosen based on pharmacokinetic modelling that suggested a decreased concentration of drug in the tissue compartment when administered following IVIG.¹¹ Second IVIG (2 g/kg) was administered according to local practice over 8–12 h. Depending on local standard of care for patients in both treatment groups, aspirin dose was either 30–50 mg/kg/day or 80–100 mg/kg/day until discharge and then 3–5 mg/kg/day until the patient was off study. Patients who did not become afebrile 24 h to 7 days after the end of their study-assigned treatment crossed over to receive the other study medication. Patients who still had persistent fever after receiving their crossover treatment were treated at the discretion of the local team.

Patients' temperatures were measured at all timepoints by the oral, rectal, or axillary route to accommodate variations in hospital and nursing practices across the 30 sites. Fever was defined as 38.0°C (oral or rectal route) or 37.5°C (axillary route).¹² After discharge from hospital, parents recorded daily temperatures at home with thermometers provided at the time of discharge and continued recording temperatures until they returned

for their first clinic visit. A broad window (5–18 days after completion of study treatment) was allowed for the first clinic visit (study completion) to accommodate wide practice variation across the 30 participating sites.

Data for white blood cell count, absolute neutrophil count, haemoglobin concentration normalised for age, platelet count, and C-reactive protein concentration at baseline (defined as pre-IVIG at Kawasaki disease diagnosis), 24 h (plus or minus 2 h) after completion of study treatment, 24 h (plus or minus 2 h) after completion of crossover study treatment (if administered), and at study completion (defined as 5–18 days following completion of study treatment) were entered into the REDCap database. Haemolytic anaemia due to antibodies in the IVIG was defined as a drop in haemoglobin concentration by 2 g/dL or more 24 h after completion of study drug in conjunction with other supporting laboratory data including a positive direct antibody test, spherocytes on the peripheral smear, or an elevated haptoglobin level. Erythrocyte sedimentation rate was only compared at baseline and study completion; it was not measured after completion of study treatment because IVIG causes red blood cells to sediment faster.

Sites were provided with a manual of operations from the National Institutes of Health-sponsored Pediatric Heart Network clinical trial for Kawasaki disease.¹³ In an effort to standardise echocardiographic imaging across sites, a single echocardiogram of a non-study patient with Kawasaki disease was submitted by every site and the technical quality assessed by the Director of Non-Invasive Imaging (BFP) at Rady Children's Hospital San Diego (San Diego, CA, USA). A written assessment of the echocardiogram quality with suggestions for improvement as needed was sent to every site. Patient height, weight, and internal dimension of the right coronary artery, left anterior descending coronary artery, and circumflex artery were recorded at baseline and at study completion. Z scores (internal diameter of the right and left anterior descending normalised for body surface area and expressed as SD units from the mean) were calculated by the Data Coordinating Center in the REDCap database. Z-worst was defined as the highest Z score for the right coronary artery, left anterior descending coronary artery, or circumflex artery from the echocardiograms at baseline and at study completion.

A Data and Safety Monitoring Board (DSMB) reviewed adverse events and serious adverse events by treatment group every 6 months in a closed session attended only by DSMB members and the study statistician. Attribution of relatedness of all adverse events to study treatments was adjudicated by an adverse events committee comprised of three experts in paediatric infectious disease or rheumatology.

Outcomes

The primary outcome was resolution of fever at 24 h after initiation of study treatment with no recurrence of fever

