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

Samantha C. Roberts[a,*], Sonia Jain[b], Adriana H. Tremoulet[b,c], Katherine K. Kim[c], Jane C. Burns[a,b], KIDCARE Multicenter Study Group, Vikram Anand[d], Marsha Anderson[e], Jocelyn Ang[f], Emily Ansusinha[g], Moshe Arditi[h], Negar Ashouri[i], Allison Bartlett[j], Archana Chatterjee[k], Roberta DeBiasi[l], Cornelia Dekker[m], Chandani DeZure[n], Lisa Didion[o], Samuel Dominguez[p], Rana El Feghaly[q], Guliz Erdem[r], Natasha Halasa[s], Ashraf Harahsheh[t], Mary Anne Jackson[u], Preeti Jaggi[v], Supriya Jain[w], Pei-Ni Jone[x], Neeru Kaushik[y], Gregory Kurio[z], Anna Lillian[aa], David Lloyd[ab], John Manaloor[ac], Amy McNelis[ad], David E. Michalik[ae], Jane Newburger[af], Charles Newcomer[ag], Tiffany Perkins[ah], Michael Portman[ai], Jose Romero[aj], Tova Ronis[ak], Anne Rowley[al], Kathryn Schneider[am], Jennifer Schuster[an], S. Kristen Sexson Tejtel[ao], Kavita Sharma[ap], Kari Simonsen[aq], Jacqueline Szmuszkovicz[ar], Dongngan Truong[as], James Wood[at], Sylvia Yeh[au]

[a] Rady Children's Hospital, 7910 Frost St Suite 300, San Diego, CA, 92123, United States
[b] University of California San Diego, 9500 Gilman Dr., La Jolla, CA, 92093, United States
[c] University of California Davis, Betty Irene Moore School of Nursing, 2450 48th Street, Sacramento, CA 95817, United States
[d] Cedars-Sinai Medical Center, 8700 Beverly Blvd, West Hollywood, CA, 90048, United States
[e] Children's Hospital Colorado, 13123 East 16th Avenue, B100, Aurora, CO, 80045, United States
[f] Children's Hospital of Michigan, Wayne State University School of Medicine, 540 E Canfield St, Detroit, MI, 48201, United States
[g] Children's National Health System, 111 Michigan Ave NW, Washington, DC, 20010, United States of America
[h] Cedars-Sinai Medical Center, 8700 Beverly Blvd, West Hollywood, CA, 90048, United States of America
[i] Children's Hospital of Orange County, 1201 W. La Veta Avenue, Orange, CA, 92868, United States
[j] The University of Chicago, Department of Pediatrics, 5841 South Maryland Avenue, MC6054, Chicago, IL, 60637, United States
[k] University of South Dakota, Sanford School of Medicine, 1400 W 22nd St, Sioux Falls, SD, 57105, United States
[l] Children's National Health System, 111 Michigan Ave NW, Washington, DC, 20010, United States
[m] Stanford School of Medicine, 300 Pasteur Drive, Room H313, Stanford, CA, 94305-5208, United States
[n] Children's National Health System, 111 Michigan Ave NW, Washington, DC, 20010, United States
[o] Batson Children's Hospital, 2500 North State Street, Jackson, MS, 39216, United States
[p] Children's Hospital Colorado, 13123 East 16th Avenue, B100, Aurora, CO, 80045, United States
[q] Children's Mercy, 2401 Gillham Road, Kansas City, MO, 64108, United States
[r] Nationwide Children's Hospital, 700 Children's Drive Suite T6B, Columbus, OH 43205, United States
[s] Vanderbilt School of Medicine, 1161 21st Ave South, Nashville, TN, 37232, United States
[t] Children's National Health System, 111 Michigan Ave NW, Washington, DC, 20010, United States
[u] Children's Mercy, 2401 Gillham Road, Kansas City, MO, 64108, United States
[v] Emory University School of Medicine, 1405 Clifton Rd. NE, Atlanta, GA 30322, United States
[w] Maria Fareri Children's Hospital at Westchester Medical Center and New York Medical College (NYMC), 100 Woods Road, Valhalla, NY, 10595, United States
[x] Children's Hospital Colorado, 13123 East 16th Avenue, B100, Aurora, CO, 80045, United States
[y] UCSF Benioff Children's Hospital-Oakland, 747 52nd street, Oakland, CA, 94609, United States
[z] UCSF Benioff Children's Hospital-Oakland, 747 52nd street, Oakland, CA, 94609, United States
[aa] Intuit, San Diego, CA, United States
[ab] Emory University School of Medicine, 1405 Clifton Rd. NE, Atlanta, GA 30322, United States
[ac] Indiana University School of Medicine, 705 Riley Hospital Dr, RI 3032, Indianapolis, IN, 46202, United States
[ad] UCSF Benioff Children's Hospital-San Francisco, 1691Mar West St, Tiburon, CA 94920, United States
[ae] Miller Children's Hospital, Long Beach, 2801 Atlantic Avenue, Long Beach, CA, 90806, United States
[af] Children's Hospital Boston, 300 Longwood Ave., Boston, MA, 02115, United States
[ag] David Geffen School of Medicine at UCLA, 10833 Le Conte Avenue, A2-383 MDCC, Los Angeles, CA, 90095, United States

