Multisystem Inflammatory Syndrome Therapies in Children (MISTIC) Trial

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A. Study Aims

Primary Aim: To determine the anti-inflammatory treatment from first randomization that has the lowest rate of second randomization.
Primary Outcome: The difference in need for second randomization between the best and second-best treatment.

Secondary Aim 1: To determine the anti-inflammatory treatment regimen from first and second randomizations that has the lowest rate of needing additional anti-inflammatory treatment.

Secondary Aim 2: To determine the anti-inflammatory treatment regimen that results in the highest rate of sustained cessation of fever 12 hours following first or second randomization (measured from start of first dose of study drug administration)

Secondary Aim 3: To determine the anti-inflammatory treatment regimen with the shortest number of days with inotropic support.

Secondary Aim 4: To determine the anti-inflammatory treatment regimen that results in the most rapid reduction by 50% of the worst CRP after diagnosis.

Secondary Aim 5: To determine the anti-inflammatory treatment regimen that results in the most rapid return to a sustained left ventricular ejection fraction of at least 55% off of inotropic support from the start of the IVIG infusion.

Secondary Aim 6: To determine the anti-inflammatory treatment regimen that results in the fewest serious adverse events attributed to study drug.

B. Background

B.1. Background on MIS-C

Early on in the COVID-19 pandemic, it was striking how few children were suffering from serious illness with SARS-CoV-2 infections. However, in March 2020, children exposed to SARS-CoV-2 a month earlier presented with fever and significant inflammation, often requiring treatment in the intensive care unit. This new illness, which affected myocardial function and led to heart failure and shock in some children, was named Multisystem Inflammatory Syndrome-Children (MIS-C).[1] The clinical presentation shared many features with Kawasaki disease (KD), a self-limited vasculitis that can cause coronary artery aneurysms.[2] Children with MIS-C presented with fever and some had rash, conjunctival injection, erythema of the lips, and even coronary artery aneurysms, all signs associated with KD. For this reason, when the first patients presented to intensive care units in Italy, England and then the East Coast of the United States, physicians reached for many of the therapeutics used to treat KD shock syndrome, a rare manifestation of KD. While some patients have improved with intravenous immunoglobulin (IVIG) alone, many with multisystem involvement have also required treatment with steroids, anakinra (IL-1 blockade) and/or infliximab (TNFα blockade). While most patients responded to some combination of these therapies, some children developed persistent coronary artery abnormalities or cardiac dysfunction and a few have died. Without clinical trial data to guide choice of therapy, it is imperative that a comparative effectiveness trial be urgently

undertaken, especially given the concern that there will be a resurgence of COVID-19 illness in the coming months accompanied after a short delay by a resurgence of MIS-C cases. **Thus, we have designed a comparative effectiveness trial to determine which combination of therapies (IVIG with steroids, infliximab and/or anakinra) is most effective in reducing morbidity and mortality in children with MIS-C.**