See Online for appendix

For the REDCap database see project-redcap.org

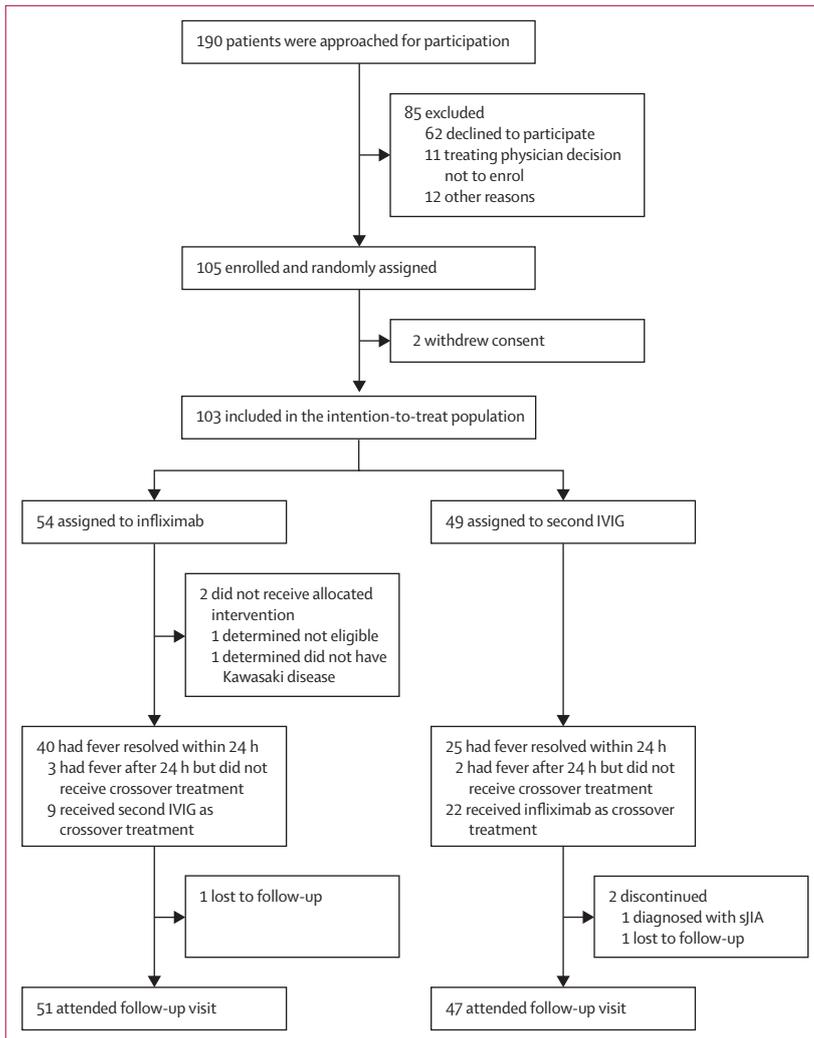


Figure: Trial profile
 IVIG=intravenous immunoglobulin. sJIA= systemic onset juvenile rheumatoid arthritis.

attributed to Kawasaki disease in the first 7 days after discharge. Secondary outcome measures included: (1) duration of fever from enrolment, (2) duration of hospitalisation after randomisation, (3) decreased inflammation as measured by the change in white blood cell count, absolute neutrophil count, and C-reactive protein concentration from baseline, at 24 h (plus or minus 2 h) after completion of the first study treatment, and study completion, (4) change of at least 0.5 SD units between baseline and study completion for the right or left anterior descending coronary artery Z score as measured by echocardiography, and (5) comparison of therapy-related adverse events as adjudicated by an adverse event committee.

Statistical methods

The sample size calculation was based on approximately 80% power to detect a difference between the group

proportions of 0.22. The target enrolment was 106 patients in total, which we estimated to yield an effect size of 0.22 (assuming a response rate of 0.67 for IVIG vs 0.89 for infliximab) based on a previously published randomised trial.⁷

Baseline characteristics were compared between treatment groups to assess for imbalance despite randomisation. Laboratory measures were also summarised and compared at each timepoint. Categorical variables were analysed with Fisher's exact test. Continuous variables were analysed with Wilcoxon's rank sum test. Safety data, including haemolytic anaemia, were summarised overall and by treatment group. Fisher's exact test was used to compare the number of patients between treatment groups who had any adverse events.

The intention-to-treat population, which included all randomly assigned patients who did not withdraw consent, were analysed for baseline characteristics and safety. The modified intention-to-treat population, which included all patients who received treatment (including crossover participants who were analysed in their initial randomised group) and who had available outcome data, were included in the analyses of the primary and secondary outcomes. All primary and secondary analyses were prespecified. Logistic regression analysis was done with the primary outcome as the dependent variable and treatment group as the main independent variable. Stratification variables and any baseline demographics that were simultaneously unbalanced at baseline and associated with the outcome ($p < 0.1$) were included in logistic regression model as covariates if both criteria were met. We planned to provide crossover summaries for the patients randomly assigned who did not withdraw consent and to use Fisher's exact test to compare crossovers between the two treatment groups.

For the secondary outcomes, which included change from baseline of inflammation measurements at 24 h (plus or minus 2 h) after completion of the first study treatment and at study completion, three separate mixed model repeated measures (MMRM) models were done. A descriptive summary (median [IQR]) was also provided for the variables. Patients who were randomly assigned, treated (in their assigned group), and who had at least one corresponding post-baseline inflammation value were included in the analysis. In the MMRM model, the change from baseline inflammation measure was the dependent variable. The independent variables were treatment group, visit (treated as categorical variable), treatment-by-visit interaction, and corresponding baseline inflammation measurement. Stratification variables and any baseline demographics that were simultaneously unbalanced at baseline and associated with the outcome ($p < 0.1$) were included in MMRM model as covariates if both criteria were met.

Another secondary outcome, Z-worst score, was summarised at baseline and study completion. The Haycock equation for body surface area and Dallaire equation for Z score calculation were applied to the

height, weight, and coronary artery dimensions provided by the sites.^{14,15} The Wilcoxon rank sum test was used to compare the Z-worst scores between the two treatment groups. A frequency table was provided for the binary Z-worst change by 0.5 SD or more, and Fisher's exact test was done to compare the two treatment groups. For other secondary outcomes (fever days from the time from enrollment, days of hospitalisation from the time of study randomisation, and change in laboratory measurements of inflammation), treatment groups were compared using the Wilcoxon rank sum test. Low platelet count might be a marker of disease severity and indicate low-grade disseminated intravascular coagulation. To explore whether the lower mean platelet count and greater proportion of patients with an initial Z-score of 2.5 or more in the second IVIG group affected the primary outcome, a sensitivity analysis was done in which we adjusted for baseline platelet and categorical Z-worst (cutoff of 2.5). The AHA guidelines consider a Z score of 2.5 or more to be an aneurysm.⁸ p values less than 0.05 were considered statistically significant. Statistical analysis was done using R software version 3.6.1.

