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Corticosteroids plus standard of care treatment versus standard of care treatment alone to prevent heart complications in Kawasaki disease

Submission date 23/03/2020	**Recruitment status** No longer recruiting	[X] Prospectively registered [X] Protocol [_] Statistical analysis plan [_] Results [_] Individual participant data [X] Record updated in last year
Registration date 31/03/2020	**Overall study status** Completed	
Last Edited 19/02/2025	**Condition category** Circulatory System	

Plain English summary of protocol

Background and study aims

This study will work out the best way to treat children and adolescents aged between 30 days and 15 years who have Kawasaki disease. Kawasaki disease is a disease where arteries, particularly the coronary arteries in the heart, become inflamed, sometimes causing irreversible heart damage, heart attacks or even death. Kawasaki disease is currently the most common cause of acquired heart disease in childhood, and an important preventable cause of heart disease in the young. These heart complications may occur within a few weeks of getting the disease, or more typically, some years after recovery due to narrowing of the coronary arteries causing lack of blood supply to the heart. To prevent this heart damage, the fact that a child or young person has Kawasaki disease has to be recognised by clinicians early, and promptly treated with anti-inflammatory medicines.

The problem is that Kawasaki disease presents with a range of symptoms that are common in normal childhood infections, including a high fever for five days or more, rash, bloodshot eyes, “strawberry” red tongue, cracked, dry lips, swollen lymph glands in the neck, and redness and swelling of the palms and soles. No one knows what causes Kawasaki disease, and this is an area of ongoing and intense research around the world. Experts suggest that wind-borne toxins derived from agriculture might be important triggers, combined with genetic susceptibility, although this is by no means firmly established. As such, there is no laboratory diagnostic test available for Kawasaki disease, and diagnosis therefore depends on early recognition of the clinical features.

Intravenous immunoglobulin (IVIG) is a blood product derived from many different pooled healthy blood donors, containing antibodies naturally produced by the immune system. IVIG is the standard treatment given in Kawasaki disease to “dampen down” inflammatory processes which occur in the first few days of the illness. Many children and adolescents still develop significant heart damage despite IVIG. In the UK, heart damage has been found in 19% of cases despite IVIG; in other countries it is as high as 42%. Corticosteroids (‘steroids’) have been used for decades to treat similar inflammatory conditions, but are not yet widely used as an initial treatment for Kawasaki disease. The aim of this study is to find out whether giving corticosteroids upfront (in addition to IVIG) to children and adolescents with Kawasaki disease across Europe reduces the high rate of heart complications.

Who can participate?
Children aged between 30 days and 15 years with Kawasaki disease

What does the study involve?
All children and adolescents in the study will get the current recommended standard treatment of IVIG and aspirin. They will then be split into two groups, by chance (called randomisation). One group will not receive any extra treatment other than the standard IVIG and aspirin. The second group will receive additional treatment with prednisolone (corticosteroids) by mouth (or intravenously, into a vein, if needed) immediately. They will take steroids for around 2-3 weeks, depending on how quickly they get better. Everyone will have frequent assessments of their inflammatory status (temperature and inflammatory blood test markers) to work out whether they still need additional IVIG treatment 2 days after they start treatment. Five days later, they will all be re-evaluated again to work out whether they still need extra treatment if the inflammation has not settled completely. Whichever group they started in, children and adolescents will get any extra treatment they then need.
The researchers will follow the children and adolescents for 12 weeks through face-to-face visits to find out whether they have had any problems – they will mostly stay in hospital for the first 5-7 days, and there are just three visits after this first week. This duration of follow-up is standard for routine clinical care of Kawasaki disease. The researchers will particularly focus on:
• Looking for any damage to their coronary arteries (or other heart damage) using heart ultrasound (echocardiography) scans
• Whether they experienced any side effects from the medicines they received
• Whether they needed to receive any additional treatments
• How long they had to stay in hospital
• Whether they have to be admitted to hospital again
• How rapidly their blood tests normalised
• How much all their care costs
• If the treatments overall improve their quality of life

What are the possible benefits and risks of participating?
Whilst there may not be any direct benefit in taking part in the study, participation will be invaluable to help improve future care for these children and adolescents.