B.2. Rationale for the use of steroids, infliximab and anakinra in MIS-C

Given the Kawasaki disease-like presentation of MIS-C, physicians around the globe have treated the majority of these patients with IVIG, the standard of care for KD patients. Some patients have also appeared to improve with low dose steroids, infliximab or anakinra. There are several lines of evidence that support the use of these therapies. IVIG boosts the host's anti-inflammatory response by stimulating tolerogenic myeloid dendritic cells which in turn inhibit the differentiation of naıve T cells to a pro-inflammatory phenotype.[3] Low-dose steroids have been demonstrated to significantly reduce the incidence of coronary artery abnormalities in KD patients treated with IVIG and low-dose steroids as compared to IVIG alone.[4] Given that tumor necrosis factor alpha (TNFa) is increased in acute KD and highest in children with coronary artery aneurysms, infliximab, a monoclonal antibody that attaches to and reduces circulating TNFa, has been used to treat KD.[5, 6] I led a team of investigators in a Phase III, randomized, blinded trial of infliximab in IVIG-resistant KD.[7] That trial further demonstrated the safety and tolerability of infliximab. In addition, children in the infliximab group had greater mean reduction in C-reactive protein levels and a faster decrease in the internal diameter of the left anterior descending coronary artery. Further work by our group demonstrated that children with KD and coronary artery aneurysms need high doses of infliximab given the substantially elevated plasma levels of soluble TNFa receptor.[8] This work supports the rationale for a dose of 10 mg/kg of infliximab, currently used in the PCORI-funded Kawasaki Disease Comparative Effectiveness (KIDCARE) study. Another cytokine that has data supporting its relevance in the inflammatory cascade of KD is interleukin-1 (IL1). The IL-1 related genes are upregulated in KD peripheral blood during the acute phase of the illness.[9] This is further supported by the fact that anakinra blocks the arterial inflammation in the mouse model of KD.[10] Thus, I designed and currently lead a Phase I/IIa study of anakinra in children with KD and coronary artery aneurysms.[11] In the 22 children enrolled, there have been no serious adverse events in children treated with anakinra up to 11 mg/kg/day for up to a 6-week period. Adults with the COVID-19-associated hyperinflammatory response treated with anakinra at 10 mg/kg/day IV had a faster clinical improvement than those either not receiving anakinra or receiving a lower dose of 5 mg/kg subcutaneously.[12]

Significance

The results of this comparative effectiveness trial will be immediately actionable to guide management of children around the globe who suffer from MIS-C. The results could help governments and agencies (including WHO and CDC) understand which medications need to be available in sufficient quantity to respond to a surge of MIS-C patients.

C. Study design

C.1. Overview

This study is a multi-site, randomized, pragmatic, comparative effectiveness trial of children with MIS-C. We will apply the patient-centered, "small N Sequential Multiple Assignment Randomized Trial" (snSMART) designed for rare disease trials as it efficiently evaluates multiple treatments within an individual.[13-15] The current standard of care is that all MIS-C patients are initially treated with IVIG and

receive additional therapy if they are severely ill or do not improve clinically. This study design will randomize subjects who have received IVIG but clinically warrant further anti-inflammatory therapy to one of three treatment arms and allow for re-randomization to one of the two remaining arms if clinically warranted (Figure 1; See Human Subjects: Criteria for Additional Anti-inflammatory Therapy due to Non-Response to IVIG or Severe MIS-C).

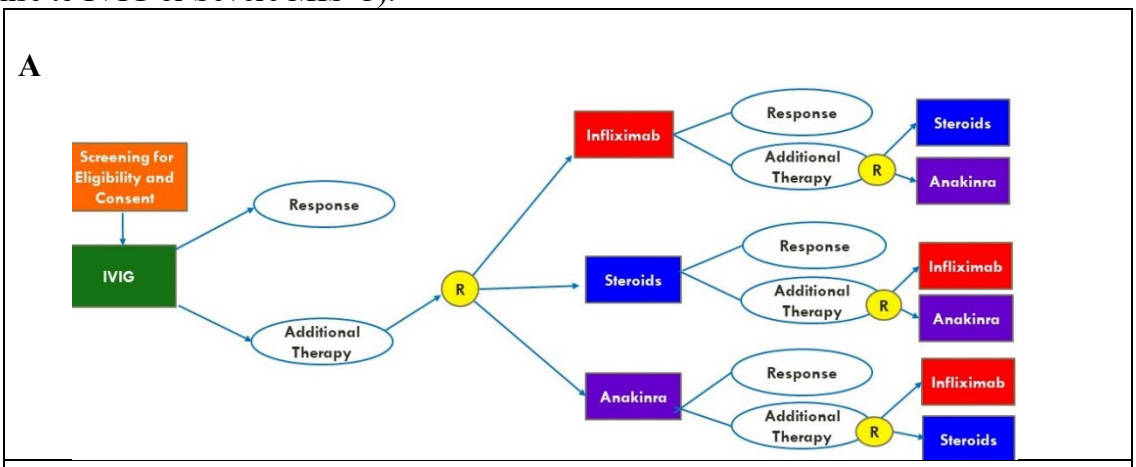

Figure 1. snSMART study for MIS-C patients

C.2. Stratification

Randomization will occur within strata defined by site to reduce the influence of site-to-site practice variation on the outcome measures.