This clinical trial is registered with ClinicalTrials.gov, NCT03065244.

Role of the funding source

The study sponsor, Patient-Centered Outcomes Research Institute, had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between March 1, 2017, and Aug 31, 2020, 190 patients were approached for participation (figure) and 105 patients were randomly assigned to treatment. After two families withdrew consent, 103 patients were included in the intention-to-treat analysis. An additional two patients randomly assigned to infliximab were withdrawn and did not receive the assigned treatment; one had an alternative diagnosis established and the second patient was determined not to have had a recurrent fever. Baseline demographic characteristics of patients randomly assigned to infliximab (n=54) and second IVIG (n=49) are shown in table 1.

The primary outcome, resolution of fever at 24 h after initiation of study treatment with no recurrence of fever attributed to Kawasaki disease in the first 7 days after discharge, was met by 40 (77%) of 52 patients in the infliximab group and 25 (51%) of 49 patients in the second IVIG group (odds ratio [OR] 0.31, 95% CI 0.13–0.73, p=0.0076). Therefore, 12 patients assigned to infliximab and 24 to IVIG had fever beyond 24 h after initiation of their first study treatment. Of the 12 patients assigned to infliximab, one developed fever beyond 24 h but did not receive second IVIG as crossover treatment because of haemolytic anaemia attributed by the site principal investigator to the initial IVIG treatment (before study entry). The

	Infliximab group (n=54)	Second IVIG group (n=49)	p value
Age at enrolment, years	3.6 (2.0 to 6.4)	2.1 (1.7 to 5.0)	0.11
Age group, years			0.3
≤1	11 (20%)	6 (12%)	
>1	43 (80%)	43 (88%)	
Sex			0.55
Male	29 (54%)	30 (61%)	
Female	25 (46%)	19 (39%)	
Illness day at first intravenous immunoglobulin treatment*	6.0 (5.0 to 7.0)	6.0 (5.0 to 8.0)	0.54
Illness day at randomisation	8.0 (7.0 to 9.8)	9.0 (7.0 to 11.0)	0.27
Incomplete Kawasaki disease	11 (20%)	15 (31%)	0.26
Race			0.92
Asian	6 (11%)	5 (10%)	
Black or African American	10 (19%)	9 (18%)	
White	29 (54%)	31 (63%)	
Other	1 (2%)	0	
Multirace	6 (11%)	3 (6%)	
Unknown	2 (4%)	1 (2%)	
Hispanic ethnicity	17 (32%)	12 (25%)	0.63
Laboratory data at diagnosis			
White blood cells, ×10 ⁹ cells per L	12.8 (8.5 to 16.7)†	13.6 (10.7 to 19.2)‡	0.21
Absolute neutrophil count§	8449.0 (5551.5 to 12 160.9)	9384.0 (6865.5 to 12 752.5)	0.28
Haemoglobin concentration normalised for age, SD units	-2.3 (-3.0 to -1.3)†	-2.3 (-3.5 to -1.4)‡	0.53
Platelets, 10 ⁹ per L	324.0 (241.0 to 398.0)†	359.5 (275.8 to 532.8)¶	0.04
Erythrocyte sedimentation rate, mm/h	56.5 (41.3 to 86.3)	68.5 (44.8 to 89.3)¶	0.31
C-reactive protein, mg/dL	14.1 (5.9 to 20.1)†	9.0 (5.1 to 17.3)¶	0.33
Z-worst at baseline**	1.1 (0.7 to 1.7)	1.4 (0.8 to 2.1)	0.28

Data are median (IQR) or n (%), unless stated otherwise. p values were calculated by Wilcoxon rank sum test for continuous variables and Fisher's exact test for categorical variables. IVIG=intravenous immunoglobulin. *Illness day 1 is the first day of fever. †Data available for 53 patients. ‡Data available for 49 patients. §Data available for 51 patients in the infliximab group and 47 in the second intravenous immunoglobulin group. ¶Data available for 48 patients. ||Data available for 52 patients. **Z-worst was defined as the highest Z score for the right coronary artery, left anterior descending coronary artery, or circumflex artery from the echocardiograms; data are complete except for one patient treated with infliximab IVIG=intravenous immunoglobulin.