Where is the study run from?
The trial is run from hospitals across the Austria, Belgium, Czech Republic, Estonia, Finland, France, Germany, Greece, Ireland, Italy, Netherlands, Poland, Spain, Sweden and UK
The trial will be coordinated by the MRC CTU at UCL, UK

When is the study starting and how long is it expected to run for?
May 2017 to April 2025

Who is funding the study?
Innovative Medicines Initiative 2 Joint Undertaking (JU) that supports the conect4children (c4c) research consortium

Who is the main contact?
KD-CAAP Trial Team
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Study website
http://kdcaap.mrcctu.ucl.ac.uk/

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Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number
2019-004433-17

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
CPMS 43422

Study information

Scientific Title
Multi-centre, randomised, open-label, blinded endpoint assessed trial of corticosteroids plus intravenous immunoglobulin (IVIG) and aspirin, versus IVIG and aspirin for prevention of coronary artery aneurysms in Kawasaki disease (KD-CAAP: Kawasaki Disease Coronary Artery Aneurysm Prevention trial)

Acronym
KD-CAAP

Study objectives
Adding immediate corticosteroid treatment to standard of care IVIG and aspirin will reduce coronary artery aneurysm (CAA) rates in unselected Kawasaki disease (KD) patients across Europe compared with intravenous immunoglobulin (IVIG) and aspirin alone.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 18/02/2020, North East – Newcastle & North Tyneside 1 Research Ethics Committee (NHSBT Newcastle Blood Donor Centre, Holland Drive, Newcastle upon Tyne, NE2 4NQ, UK; +44 (0)207 104 8084; newcastlenorthtyneside1.rec@hra.nhs.uk), REC ref: 20/NE/0014

Study design
Randomized; Interventional; Design type: Treatment, Drug

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Prevention

Participant information sheet
Not available in web format, please use the contact details to request a patient information sheet

Health condition(s) or problem(s) studied
Coronary artery aneurysms in Kawasaki disease

Interventions
Children/adolescents who fulfil the eligibility criteria and have provided informed consent will be randomised 1:1 to receive immediate adjunctive open-label corticosteroids or not, plus standard of care IVIG and aspirin. Minimisation (with a random element) will be used to force balance between randomised groups (i.e. stratify randomisation) according to country, age (<1 versus ≥1 years) and sex.

All children/adolescents will receive intravenous immunoglobulin (IVIG) at 2 g/kg given as per local standard of care; and aspirin at a dose of 40 mg/kg/day until the patient is afebrile, thereafter at 3-5 mg/kg/day for at least 21 days after the fever resolves as per standard of care.

Children randomised to receive corticosteroids will be given oral prednisolone at 2 mg/kg/day or intravenous methylprednisolone at 1.6 mg/kg/day if oral prednisolone is not tolerated.

In both groups, patients will be assessed at day 2 (+/-12h) and will receive a second dose of IVIG if they have CRP>50% of baseline and still > 10 mg/L, OR temperature (T) ≥38 °C.

At day 5 (+/-12h) further management is again dictated by temperature and CRP:
1. If CRP ≤10 mg/L and T<38 °C, no further additional treatment is required. Aspirin should be continued as per above, and children/adolescents in the experimental group should begin tapering corticosteroids.
2. If CRP >10 mg/L (regardless of temperature) or T≥38 °C rescue treatment should be considered at discretion of local investigator.
Corticosteroid tapering is allowed from day 5 onwards provided there is resolution of fever

(temperature <38 °C) and CRP ≤10 mg/L, and should be completed over 15 days in 5-day steps from 2 to 1 to 0.5 mg/kg/day, then to 0 mg.

Children/adolescents within the trial will be followed up for a total of 12 weeks.