C.3. Randomization & Drug Dosing

All patients will receive IVIG at the standard dose of 2 g/kg (max 100g; for obese patients, dosed based on ideal body weight). If they need additional anti-inflammatory therapy due to non-response to IVIG, they will subsequently be randomized to receive steroids (2 mg/kg/day IV or orally divided q12h; max 60 mg/day), infliximab (10 mg/kg IV once) or anakinra (up to 10 mg/kg/day IV or SQ with max of 200 mg q6h) (See Human Subjects: Criteria for Additional Anti-inflammatory Therapy due to Non-Response to IVIG or Severe MIS-C). The dose of anakinra up to 10 mg/kg/day IV or SQ with a max of 200 mg q6h has become a standard dose of anakinra being used to treat patients with hyperinflammatory syndrome due to COVID-19 as well as MIS-C [12, 16].

A stratified randomization scheme will be employed with randomly permuted blocks. Randomization assignments will be generated by the study biostatistician, Dr. Jain, and implemented electronically by the electronic data capture system after confirmation of trial eligibility and consent.

C.4. Covariate Measures

A variety of patient and clinical factors may be associated with outcome. It is of interest to determine which patient and clinical factors, in addition to anti-inflammatory treatment, are associated with outcome. In addition, adjustment for these factors when examining treatment effect may make the treatment comparison more efficient (powerful) in secondary analyses and, also remove bias related to small imbalances, if any, not addressed by randomization. Such covariates include age at enrollment, sex, race/ethnicity, weight, pre-existing medical conditions, illness day at study entry, and medication use at the time of admission.

C.5. Schedule of Events

The schedule of all tests and laboratory studies is depicted in the following table:

Time point	Baseline (prior to any therapy)	12h after IVIG completed (prior to additional tx)	12h after first randomized therapy completed (prior to add'l therapy)	12h after second randomized therapy (or just prior to discharge if no further randomization)	2 weeks after discharge	6 weeks after discharge
Visit Window		**+1 day**	**+1 day**	**+ 1 day**	**±10 days**	**± 10 days**
Informed Consent/Assent	X					
Subject ID# Assigned	X					
Inclusion/Exclusion Criteria	X					
Weight and Height Measurements	X				X	X
Medical history	X					
Demographics	X					
Concomitant Meds	X	X	X	X	X	X
Physical Exam	X	X	X	X	X	
Urine Pregnancy Test[a]	X					
Clinical Laboratory tests (e.g. CBC, CRP)*	X	X	X	X	X	X
Research Study Samples 8.5 mls/timepoint**	X	X	X	X	X	X
Echocardiogram*	X	X	X	X	X	X
Adverse events assessment	X	X	X	X	X	X

a. For females of child-bearing potential

* Most closely associated with study lab draw if available

** Over a 30-day period, the total volume of research samples will not exceed 2ml/kg. Research samples volumes will be adjusted as needed depending on patient's weight.

Administration and Duration of Therapy

Here are general guidelines for the administration of the anti-inflammatory therapies in this comparative effectiveness study. These serve as general guidance for the study sites. The drug dose, route, start time and stop time will be recorded. Deviations from what is listed below will be noted but not considered protocol deviations:

1. IVIG will be administered as a single IV dose of 2 g/kg over 12 hours (max 100g; for obese patients, dosed based on ideal body weight).
2. Infliximab will be administered as a single IV dose of 10 mg/kg over 2 hours.
3. Methylprednisolone (steroids) will be administered as 2 mg/kg IV divided every 12 hours (max 60 mg). At the time of hospital discharge the patient will be switched to oral prednisone (one consolidated dose daily at 2 mg/kg) and given a steroid taper that will take 2 to 3 weeks to complete.
4. Anakinra will be administered at a dose of up to 10 mg/kg/day IV or SQ with 200 mg every 6 hours as the max dose. This is discontinued with a taper during the hospitalization over 2-4 days once a patient is stable with significantly improved clinical course and laboratory profile.