Table 1: Baseline and clinical characteristics (intention-to-treat population)

principal investigator declined to give additional IVIG as crossover treatment and the patient eventually became afebrile without additional therapy. Two additional patients assigned to infliximab developed fever beyond 24 h, but did not receive crossover treatment and subsequently became afebrile without treatment. Of 24 patients assigned to second IVIG infusion who had fever beyond 24 h after initiation of their first study treatment, one patient was subsequently diagnosed with systemic-onset juvenile idiopathic arthritis and one patient developed fever beyond 24 h, but did not receive crossover infliximab treatment and subsequently became afebrile without treatment. After initial randomised study treatment, 31 patients received the crossover treatment: nine patients initially treated with infliximab and 22 patients initially treated with second IVIG (p=0.0024). Of 31 patients who received crossover treatment, seven (78%) of nine patients who

	Infliximab group (n=54)		Second IVIG (n=49)		p value
	n	Measure	n	Measure	
White blood cells, $\times 10^9$ cells per L					
Baseline	53	12.8 (8.5 to 16.7)	49	13.6 (10.7 to 19.2)	0.21
24 h (plus or minus 2 h) after completion of study treatment	52	13.9 (9.8 to 16.2)	48	12.4 (9.2 to 16.5)	0.47
Study completion	47	9.0 (7.3 to 11.6)	45	7.7 (6.5 to 9.7)	0.051
Absolute neutrophil count					
Baseline	51	8449.0 (5551.5 to 12160.9)	47	9384.0 (6865.5 to 12752.5)	0.28
24 h (plus or minus 2 h) after completion of study treatment	50	5532.1 (3143.3 to 8753.3)	45	6120.0 (3694.6 to 9776.0)	0.54
Study completion	46	3322.5 (1833.0 to 4555.0)	48	3133.9 (2040.8 to 4109.8)	0.56
Haemoglobin concentration normalised for age					
Baseline	53	-2.3 (-3.0 to -1.3)	49	-2.3 (-3.5 to -1.4)	0.53
24 h (plus or minus 2 h) after completion of study treatment	51	-2.8 (-3.9 to -1.6)	48	-3.7 (-5.5 to -2.6)	0.0042
Study completion	47	-1.9 (-2.6 to -0.5)	45	-1.8 (-3.5 to -1.1)	0.13
Platelets, 10^9 per L					
Baseline	53	324.0 (241.0 to 398.0)	48	359.5 (275.8 to 532.8)	0.042
24 h (plus or minus 2 h) after completion of study treatment	52	466.0 (361.8 to 560.3)	48	511.5 (402.3 to 690.3)	0.062
Study completion	47	480.0 (390.5 to 571.0)	45	490.0 (356.0 to 583.0)	0.87
Erythrocyte sedimentation rate, mm/h*					
Baseline	52	56.5 (41.3 to 86.3)	48	68.5 (44.8 to 89.3)	0.31
Study completion	45	48.0 (32.0 to 62.0)	40	65.5 (45.0 to 98.3)	0.0079
C-reactive protein, mg/dL					
Baseline	53	14.1 (5.9 to 20.1)	48	9.0 (5.1 to 17.3)	0.33
24 h (plus or minus 2 h) after completion of study treatment	51	4.9 (2.1 to 9.3)	47	3.1 (1.7 to 8.6)	0.37
Study completion	44	0.5 (0.5 to 0.7)	42	0.5 (0.5 to 0.6)	0.59

Data are median (IQR), unless otherwise stated. p values were calculated by Wilcoxon rank sum test. Erythrocyte sedimentation rate data were collected only at baseline and study completion. IVIG=intravenous immunoglobulin.

Table 2: Laboratory measures of inflammation at baseline, 24 h (plus or minus 2 h) after completion of study treatment, and at study completion

crossed over to second IVIG infusion and 18 (82%) of 22 who crossed over to infliximab became afebrile after their crossover treatment ($p > 0.99$). The six patients with persistent fever (four who received infliximab and two who received second IVIG as their cross-over treatment) were treated with either ciclosporin ($n=1$) or steroids ($n=5$) at the discretion of the treating physician.

Patients assigned to second IVIG infusion had a mean of 2.5 fever days (SD 2.5) from enrolment versus 1.5 fever days (1.4) for patients assigned to infliximab ($p=0.014$). Days of hospitalisation from the time of study randomisation was longer for the patients in the second IVIG group (mean 4.5 days, SD 2.5) than in the infliximab group (3.2 days, 2.1; $p=0.0005$).

There were no significant differences between treatment groups for the median values of laboratory measures of inflammation, including white blood cell count, absolute neutrophil count, and C-reactive protein concentration, at any timepoint (table 2). Only the median baseline platelet count was significantly higher in patients in the second IVIG group than in patients in

the infliximab group ($p=0.042$). Of the three patients with platelet counts lower than 100 000 per mL, two were in the infliximab group and one in the second IVIG group. The median erythrocyte sedimentation rate, a marker of inflammation, was significantly higher at study completion in the patients who received second IVIG than in those in the infliximab group ($p=0.0079$). At the 24-h timepoint, the median haemoglobin concentration normalised for age was significantly lower in the group who received a second IVIG than in patients in the infliximab group ($p=0.0042$), which was an adverse event not expected when the study started. However, by the time of the follow-up visit, there was no significant difference between the treatment groups ($p=0.13$). The change from baseline by treatment and by timepoint was also analysed for white blood cell count, absolute neutrophil count, and C-reactive protein concentration, and no significant changes were noted in the univariate analysis or in the longitudinal MMRM models.

