

The Kawasaki Disease Comparative Effectiveness (KIDCARE) trial: A phase III, randomized trial of second intravenous immunoglobulin versus infliximab for resistant Kawasaki disease

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**Abstract:**

**Background:** Although intravenous immunoglobulin (IVIG) is effective therapy for Kawasaki disease (KD), the most common cause of acquired heart disease in children, 10-20% of patients are IVIG-resistant and require additional therapy. This group has an increased risk of coronary artery aneurysms (CAA) and there has been no adequately powered, randomized clinical trial in a multi-ethnic population to determine the optimal therapy for IVIG-resistant patients.

**Objectives:** The primary outcome is duration of fever in IVIG-resistant patients randomized to treatment with either infliximab or a second IVIG infusion. Secondary outcomes include comparison of inflammatory markers, duration of hospitalization, and coronary artery outcome. An exploratory aim records parent-reported outcomes including signs, symptoms and treatment experience.

**Methods:** The KIDCARE trial is a 30-site randomized Phase III comparative effectiveness trial in KD patients with fever  $\geq 36$  hours after the completion of their first IVIG treatment. Eligible patients will be randomized to receive either a second dose of IVIG (2g/kg) or infliximab (10 mg/kg). Subjects with persistent or recrudescing fever at 24 hours following completion of the first study treatment will cross-over to the other treatment arm. Subjects will exit the study after their first outpatient visit (5-18 days following last study treatment). The parent-reported outcomes, collected daily during hospitalization and at home, will be compared by study arm.

**Conclusion:** This trial will contribute to the management of IVIG-resistant patients by establishing the relative efficacy of a second dose of IVIG compared to infliximab and will provide data regarding the patient/parent experience of these treatments.

**Keywords:** Kawasaki disease, infliximab, IVIG, IVIG-resistance

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## 1. Introduction and rationale (Max WC=500-with removal of the below we are at exactly 500 words):

Kawasaki disease (KD) is a self-limited vasculitis of unknown etiology that is the most common cause of acquired heart disease in children in developed countries [1]. Infusion of intravenous immunoglobulin (IVIG) reduces the incidence of coronary artery aneurysms (CAA) from 25% to approximately 5% [2]. However, for the 10-20% of IVIG-resistant patients (defined as having an oral or rectal temperature ( $T$ )  $\geq 38.0^{\circ}\text{C}$  at least 36h following the end of the initial IVIG infusion), there is no evidence-base to guide treatment and this group has an increased risk of coronary artery aneurysms. In a study of 362 consecutive KD patients, 9 of 60 IVIG-resistant patients (15%) versus 9 of 302 (3%) IVIG-responsive patients developed CAA[3]. Recent data from Japan suggests that the rates of IVIG-resistance have risen from 7% in 2003 to 23% in 2014 with a concomitant increase in CAA[4].

### 1.1 Rationale

There is clinical equipoise regarding the best treatment for IVIG-resistant patients and either a second infusion of IVIG or infliximab is the most common second treatment[5-8]. Some centers also treat with steroids (Yang, Liu et al. 2015). The American Heart Association (AHA) KD guidelines assign an Evidence level of C (Consensus opinion of experts) to re-treatment with either second IVIG or infliximab [9]. However, the stakes are high for this subgroup of patients as CAA due to persistent inflammation may lead to permanent damage to the arterial wall with an associated risk of myocardial infarction, arrhythmias, or sudden cardiac death [10, 11].

### 1.2 Study Aims:

Our first aim will test the hypothesis that infliximab will be superior to a second IVIG infusion for treatment of IVIG resistant patients. The resolution of fever ( $T < 38^{\circ}\text{C}$  rectally or orally or  $37.5^{\circ}\text{C}$  axillary) at 24h after initiation of study treatment with no recurrence of fever attributed to KD in the first 7 days after discharge will be the primary outcome measure. Aim 2 will test the hypothesis that infliximab will be associated with fewer therapy-related adverse events as adjudicated by the Adverse Event Committee. Aim 3 will test the hypothesis that infliximab treatment will result in more rapid resolution of inflammation compared to second IVIG as measured by the change in white blood cell count (WBC), absolute neutrophil count (ANC), and C-reactive protein (CRP) concentration between baseline, 24 hours and 5- 18 days following study treatment. Aim 4 will test the hypothesis that infliximab treatment will result in a reduction from baseline in right and left anterior descending coronary artery Z score of  $\geq 0.5$  standard deviation units as compared to second IVIG at 5- 18 days following study treatment as measured by echocardiography. An exploratory aim will evaluate patient reported outcomes (PROs) and use of a parent observation tool to record discomfort, psychosocial concerns, and other experiences of treatment during the child's in-hospital stay and outpatient evaluation.