C.6. Study Procedures

C.6.1. Sample and Data Collection

A Global Unique Identifier (GUID) will be generated for all patients in the study. Patient's date of birth, first and last name, date of admission and date of discharge will be stored in a HIPAA-secure REDCap database at UCSD. We will also collect clinical, laboratory and echocardiographic data obtained as part of the routine care of the patient (e.g. hematology and chemistry results, medications). Blood samples will be limited to 8.5 ml of blood distributed between red top tubes for serum, purple top tubes for plasma, and PAX-gene tubes for whole blood RNA (1) baseline (prior to any therapy), (2) 12h after completion of IVIG and prior to additional anti-inflammatory therapy, (3) 12h after completion of first randomized therapy and prior to additional anti-inflammatory therapy (if randomized to receive additional therapy), (4) 12h after completion of second randomized therapy or just prior to discharge if no further randomization, (5) 2 weeks (+/- 10 days) after discharge, and (6) 6 weeks (+/- 10 days) after discharge. Over a 30-day period, the amount of blood drawn will not exceed 2 ml/kg. Scavenged blood samples left over from routine laboratory testing will also be collected.

C.6.2. Echocardiograms

Echocardiogram review will include measurements of (1) the coronary arteries: internal lumen of the proximal right and proximal left anterior descending coronary arteries, normalized to body surface area according using z-scores and American Heart Association classification schema for coronary artery aneurysms and (2) ventricular function, valves and effusion, including quantitative assessment of left ventricular (LV) size and systolic function (LV end-diastolic volume, ejection fraction, shortening fraction), presence and degree of mitral and aortic regurgitation by standard color flow mapping and pulsed Doppler techniques, and parameters of LV diastolic function with tissue Doppler imaging and MV inflow. All quantitative measures will be measured on three consecutive beats and values will be averaged.

D. Defined population with inclusion/exclusion criteria

We project enrollment of 180 children with MIS-C. We anticipate that 50 (27%) children will improve with IVIG alone, while 130 (73%) will require additional treatment post-IVIG resulting in randomization across the three interventions over the study period.

D.1. Inclusion Criteria (modified from World Health Organization Case Definition [17])

1. An individual aged <21 years presenting with
   a. Fever (≥38.0°C for ≥24 hours; may be by subjective report)
      AND
   b. Two or more of the following (from two different systems; e.g. one from cardiac and one from mucocutaneous):

Cardiac - Hypotension - Shock - Arrhythmia - Tachycardia - Left ventricular ejection fraction <55% - Valvulitis	Immunologic - Lymphadenopathy (unilateral cervical or diffuse) Mucocutaneous - Bilateral conjunctival injection - Extremity swelling or erythema - Rash - Lip erythema/Strawberry tongue

- Coronary artery enlargement (LAD or RCA Z-score ≥ 2.5) - Pericardial effusion Gastrointestinal - Diarrhea - Nausea/vomiting - Significant abdominal pain	Neurologic - Altered mental status - Focal neurological deficits - Headache - Meningismus

AND

c. Laboratory evidence of inflammation, including but not limited to, an elevated C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), fibrinogen, procalcitonin, D-dimer, ferritin, lactic acid dehydrogenase (LDH), neutrophilia, lymphopenia or hypoalbuminemia

AND

d. No alternative plausible diagnoses based on clinical judgement;

AND

e. Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; or likely contact with patients with COVID-19

AND

f. Parent or legal guardian (or self if at least 18 years old) able and willing to provide informed consent and subject willing and able to provide assent when appropriate.

D.2. Exclusion Criteria

1. Known immunodeficiency
2. Pre-existing medical condition that precludes receiving one or more of the study medications (e.g. TB, drug allergy to study medication).