Of the 58 patients who received IVIG as either their first ($n=49$) or second study treatment ($n=9$), nine (16%)

were identified as having developed haemolytic anaemia (appendix pp 3–5). A tenth patient who received only infliximab as the study treatment had haemolytic anaemia that was attributed to the initial standard-of-care IVIG infusion. An additional ten patients (seven who received IVIG as their first study treatment and three who received IVIG as their second study treatment) had at least a 2 g/dL drop in haemoglobin concentration (appendix pp 3–5). Thus, 19 (33%) of 58 patients who received IVIG as either their first or second study treatment developed haemolytic anaemia (three required transfusion) versus three (7%) of 43 patients who received only infliximab as their study treatment (none were transfused; $p=0.0028$). Of the 16 patients across both groups with at least a 2 g/dL drop in haemoglobin concentration for whom the blood type was known, ten had blood type A, three had blood type B, one had blood type AB, and two had blood type O. Overall, of the 96 patients for whom the IVIG brand was known, 43 (45%) were treated with the Gammagard, which included 15 (68%) of the 22 patients in total who developed haemolytic anaemia. Weight-based dosing of IVIG for obese patients has been reported as a risk factor for haemolytic anaemia.¹⁶ However, only five (23%) of the 22 patients across both groups who developed presumed haemolytic anaemia were classified as overweight or obese based on paediatric criteria from the US Centers for Disease Control. Of three patients who had a decrease in haemoglobin concentration of 2 g/dL or more (significant anaemia) and received only infliximab as their study treatment, one was obese and two were classified as having a healthy weight.

There was no difference in median coronary artery Z-worst score between the groups at baseline or at study completion (table 3). Overall, ten (10%) of 101 patients for whom echocardiogram data were available had a Z-worst of at least 2.5 at study completion: four received infliximab, one received second IVIG, and five crossed over to receive both treatments (three had IVIG and two had infliximab as first treatment). An increase of at least 0.5 SD units in the coronary artery Z-worst score from baseline to study completion occurred in eight (18%) of 45 patients who received infliximab as their first study treatment and three (7%) of 45 patients who received second IVIG ($p=0.20$). At baseline, one (2%) of 50 patients assigned to infliximab and seven (14%) of 49 patients assigned to second IVIG had Z-worst scores of at least 2.5 ($p=0.031$). Of patients with a Z-worst score at baseline of less than 2.5, five (10%) of 49 patients in the infliximab group and three (7%) of 42 patients in the second IVIG group progressed to a Z-worst score of at least 2.5 at study completion ($p=0.72$). Of 31 patients who received crossover treatment, all but two had a baseline Z-worst score of less than 2.5 and five patients went on to develop aneurysms in one or both coronary arteries. One patient whose baseline Z-worst score was 2.86 in the infliximab group received no additional

	Infliximab group	Second IVIG group	p value
Z-worst			
Baseline	1.13 (0.73–1.73)	1.37 (0.76–2.05)	0.28
Study completion	1.12 (0.44–1.68)	1.07 (0.62–1.42)	0.58
Z-worst ≥ 2.5			
Baseline*	1/50 (2%)	7/49 (14%)	0.031
Study completion	6/47 (13%)	4/45 (9%)	0.74
Z-worst change by ≥ 0.5 SD	8/45 (18%)	3/45 (7%)	0.20

Data are median (IQR) or n/N (%), unless stated otherwise. Z-worst was defined as the highest Z score for the right coronary artery, left anterior descending coronary artery, or circumflex artery from the echocardiograms. p values were calculated by Wilcoxon rank sum test for continuous Z-worst score and Fisher's exact test for binary variables. IVIG=intravenous immunoglobulin. *Z-worst scores at baseline for each patient by treatment group: 2.86 for infliximab, 4.49, 4.45, 2.82, 2.80, 2.76, 2.65, and 2.53 for second IVIG.

Table 3: Z-worst at baseline, study completion, and change over time

treatment and developed a giant aneurysm (Z-worst score 15.01) by the time of study completion.

The results of the sensitivity analysis (comparison of second IVIG with infliximab: OR 0.23, 95% CI 0.09–0.59; $p=0.0023$) showed a similar trend as for the primary outcome model, which did not adjust for baseline platelet and categorical Z-worst (cutoff of 2.5).

There were 45 adverse events in the infliximab group and 65 adverse events in the second IVIG group (appendix p 1). 24 (44%) of 54 patients in the infliximab group and 33 (67%) of 49 patients in the second IVIG group had at least one adverse event ($p=0.029$). There were a total 51 serious adverse events: 15 in the infliximab group and 36 in second IVIG group. 37 patients had at least one serious adverse event; ten (18%) patients in the infliximab group and 27 (55%) in the second IVIG group ($p=0.0002$). Serious adverse events that were deemed definitely or probably related to study treatment were experienced by none of the patients who received only infliximab and by nine (15%) of 58 patients who received IVIG as either their first or second study treatment. Haemolytic anaemia was the serious adverse event in all nine patients. There were no reported deaths in this study.