## 2. Methods

### 2.1 Study Design

This is a 3-year, 30 site, Phase III, two-arm, randomized, multi-center study to compare infliximab to a second IVIG infusion for treatment of persistent or recrudescing fever in children with KD who fail to become afebrile after the first IVIG infusion. Once eligibility and consent

are confirmed, subjects will be assigned to a treatment arm according to a pre-specified randomization scheme stratified by center and then sex (male/female) and age (dichotomous variable  $>12$  months or  $\leq 12$  months) via a randomly permuted block design. It would not be possible to blind the treatment as the infusion times and nursing protocols are very different for the two treatments. Infliximab is given over two hours and IVIG is given over 8-12 hours with specific nursing monitoring for infusion reactions and incremental increases in the infusion rate.

For this trial, the dose of infliximab will be 10 mg/kg IV. A Phase III clinical trial of adjunctive primary therapy with infliximab at 5 mg/kg demonstrated that infliximab was safe and well-tolerated even in infants less than 6 months of age [12]. Further study of KD patients enrolled in this trial demonstrated that pre-treatment soluble TNF $\alpha$  receptor 1 (sTNFR1) levels are elevated in acute KD and are higher in KD patients with CAA compared to those with normal CA[13]. At 24 hours following infusion of infliximab 5 mg/kg, KD patients with CAA had lower levels of free (unbound) infliximab compared to those with normal CA. These data suggest that 5 mg/kg of infliximab may be insufficient for many KD patients and thus a single dose of 10 mg/kg of infliximab is warranted for this study[13]. Infliximab at a dose of 10 mg/kg has been used at RCHSD for the treatment of 88 acute KD patients with either CAA or IVIG-resistance with no adverse events related to this therapy.

Study subjects who fail to become afebrile 24 hours after the end of their study-assigned treatment will be deemed “treatment failures” and will cross-over to treatment with the other study medication. Thus, a subject randomized to receive 2nd IVIG would cross-over to receive infliximab if fever continues at 24 hours after the start of the 2nd IVIG infusion (**Figure 1**).

### *2.2 Inclusion and exclusion criteria*

Infants and children at least 4 weeks of age and with fever between 36 hours to seven days after completion of their initial IVIG treatment who meet the American Heart Association criteria for complete or incomplete KD are eligible for this study (**Table 1**). Exclusion criteria include initial treatment with IVIG after the 10<sup>th</sup> day of fever and treatment with steroids or other medication for intensification of initial therapy.

### *2.3 Study Measures*

The primary outcome measure is fever 24 hours after the initiation of the study treatment. All temperature measurements will be taken orally, rectally or axillary. To accommodate variations in hospital and nursing practices across the 30 sites, axillary temperature measurements will be allowed, but not encouraged.

Additional secondary outcomes include comparison between treatment arms of treatment-related adverse events, white blood cell count (WBC), absolute neutrophil count (ANC), hemoglobin (Hgb) concentration, platelet count, and C-reactive protein (CRP, mg/dl) concentration between baseline (pre-IVIG at diagnosis), 24 hours ( $\pm 2$  hours) post-end of study treatment and 5-18 days following completion of study treatment. Body temperature is assessed at 24 hours after completion of the first and cross-over (if applicable) study treatment. Parents assess daily temperatures at home with thermometers provided at the time of discharge from the hospital.