D.3. Criteria for Additional Anti-inflammatory Therapy due to Non-Response to IVIG or Severe MIS-C:

Randomization to additional therapy is at the discretion of the treating physician (but not required) for patients who meet one or more of the following criteria:

1. Fever (38°C) ≥12h after completion of IVIG
2. Fever (38°C) ≥12h after completion of IVIG and initial randomized treatment arm
3. Persistent or worsening inflammation, including but not limited to:
   a. CRP increase ≥ 20% from baseline >24h after completion of IVIG alone or IVIG and initial randomized treatment arm
4. Organ dysfunction, including but not limited to:
   a. Coronary artery Z score ≥ 2.5
   b. Left ventricular dysfunction (ejection fraction ≤ 55%)
   c. Valvulitis
   d. Hypotension
   e. Need for inotropic support
5. Persistent or worsening organ dysfunction, including but not limited to:
   a. Worsening coronary artery Z score
   b. Worsening left ventricular dysfunction
   c. Worsening valvulitis
   d. New need for, or increase in, inotropic support

E. Statistics

E.1. Statistical Analysis Plan

Since this is a superiority, snSMART study design, an intent-to-treat (ITT) approach will be used to analyze the data regarding patient outcomes. A per protocol analysis of completers will be performed as a sensitivity analysis analogous to the ITT analyses. 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 Hochberg adjustments will be made for multiple comparisons. A p-value of 0.05 will be considered statistically significant unless otherwise specified. Statistical analyses will be conducted using the statistical software R 3.6.1. (www.rproject.org) and either rjags or Stan. Demographic and baseline characteristics will be compared among the study arms using Fisher's exact test for categorical variables, and ANOVA / pairwise two-sample t-tests for continuous variables. Appropriate non-parametric alternatives will be considered, if parametric assumptions fail.

E.2. Sample Size and Power

We project enrollment of 180 children with MIS-C. We anticipate that 50 (27%) children will improve with IVIG alone, while 130 (73%) will require additional treatment post-IVIG resulting in randomization across the three interventions over the study period. With a worst-case attrition rate of 17%, we will achieve 108 evaluable subjects for the snSMART design. All sample size calculations were performed using the snSMART Sample Size App [https://umich-biostatistics.shinyapps.io/ snsmart _sample_ size_app/]. This two-stage design uses a Bayesian joint stage model for estimating the response rates of each individual treatment in a three-arm snSMART design. The approach distinguishes the best treatment from the second-best treatment using the Bayesian joint stage model. We require approximately 36 subjects per arm (108 in total for three agents) at the initial randomization. The probability of successfully identifying the best treatment is 0.85, when the difference of response rates between the best and second-best treatment is at least 0.25 and the response rate of the best treatment is 0.75. We conducted sensitivity analyses for the power using the joint-stage regression model (JSRM) method of Chao et al (2020) that used Dunnett's approach under generalized estimating equations (GEE) and obtained similar results for approximately 85% power and alpha=0.05. Therefore, an anticipated sample size of approximately 108 evaluable subjects should provide reasonable evidence for a treatment effect in this rare disease setting. Note that if attrition is slightly worse at 25%, then we would require an overall N of 144, in which we would still be well-powered with this sample size. In addition, if the improvement across all treatments is higher than hypothesized (e.g. The probability of successfully identifying the best treatment is 0.85, when the difference of response rates between the best and second-best treatment is at least 0.2 and the response rate of the best treatment is 0.9), we will require approximately the same sample sizes as described above.

E.3. Analysis of the Primary Outcome for Aim 1

Comparison between the three treatment arms with respect to the primary endpoint of best clinical response rate will be compared using a Fisher's exact test for proportions. Differences in the rates between the multiple arms, along with the odds ratio (OR) and their 95% confidence intervals will be reported. A Bayesian Joint Stage Model will be considered, which uses all data from both randomized and re-randomized subjects in estimation and inference, using "linkage parameters" to connect the data from each randomization. This approach provides an unbiased and efficient estimation of the treatment effects and dynamic treatment regimens. Also, as a sensitivity analysis, a multivariable log Poisson joint-stage model will be performed to study the association between clinical, biomarker and demographic factors and intervention arm, adjusting for baseline demographic, stratification factors, and clinical characteristics.