Discussion

The KIDCARE trial compared two standard therapies for children with Kawasaki disease and persistent or recrudescent fever 36 h to 7 days after completion of their initial IVIG infusion—second IVIG infusion or infliximab. Patients assigned to infliximab had fewer days of fever, less need for additional therapy, less severe anaemia, fewer serious adverse events attributed to study treatment, and shorter hospitalisation compared with patients assigned to a second infusion of IVIG. The prolonged hospitalisation was related in part to the longer time required for second IVIG infusion (8–12 h vs 2 h for infliximab) and in part to the excess number of patients who required a crossover study treatment. No differences were noted between the two treatment groups regarding the resolution of laboratory markers of

For more on Centers for Disease Control weight classification see <https://www.cdc.gov/healthyweight/bmi/calculator.html>

inflammation or coronary artery outcome. Specifically, there were no significant differences in white blood cell count, absolute neutrophil count, C-reactive protein, or worst coronary artery Z score at any study timepoint between the treatment groups. The elevated erythrocyte sedimentation rate at study completion in the IVIG group was likely an artifact of higher concentrations of the positively charged IgG molecule that falsely elevates the erythrocyte sedimentation rate. The trial was not designed to address prevention of coronary artery aneurysm because such trial would have required a much larger sample size and a core echocardiographic laboratory for standardised coronary artery measurements across sites. Clinicians who treat patients with Kawasaki disease need guidance for two different clinical situations: best practice for patients at risk for aneurysms because of elevated Z scores on the initial echocardiogram, and best practice for patients with normal initial echocardiograms but persistent fever after initial IVIG infusion. The KIDCARE trial addressed best practice for the second group.

The most common adverse event in our study was haemolytic anaemia. Haemolytic anaemia as a complication of IVIG was first reported two decades ago in a Japanese patient.⁷ The occurrence of haemolytic anaemia following IVIG infusion has been clearly associated with non-blood group O antibodies and is a dose-related effect.^{16,18} Anti-blood group IgG₂ antibodies bind to red cells that are cleared by macrophages through a FCγR2-receptor mediated mechanism.¹⁹ The anti-blood group antibody titres vary among IVIG brands currently used in the USA.

Alternative treatments for IVIG resistance that have been reported include infliximab (5 mg/kg), steroids (methylprednisolone 2 mg/kg/day or 30 mg/kg pulse steroids), ciclosporin, anakinra, and plasmapheresis.⁸ Several retrospective case series have been reported, the largest of which included 412 patients from Japan, of whom 363 (84%) infliximab-treated patients became afebrile with no safety issues.²⁰ In a two-centre, retrospective study from the USA of either second IVIG infusion or infliximab as the first re-treatment, patients with IVIG resistance who were treated with infliximab had more rapid resolution of fever and inflammatory markers, fewer days spent in hospital, and lower costs of care.²¹ There was no difference in coronary artery outcomes between groups, although the study lacked sufficient power to measure an effect.²¹ In an open-label, observational study from Japan of infliximab (5 mg/kg) for IVIG resistance, 291 patients were enrolled.²² The majority had already received a second IVIG dose or other therapies and the authors concluded that the safety profile was excellent. Three small, randomised clinical trials of second IVIG versus infliximab (5 mg/kg) enrolling between 24 to 43 subjects have been reported from the USA,⁷ Korea,²³ and Japan.²⁴ Although all trials showed trends of defervescence in favour of infliximab,

the small numbers of patients precluded any robust conclusions and the trials should be viewed only as hypothesis-generating. In the current trial, we used 10 mg/kg of infliximab based on the favourable safety profile and the pharmacokinetics of infliximab modelled from two randomised studies in patients with Kawasaki disease.¹¹ This analysis suggested that IgG from previous administration of IVIG might compete for recycling through the neonatal FCγ-receptor. Thus, it was estimated that higher doses of infliximab would be required to achieve the same tissue concentrations of TNF blockade compared with administration of infliximab in the absence of IVIG.

A different strategy pursued by several investigators has been to select drugs that could be added to the initial IVIG regimen to prevent recrudescence fever. The RAISE study in Japan used a scoring system that was validated for Japanese patients to select those who were likely to be refractory to initial IVIG therapy.²⁵ These patients were randomly assigned to receive either 2 mg/kg of prednisolone for 3–5 weeks (based on normalisation of C-reactive protein concentrations) plus standard therapy or standard therapy alone. There were significantly fewer patients with coronary artery abnormalities in the group receiving prednisolone plus IVIG (3% vs 23%, risk difference 0.20, 95% CI 0.12–0.28, $p < 0.0001$). However, a caveat to the adoption of this protocol for other countries is that although this scoring system works well in Japanese patients, it has poor predictive value in mixed ethnic populations.^{3,26} Two randomised controlled trials of intensification of initial therapy with either high-dose pulse methylprednisolone or infliximab were not successful in preventing IVIG resistance.^{27,28}

The findings in the present study challenge the AHA guidelines that suggest the use of second IVIG over infliximab or steroids for treatment of IVIG resistance.⁸ Similarly, Kawasaki disease treatment guidelines from Japan also recommend a second IVIG infusion as first-line treatment for IVIG resistant patients.²⁹ The relative cost of infliximab versus second IVIG for IVIG resistance was the subject of an analysis published in 2021, which found a cost savings of US\$824759 per 100 patients treated with 10 mg/kg infliximab for IVIG resistance versus second IVIG.³⁰ The cost savings was driven by lower cost per dose, shorter infusion time, and monitoring for 24 h before discharge, which resulted in a shorter length of stay.