We will also compare Z scores (defined as the largest internal diameter of either the right coronary or left anterior descending arteries normalized for body surface area and expressed as standard deviation units from the mean) between pre-IVIG at diagnosis and 5-18 days following completion of study treatment. Sites were provided with a manual of operations from the NIH-sponsored Pediatric Heart Network. In an effort to standardize echocardiographic imaging across sites, a single echocardiogram on a KD patient was submitted by every site and the technical quality assessed by Dr. Beth Printz, Director of Non-Invasive Imaging at Rady Children's Hospital San Diego. A written assessment of the echocardiogram quality with suggestions for improvement as needed was sent to every site.

A Data Safety Monitoring Board (DSMB) will review adverse events and serious adverse events (SAEs) by study arm every six months in a closed session attended only by DSMB members and the study statistician. Attribution of relatedness of SAEs to study drugs will be adjudicated by an Adverse Events Committee.

Our exploratory aim will assess whether patient/parent-reported outcomes (PROs) including signs, symptoms, and treatment experience differ between study arms. PROs are collected via a paper or online observation tool for parents to track 17 signs and common symptoms such as irritability, redness in eyes, rash, difficulty with eating and sleeping. Prevalence of each symptom is captured as a yes/no and change as better/same/worse than the previous period[14]. There is also one open-ended treatment experience question. PROs will be collected every eight hours during a two-day hospitalization, and daily for up to 18 days after discharge. Parents will be offered a choice of two formats, paper or online with emailed link. In developing the PRO tool, we consulted with clinicians and conducted in-depth, semi-structured interviews of six parents who had a child treated for KD to confirm outcomes of relevance to patients/parents..

#### *2.4 Ethics and Informed Consent*

The study protocol was reviewed and approved by the institutional review board at all participating sites. Of the 30 institutions that are participating in this research, 18 agreed to rely on UCSD as the IRB of record and signed a reliance agreement. Five sites used the Streamlined, Multisite, Accelerated Resources for Trials (SMART) IRB Reliance to facilitate the reliance agreement. Written informed consent from the parents or legal guardians and assent forms from the patient as appropriate will be obtained.

### **3. Statistical Analysis Plan**

This is a superiority clinical trial, in which an intention-to-treat population will be used. Results will be reported as point estimates (odds ratios or mean differences across groups, as appropriate) and interval estimates (95% confidence intervals). All tests of significance for the secondary outcomes will be 2-sided and Holm's adjustments will be made for multiple comparisons. A p-value  $\leq 0.05$  will be considered statistically significant. Statistical analysis will be conducted using the statistical software R 3.3.4. ([www.rproject.org](http://www.rproject.org)). Demographic and baseline characteristics will be compared between the treatment arms using Fisher's exact test for categorical variables, and a two-sample t-test for continuous variables. Appropriate non-parametric alternatives will be considered, if parametric assumptions fail. There will be no

planned interim analyses for efficacy or futility conducted for this study, but the Data and Safety Monitoring Board (DSMB) may modify this during ongoing safety monitoring.

### *3.1 Power and Sample Size*

The study is sufficiently powered for a superiority clinical trial. For the primary endpoint, if we assume 125 evaluable subjects per group (total N=250) in this 2-arm trial, we will have 81% power to detect a difference between the group proportions of 0.155. We assume that the reference group proportion (i.e. 2nd IVIG arm is 67%) will be similar to our published clinical trial [7]. The infliximab arm proportion is assumed to be 92% (based on published clinical trial, i.e. 11 of 12 patients responding). To be conservative, the power was computed for the case in which the actual infliximab arm proportion is lower at 82.5%. Statistical power is based on a two-sided, two sample binomial test for proportions, and a two-sided  $\alpha=0.05$  was used. Subjects will be in the study for two weeks (5-18 day window) following administration of study drug and there is a possibility that subjects could be lost to follow-up. Assuming 5% attrition, we will need to enroll 263 subjects to get 250 evaluable patients.

### *3.2 Analysis of Primary Outcome*

The primary outcome of the study is cessation of fever ( $<38^{\circ}\text{C}$  rectally or orally;  $<37.5^{\circ}\text{C}$  axillary) within 24h of initiation of study drug infusion, which is a dichotomous (binary) variable. Comparison between the infliximab and second IVIG arms will be compared using a Fisher's exact test for proportions. Differences in the rates between the two groups, along with the odds ratio (OR) and their 95% confidence intervals will be reported. As a secondary/sensitivity analysis, multivariable logistic regression analysis will be performed to study the association between clinical and demographic factors (age  $< 1$  yr., sex, ESR, WBC, Hgb, ANC, CRP) and treatment arm, adjusting for baseline demographic, stratification variables, and clinical characteristics. Variables significantly associated with outcome ( $p<0.10$ ) will be included in a multivariable logistic regression model as covariates. To avoid inflation of the Type I error, we will use permutation tests for inference.