* Corresponding author at: Rady Children's Hospital San Diego, 7910 Frost St Suite 300, San Diego, CA, 92123, United States.
E-mail addresses: sroberts@ucsd.edu (S.C. Roberts), sojain@ucsd.edu (S. Jain), atremoulet@ucsd.edu (A.H. Tremoulet), kathykim@ucdavis.edu (K.K. Kim), jcburns@ucsd.edu (J.C. Burns).

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[ah] Children's National Health System, 111 Michigan Ave NW, Washington, DC, 20010, United States
[ai] Seattle Children's, 4800 Sand Point Way NE, Seattle, WA, 98105, United States
[aj] Arkansas Children's Hospital, 1 Children's Way, Little Rock, AR, 72202-3591, United States
[ak] Children's National Health System, 111 Michigan Ave NW, Washington, DC, 20010, United States
[al] The Ann & Robert H. Lurie Children's Hospital of Chicago, 310 E Superior Street, Morton 4-685B, Chicago, IL, 60611, United States
[am] Batson Children's Hospital, 2500 North State Street, Jackson, MS, 39216, United States
[an] Children's Mercy, 2401 Gillham Road, Kansas City, MO, 64108, United States
[ao] Texas Children's Hospital, 6621 Fannin St., MC-19345-C, Houston, TX, 77030, United States of America
[ap] Children's Health, University of Texas Southwestern Medical Center, 1935 Medical District Drive, Dallas, TX 75235, United States
[aq] University of Nebraska Medical Center, 982162 Nebraska Medical Center, Omaha, NE 68198-2162, United States
[ar] Children's Hospital Los Angeles, Division of Cardiology, 4650 Sunset Blvd., Los Angeles, CA, 90027, United States
[as] University of Utah Health Care, 81 N. Mario Capecchi Drive, Salt Lake City, UT, 84113, United States
[at] Indiana University School of Medicine, 705 Riley Hospital Dr, RI 3032, Indianapolis, IN, 46202, United States
[au] Harbor-UCLA Medical Center, 1124 W. Carson St., Torrance, CA, 90509, United States

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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 ≥36 h after the completion of their first IVIG treatment. Eligible patients will be randomized to receive either a second dose of IVIG (2 g/kg) or infliximab (10 mg/kg). Subjects with persistent or recrudescent fever at 24 h 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.

1. Introduction and rationale

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) ≥ 38.0 °C at least 36 h 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 [30]. 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 ($T < 38$ °C rectally or orally or 37.5 °C axillary) at 24 h 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 h 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 ≥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, multicenter study to compare infliximab to a second IVIG infusion for treatment of persistent or recrudescent 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 ≤ 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 2 h and IVIG is given over 8–12 h 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 < 6 months of age [12]. Further study of KD patients enrolled in this trial demonstrated that pre-treatment soluble TNFα 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 h 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 h 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 h after the start of the 2nd IVIG infusion (Fig. 1).

2.2. Inclusion and exclusion criteria

Infants and children at least 4 weeks of age and with fever between 36 h 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 10th day of fever and treatment with steroids or other medication for intensification of initial therapy.