Although this study provides the first adequately powered comparison between two treatments for IVIG resistance, we recognise several limitations. There was no centralised interpretation of echocardiograms by a core laboratory and thus the assessment of coronary artery changes stratified by treatment must be cautious. However, body surface area and Z-worst score calculations were standardised across study sites by the Data Coordinating Center. Some sites chose to intensify therapy immediately for patients with an abnormal initial

echocardiogram (Z-worst score ≥ 2.5) or other high-risk features and thus such patients were not enrolled in this study. This strategy could have resulted in a selection bias toward inclusion of patients with lower risk of poor outcomes. The lower mean platelet count and higher number of patients ($n=7$) with a baseline Z-worst score of at least 2.5 in the second IVIG group could suggest imbalance in disease severity between the treatment groups. However, a sensitivity analysis adjusting for these variables showed similar results for the primary outcome. Although the study sought to achieve geographical and racial diversity, enrolment of patients was not uniform across the 30 sites, which resulted in a disproportionate number of patients enrolled at the San Diego site with a large proportion of Hispanic patients. Although haemolytic anaemia emerged as a serious side-effect of second IVIG infusion, the clinical evaluation of these patients was not complete across all sites, which precluded a detailed description of these events. Further, the study was not designed to determine outcomes beyond the first clinic visit so effects of therapy that might have occurred beyond this timepoint were not collected. Finally, an open-label study always has the potential for introducing unintentional bias.

Future studies should compare infliximab to methylprednisolone for treatment of IVIG resistance in patients with Kawasaki disease. Until then, infliximab is a safe, well tolerated, and effective treatment for this patient population and has significant advantages over second IVIG infusion.

Contributors

JCB designed the study, enrolled participants, interpreted the data, and wrote the manuscript. SCR collected the data and revised the manuscript. AHT enrolled participants, collected data, and revised the manuscript. KKK designed the study and revised the manuscript. SJ designed the study, did the statistical analysis, wrote the manuscript, and revised the manuscript. FH did the statistical analysis and revised the manuscript. BFP critiqued the sample echocardiograms and revised the manuscript. NA, SSJ, DEM, KS, DTT, and JBW enrolled participants, collected data, reviewed the results, and revised the manuscript. The KIDCARE Multicenter Study Group enrolled participants, collected data, and revised the manuscript. JCB, SCR, AHT, SJ, and FH verified the raw data, and authors had access to all the data in the study and participated in the decision to submit.

Declaration of interests

We declare no competing interests.

Data sharing

Individual participant data that underlie the results (text, tables, figures, and appendix) reported in this Article, after de-identification, will be shared between 9 months and ending 36 months following publication of the Article. Requests will be honoured from researchers who provide a methodologically sound proposal and who execute a Data Use Agreement with the University of California San Diego. Requests should be directed by email to the corresponding author.

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References

- 1 Newburger JW, Takahashi M, Burns JC. Kawasaki disease. *J Am Coll Cardiol* 2016; **67**: 1738–49.