### *3.3 Analysis of Secondary Outcomes*

Adverse events will be compared using a Fisher's exact test for proportions. Differences in the rates between the two groups, along with the odds ratio (OR) and their 95% confidence intervals will be reported.

Additional secondary outcomes will test the hypothesis that infliximab treatment will result in more rapid resolution of inflammation compared to second IVIG as measured by WBC, ANC, and levels of CRP at 24 hours and 5-18 days following study treatment. Comparisons between the infliximab and second IVIG arms will be compared using a two-sample, two-sided t-test at each time point separately. Point estimates and their 95% confidence intervals will be reported. As a secondary/sensitivity analysis, multiple linear regression at each time point will be performed to study the association between clinical and demographic factors (age  $< 1$  yr., sex, ESR, WBC, and ANC) and intervention arm, adjusting for baseline demographic, stratification

variables, and clinical characteristics, including baseline CRP. Variables significantly associated with both treatment group and outcome ( $p < 0.10$ ) will be included in a multiple regression model as covariates. Appropriate non-parametric alternatives will be considered, if parametric assumptions fail. A mixed model repeated measures (MMRM) model with three repeated measures (baseline, 24 hours, and at 5-18 days after the completion of the study treatment) will evaluate changes between the study arms for the major dependent variables, i.e. WBC, ANC, and CRP. Participants will only be included in the MMRM model if they have both a baseline and at least one post-baseline measurement. The model will include as the dependent variable the change from baseline in the inflammation variable at each post-baseline visit for each dependent inflammation marker separately. Independent variables in the MMRM model will include treatment arm, visit, treatment arm-by-visit interaction, the inflammation variable at baseline and other covariates. Visits will be treated as a categorical variable. Unstructured variance-covariance structure will be used.

We will also test the hypothesis that infliximab treatment will result in a change in coronary artery Zworst score of  $\geq 0.05$  standard deviation units measured by echocardiography as compared to second IVIG at 5-18 days following the completion of study treatment. There is a concern about inter-rater reliability of different readers for the echocardiograms at the 30 sites. To minimize variability, the Coordinating Center has developed manuals used in previous clinical trials to help standardize performance of echocardiograms and the measurement of the coronary arteries. During the run in period, a de-identified echocardiogram on a KD patient will be submitted to the coordinating center at UCSD and the quality will be assessed and feedback given to the center PI.

### 3.4 Analysis of Exploratory Aim

Descriptive analysis of the PRO questionnaire responses will include a) symptom prevalence described as frequencies and percentages for each; b) symptom load calculated as the number of signs and symptoms experienced; and c) symptom resolution determined by length of time each was present after treatment initiation and change in perception (better/worse/same) over time. These measures will be summarized descriptively (point estimates and confidence intervals). The amount of missing data will also be evaluated and compared between study arms. Comparisons by study arm will be evaluated by a two-sample t-test if parametric assumptions hold. If the assumptions are violated, we will compare treatment arms by the Wilcoxon rank sum test. No adjustments for multiple comparisons will be made, since the questions have been determined *a priori* as the questions of interest that will determine parental preference to the treatment arms. We will also explore the feasibility of ascertaining patterns in the trajectory of symptoms based on prevalence, load, or resolution by applying multivariate trajectory analysis [15, 16]. For example, we will evaluate whether there are trends in the prevalence of symptoms differ over time (e.g., decreases then increases, consistently decreases, resolves faster or slower) among subgroups. Open-ended questions will be analyzed for thematic content regarding treatment experience based on inductively coded verbatim questionnaire responses [17, 18].