Variables significantly associated with both treatment group and outcome ($p<0.10$) will be included in a multivariable model as covariates.

E.3. Analysis of Secondary Outcomes.
The secondary outcomes will follow methods similar to the primary outcomes.

F. Potential Risks

F.1. Risks of Anakinra:
The main side effect of anakinra is an infusion site reaction when administered subcutaneously. The short course of anakinra that will be administered (likely 3-7 days) should not increase the risk of infection. A decrease in the WBC may occur after prolonged use and this will be monitored. In a two-site, Phase I/IIa study of anakinra for 2 to 6 weeks in Kawasaki disease patients with coronary artery aneurysms, anakinra was well tolerated, did not alter the WBC, and did not result in any serious adverse events attributable to the study drug (manuscript being written by Dr. Tremoulet).

F.2. Risks of Infliximab:
While increased risk of infection has been reported in prolonged courses of infliximab, this has not been reported in single dose therapy as will be used in this study. In a Phase III trial of infliximab plus IVIG in Kawasaki disease patients, infliximab was well tolerated and no serious adverse events were directly attributable to infliximab infusion.[7] That said, reactivation of latent mycobacterial or fungal infection is theoretically possible and, thus, patients with a known recent history of tuberculosis or coccidiomycosis will be excluded. We will monitor for any signs of infusion reaction, although this has not been observed in more than 200 infusion for KD treatment.[7] Infliximab is a hybrid antibody with human Fc and murine Fab regions. Thus, there is a theoretical risk of allergic or anaphylactic reaction following future administration of a hybrid antibody containing murine sequences/

F.3. Risks of Steroids:
The course of low dose methylprednisolone which will be administered for approximately 4 weeks may be associated with high blood pressure, gastritis, increased appetite and facial swelling. All subjects who receive steroids will also receive an H2 blocker.

F.4. Other Risks:
Other risks or discomforts that a participant may experience during this study are:
- Risks associated with drawing blood from the arm include often, discomfort and/or bruising at the site of the puncture; and less often, fainting, the formation of a small blood clot or swelling of the vein and surrounding tissue, or bleeding from the puncture site. There could be infection at the site where the blood was drawn. These risks will be minimized by the use of careful sterile technique when drawing blood and using catheters that are already in place.
- Risks associated with EMLA cream may include minor skin irritation at the site of application.
- All research studies are accompanied by the potential loss of confidentiality. Parents will be informed of this potential in the informed consent.

Any new information about the study drug that may become available during the study that may affect a participant's willingness to continue in the study will be provided to them as soon as possible.

G. Risk Management Procedures

The study team will make every effort to minimize the risk to loss of confidentiality. All subjects will be assigned a unique study. A coded list with the study number, patient names and medical record numbers for the RCHSD/UCSD site will be maintained by the PI. This information will be stored on a password-protected computer in the PIs private locked office.

All regulatory/IRB documents will be stored in a secure location in the research coordinator's office. No PHI or personal identifying data will be recorded in the REDCap database. Patient age (rounded to the nearest 0.1 year) at enrollment will be used instead of birthdate. All AEs and SAEs occurring during the six-week study period will be captured in the Research Electronic Data Capture (REDCap) database and reported to the IRB as appropriate.

Data Safety and Monitoring Board:
The clinical trial will utilize a DSMB to evaluate ongoing data. The DSMB will be composed of a MIS-C clinical trials expert, a pharmacologist, and a biostatistician who are not investigators in this specific project and have no real or potential conflicts of interest with the clinical study.

The DSMB will regularly meet every six months (or more frequently, if desired by the committee) to review enrollment and safety data. The proposed study will not have any planned interim analyses for efficacy or futility. The safety review will be prepared by the biostatistician. An open review will include demographics and trial summary for the total population. The committee, statistician, study coordinator, and the PI will attend the open portion. During the closed review, the PI and other study personnel will not see the data reported by study arm. The committee will review safety data by arm. A formal recommendation by the DSMB committee will be given to the PI, which will be reported to the UCSD HRPP as appropriate.

F. REFERENCES

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