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 ≥ 2.5.
c. At least 2 clinical criteria with CRP ≥ 3 mg/dL or ESR ≥ 40 mm/h 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 ($T \geq 38$ °C orally or rectally or ≥ 37.5 °C axillary/ $T \geq 100.4$ °F orally or rectally or ≥ 99.5 °F axillary) between 36 h 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 TNFα 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

2.3. Study measures

The primary outcome measure is fever 24 h after the initiation of the study treatment. All temperature measurements will be taken orally,

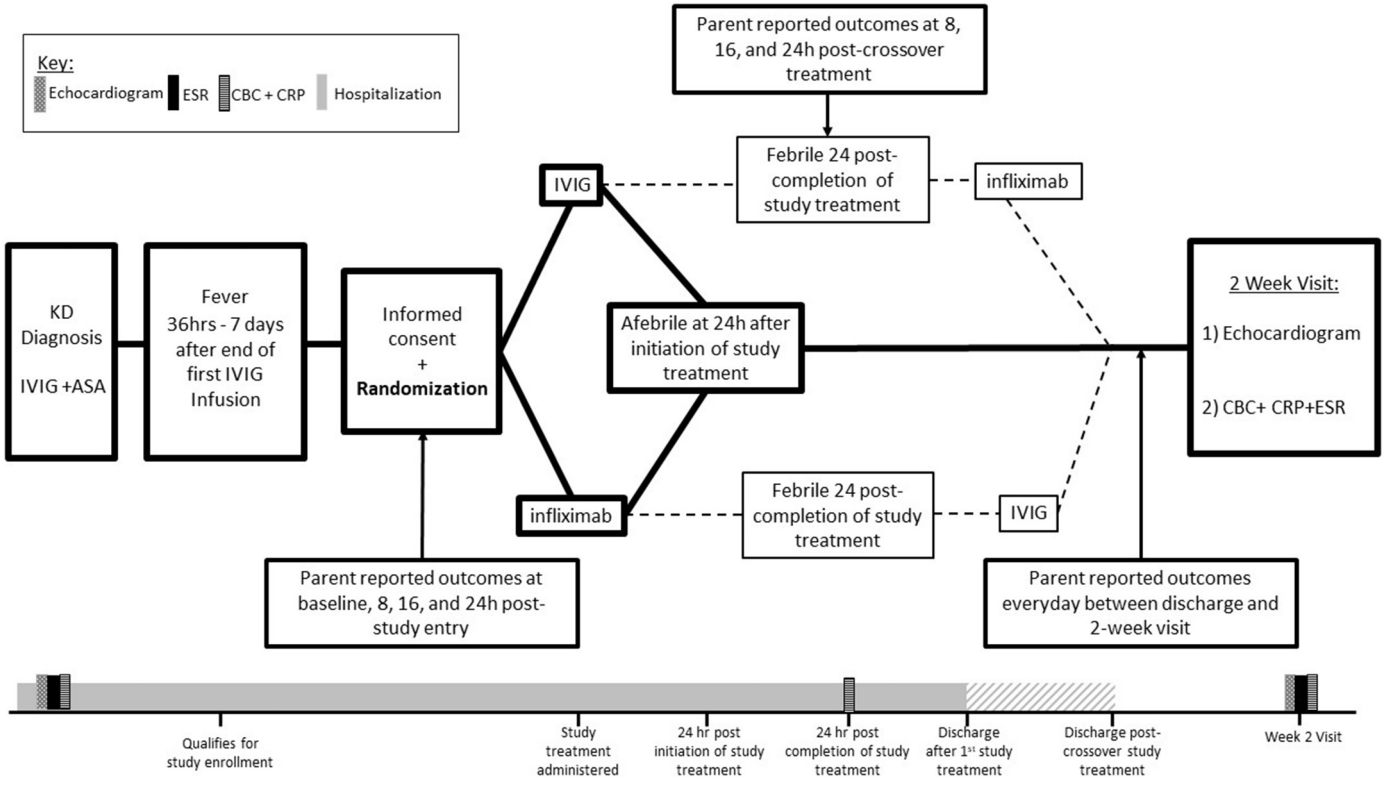

Fig. 1. KIDCARE study design.

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 h (± 2 h) post-end of study treatment and 5–18 days following completion of study treatment. Body temperature is assessed at 24 h 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 echocardogram 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 8 h 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 ≤ 0.05 will be considered statistically significant. Statistical analysis will be conducted using the statistical software R 3.3.4. (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 ($< 38\,^{\circ}C$ rectally or orally; $< 37.5\,^{\circ}C$ axillary) within 24 h 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 h 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 ($p < .10$) 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 h, 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 ≥ 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].

4. 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 (2 g/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 recrudescent 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 g/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.

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