## Discussion

The problem of IVIG-resistance was first noted in the original IVIG trials in the 1980s and the appropriate therapy for these patients has remained unresolved to the present day. Based on the apparent dose response to IVIG, administration of a second dose of IVIG to resistant patients became first-line therapy for these patients and is still widely used today [5]. However, retreatment with a second infusion of IVIG has never been subjected to a rigorous clinical trial. Given the high cost of IVIG and the recent emergence of hemolytic anemia following a second dose (2g/kg) due to anti-blood type A antibodies in the IVIG preparations, it is time to compare this therapy to alternative strategies for patients with IVIG-resistance [19-23].

Alternative treatments include infliximab (5-10 mg/kg), steroids (prednisone 2 mg/kg/day for extended period), cyclosporine, anakinra, and plasmapheresis [7, 8, 24-30]. In a two-center, retrospective study 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 in hospital, and lower costs of care [8]. There was no difference in coronary artery outcomes between groups although the study lacked sufficient power to see an effect.

A different strategy pursued by several investigators has been to select agents that could be added to the initial IVIG regimen to prevent recrudescence of fever. The RAISE study in Japan used a scoring system that works well in Japanese patients to select those who were likely to be refractory to initial therapy [31]. These patients were then randomized to receive either 2 mg/kg of prednisolone for 3-5 weeks (based on normalization of C-reactive protein levels) or placebo in addition to standard therapy. There were significantly fewer patients with coronary artery abnormalities in the group receiving prednisolone plus IVIG (3% vs. 23%, CI 0.12-0.28,  $p < 0.001$ ). A caveat to the adoption of this protocol for other countries is that the scoring system has poor predictive value in mixed ethnic populations [3, 32]. Two randomized, controlled trials of intensification of initial therapy with either high-dose pulse methylprednisolone or infliximab were not successful in preventing IVIG resistance [12, 33]. In the infliximab trial, 13% of KD patients treated with either infliximab (5 mg/kg) or placebo followed by standard 2 gm/kg IVIG plus aspirin within the first 10 days after fever onset were IVIG-resistant [12]. The group receiving infliximab did have more rapid resolution of inflammatory markers, fewer fever days, and more rapid improvement in Z score of the left anterior descending coronary artery. In summary, after decades of descriptive biology and underpowered clinical trials, there is still clinical equipoise regarding the best second treatment for IVIG-resistant patients with second infusion of IVIG and infliximab as the two leading candidates.

Rates of IVIG resistance and thus patients with aneurysms are rising. Currently, the American Heart Association (AHA) KD guidelines assign an Evidence level of C (Consensus opinion of experts) to each of the potential re-treatments listed above [34]. The stakes are high for this subgroup of patients as CAA due to persistent inflammation are a permanent disability leading to significant morbidity and increased mortality later in life [11, 35]. Complications include ischemia, myocardial infarction, congestive heart failure, and sudden death [36]. In a study of patients younger than 40 years of age undergoing cardiac catheterization for suspected ischemia,

5% of patients had coronary artery lesions consistent with KD [37]. System dynamic models suggest that by 2030, one in every 1600 adults in the U.S. will have suffered from KD [38]. Thus, it is incumbent upon the pediatric community to provide the best possible prophylaxis against the development of CAA and that is the motivation for this trial.

**Table 1. Inclusion and exclusion criteria**

**Inclusion Criteria:**

1. 4 weeks to 17 years of age,
2. Fulfill the American Heart Association case definition of KD by one of the following[39]:
  - a. Four of the five clinical KD criteria
  - b. At least 2 clinical criteria with LAD/RCA z-score  $\geq 2.5$ .
  - c. At least 2 clinical criteria with CRP  $\geq 3$  mg/dL or ESR  $\geq 40$  mm/hr and at least 3 supplemental laboratory criteria
3. Patient had fever by parental history for 3 to 10 days prior to initial IVIG treatment, and
4. Have fever (T  $\geq 38^{\circ}\text{C}$  orally or rectally or  $\geq 37.5^{\circ}\text{C}$  axillary/ T  $\geq 100.4^{\circ}\text{F}$  orally or rectally or  $\geq 99.5^{\circ}\text{F}$  axillary) between 36 hours and 7 days after end of the first IVIG infusion without other likely cause
5. Parent or legal guardian able and willing to provide informed consent