- 2 Newburger JW, Takahashi M, Beiser AS, et al. A single intravenous infusion of gamma globulin as compared with four infusions in the treatment of acute Kawasaki syndrome. *N Engl J Med* 1991; **324**: 1633–39.
- 3 Tremoulet AH, Best BM, Song S, et al. Resistance to intravenous immunoglobulin in children with Kawasaki disease. *J Pediatr* 2008; **153**: 117–21.
- 4 Kibata T, Suzuki Y, Hasegawa S, et al. Coronary artery lesions and the increasing incidence of Kawasaki disease resistant to initial immunoglobulin. *Int J Cardiol* 2016; **214**: 209–15.
- 5 Newburger JW, Takahashi M, Burns JC, et al. The treatment of Kawasaki syndrome with intravenous gamma globulin. *N Engl J Med* 1986; **315**: 341–47.
- 6 Sundel RP, Burns JC, Baker A, Beiser AS, Newburger JW. Gamma globulin re-treatment in Kawasaki disease. *J Pediatr* 1993; **123**: 657–59.
- 7 Burns JC, Best BM, Mejias A, et al. Infliximab treatment of intravenous immunoglobulin-resistant Kawasaki disease. *J Pediatr* 2008; **153**: 833–38.
- 8 McCrindle BW, Rowley AH, Newburger JW, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a scientific statement for health professionals from the American Heart Association. *Circulation* 2017; **135**: e927–99.
- 9 Tsuda E, Hamaoka K, Suzuki H, et al. A survey of the 3-decade outcome for patients with giant aneurysms caused by Kawasaki disease. *Am Heart J* 2014; **167**: 249–58.
- 10 Kim KK, Khodyakov D, Marie K, et al. A novel stakeholder engagement approach for patient-centered outcomes research. *Med Care* 2018; **56** (10 suppl 1): S41–47.
- 11 Vande Castele N, Oyamada J, Shimizu C, et al. Infliximab pharmacokinetics are influenced by intravenous immunoglobulin administration in patients with Kawasaki disease. *Clin Pharmacokinet* 2018; **57**: 1593–601.
- 12 Kanegaye JT, Jones JM, Burns JC, et al. Axillary, oral and rectal routes of temperature measurement during treatment of acute Kawasaki disease. *Pediatr Infect Dis J* 2016; **35**: 50–53.
- 13 Margossian R, Lu M, Minich LL, et al. Predictors of coronary artery visualization in Kawasaki disease. *J Am Soc Echocardiogr* 2011; **24**: 53–59.
- 14 Dallaire F, Fournier A, Breton J, Nguyen TD, Spigelblatt L, Dahdah N. Marked variations in serial coronary artery diameter measures in Kawasaki disease: a new indicator of coronary involvement. *J Am Soc Echocardiogr* 2012; **25**: 859–65.
- 15 Haycock GB, Schwartz GJ, Wisotsky DH. Geometric method for measuring body surface area: a height-weight formula validated in infants, children, and adults. *J Pediatr* 1978; **93**: 62–66.
- 16 Van Anh KY, Shah S, Tremoulet AH. Hemolysis from intravenous immunoglobulin in obese patients with Kawasaki disease. *Front Pediatr* 2020; **8**: 146.
- 17 Nakagawa M, Watanabe N, Okuno M, Kondo M, Okagawa H, Taga T. Severe hemolytic anemia following high-dose intravenous immunoglobulin administration in a patient with Kawasaki disease. *Am J Hematol* 2000; **63**: 160–61.
- 18 Nolan BE, Wang Y, Pary PP, Luban NLC, Wong ECC, Ronis T. High-dose intravenous immunoglobulin is strongly associated with hemolytic anemia in patients with Kawasaki disease. *Transfusion* 2018; **58**: 2564–71.
- 19 Bruggeman CW, Nagelkerke SQ, Lau W, et al. Treatment-associated hemolysis in Kawasaki disease: association with blood-group antibody titers in IVIG products. *Blood Adv* 2020; **4**: 3416–26.
- 20 Masuda H, Kobayashi T, Hachiya A, et al. Infliximab for the treatment of refractory Kawasaki disease: a nationwide survey in Japan. *J Pediatr* 2018; **195**: 115–20.e3.
- 21 Son MB, Gauvreau K, Burns JC, et al. Infliximab for intravenous immunoglobulin resistance in Kawasaki disease: a retrospective study. *J Pediatr* 2011; **158**: 644–49.e1.
- 22 Miura M, Kobayashi T, Igarashi T, et al. Real-world safety and effectiveness of infliximab in pediatric patients with acute Kawasaki disease: a postmarketing surveillance in Japan (SAKURA study). *Pediatr Infect Dis J* 2020; **39**: 41–47.
- 23 Youn Y, Kim J, Hong YM, Sohn S. Infliximab as the first retreatment in patients with Kawasaki disease resistant to initial intravenous immunoglobulin. *Pediatr Infect Dis J* 2016; **35**: 457–59.

- 24 Mori M, Hara T, Kikuchi M, et al. Infliximab versus intravenous immunoglobulin for refractory Kawasaki disease: a phase 3, randomized, open-label, active-controlled, parallel-group, multicenter trial. *Sci Rep* 2018; **8**: 1994.
- 25 Kobayashi T, Saji T, Otani T, et al. Efficacy of immunoglobulin plus prednisolone for prevention of coronary artery abnormalities in severe Kawasaki disease (RAISE study): a randomised, open-label, blinded-endpoints trial. *Lancet* 2012; **379**: 1613–20.
- 26 Sleeper LA, Minich LL, McCrindle BM, et al. Evaluation of Kawasaki disease risk-scoring systems for intravenous immunoglobulin resistance. *J Pediatr* 2011; **158**: 831–35.e3.
- 27 Newburger JW, Sleeper LA, McCrindle BW, et al. Randomized trial of pulsed corticosteroid therapy for primary treatment of Kawasaki disease. *N Engl J Med* 2007; **356**: 663–75.
- 28 Tremoulet AH, Jain S, Jaggi P, et al. Infliximab for intensification of primary therapy for Kawasaki disease: a phase 3 randomised, double-blind, placebo-controlled trial. *Lancet* 2014; **383**: 1731–38.
- 29 Miura M AM, Fukazawa R, Hamada H, et al. Guidelines for medical treatment of acute Kawasaki disease. *J Pediatr Cardiol Card Surg* 2021; **5**: 41–73.
- 30 Johnson SC, Williams DC, Brinton D, Chew M, Simpson A, Andrews AL. A cost comparison of infliximab versus intravenous immunoglobulin for refractory Kawasaki disease treatment. *Hosp Pediatr* 2021; **11**: 88–93.