**Exclusion Criteria:**

1. Patient treated with infliximab or steroids for present illness (e.g. RAISE protocol) (NB. pts who received oral steroids as outpatients prior to KD diagnosis (e.g. for suspected allergic reaction) but who otherwise qualify for the study will not be excluded)
2. Patient has known prior infection with tuberculosis, coccidioidomycosis, or histoplasmosis.
3. Patient has household member with active TB.
4. Use of a TNF $\alpha$  blocker within the 3 months prior to enrollment
5. Patients has any chronic disease, except asthma, atopic dermatitis, autism or controlled seizure disorder
6. Patient has a history of hypersensitivity to infliximab

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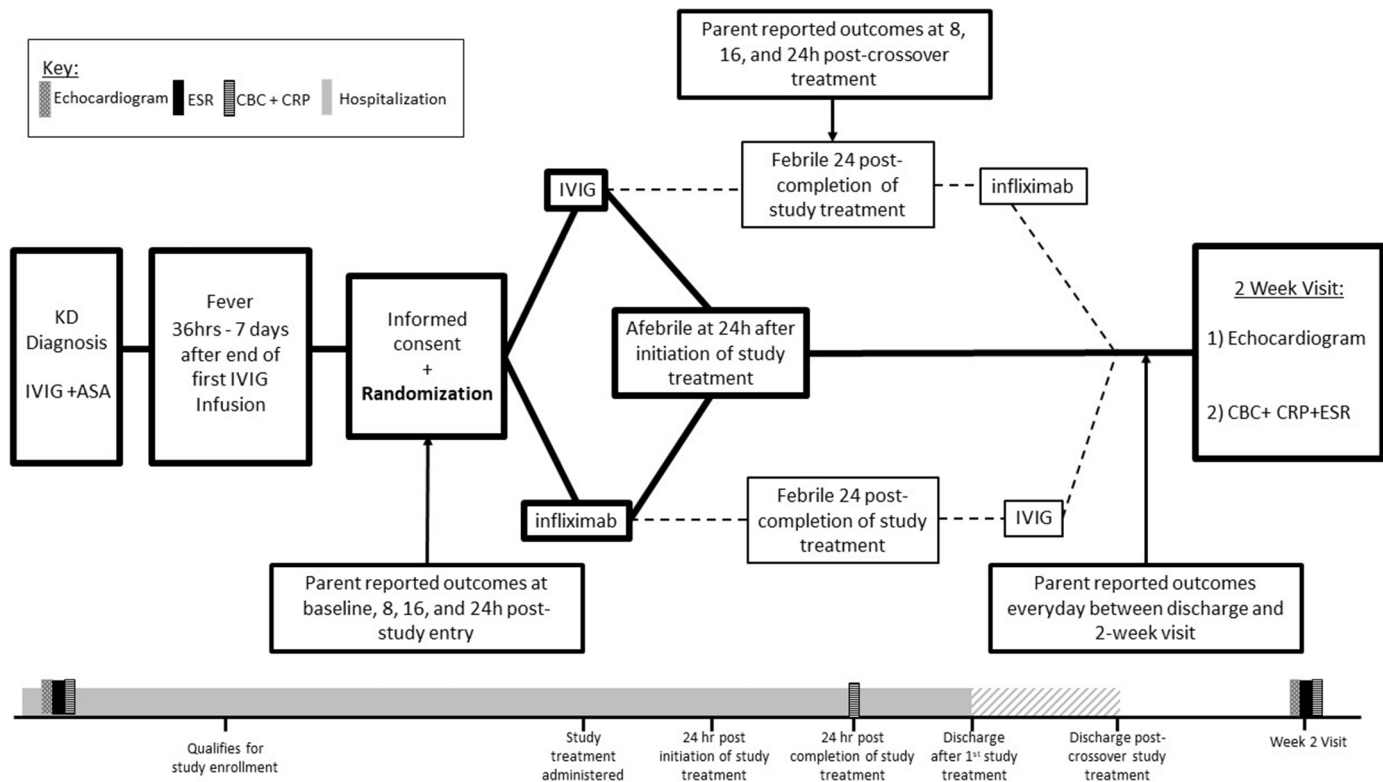


Figure 1