Intervention Type
Other

Phase
Phase III

Primary outcome measure
KD-CAAP will have two co-primary outcome measures based on repeat echocardiography undertaken at weeks 1, 2, 6 and 12 weeks:
1. Any CAA documented within the 12 weeks of trial follow-up (to assess overall effectiveness of the strategy of immediate corticosteroids in preventing CAA, expecting that some patients will receive rescue treatment before reaching this endpoint in both groups)
2. An average estimate across weeks 1, 2, and 6 of the maximum Z-score of the internal diameters of the proximal right coronary artery or left anterior descending coronary artery, adjusting for rescue treatment (to assess the efficacy of corticosteroids)

Secondary outcome measures
1. The maximum coronary Z-score individually obtained from echocardiograms at each of week 1, 2, 6 and 12
2. CAA defined solely by a luminal internal diameter z-score of ≥2.5 identified within the 12 weeks of trial follow-up from echocardiograms completed during this time period
3. Receipt of rescue treatment within the 12 weeks of trial follow-up
4. Receipt of second dose of IVIG within the 12 weeks of trial follow-up
5. Duration of fever after enrolment (time to temperature <38 °C), temperature collected from the axilla measured daily whilst child/adolescent is febrile
6. Daily serum concentrations of C-Reactive Protein from days 1-5, and at 1 and 2 weeks after enrolment, and time to normalisation of CRP (time from randomisation to first measurement ≤10 mg/L)
7. Duration of hospitalisation calculated from date of admission to date of discharge for the Kawasaki disease admission
8. Serious adverse events including deaths occurring at any time during the 12 weeks of trial follow-up
9. Grade 3 or 4 adverse events occurring at any time during the 12 weeks of trial follow-up
10. Clinical adverse events of any grade judged related to IVIG, aspirin or corticosteroids occurring at any time during the 12 weeks of trial follow-up

Overall study start date
01/05/2017

Completion date
30/04/2025

Eligibility

Key inclusion criteria

1. Aged 30 days (post-natal age) to 15 years inclusive, and below the country-specific age of consent
2. KD defined in at least one of the three following ways:
2.1. As per American Heart Association (AHA) criteria: namely fever for at least five days in addition to 4 of the following 5 criteria:
2.2.1. Bilateral non purulent conjunctivitis
2.2.2. Cervical lymphadenopathy
2.2.3. Polymorphous skin rash
2.2.4. Changes in lips or mucosa (strawberry tongue, red cracked lips, diffuse erythematous oropharynx)
2.2.5. Extremity changes (erythema, oedema of palms and soles in initial phase, and at convalescent stage skin peeling)
2.2. OR less than 5 days of fever but all five clinical criteria above
2.3. OR incomplete KD cases, as per a modified*AHA definition, namely:
2.3.1. Children/adolescents (> 1 year old) with fever greater than or equal to 5 days AND at least 2 other compatible clinical criteria as listed above; OR infants < = 1 year old with fever > = 7 days without other explanation;
AND for both age groups:
2.3.2. CRP > = 30 mg/L or erythrocyte sedimentation rate (ESR) > = 40 mm/h (or both)
AND for both age groups
2.3.3. EITHER the presence of any 3 or more of: anaemia for age (haemoglobin < lower limit of normal reference range for local laboratory) platelet count > = 450 x10^9/L or < 140 x10^9/L; albumin < 30 g/L; elevated ALT (> upper limit of normal reference range for local laboratory); white cell count > = 15 x10^9/L; urine > = 10 white blood cells per high power field
2.3.4. OR abnormal echocardiogram compatible with KD but without established CAA, with > = 3 of the following suggestive features: decreased left ventricular function, mitral regurgitation, pericardial effusion, or dilated but non-aneurysmal coronary arteries (internal diameter 2< Z< 2.5; and not meeting the exclusion criteria for aneurysmal change as defined below).
3. Written informed consent from appropriate legal representative(s), and assent from patients who have not reached the age of consent in the participating country, but are judged to have capacity for this (depending on both age and acuity of illness)

*This definition of incomplete KD is modified from the AHA definition by firstly, the exclusion of aneurysmal coronary artery changes as the sole echo finding, since this is an exclusion criterion for KD-CAAP, and secondly the inclusion of low platelet count as well as high platelet count, as highlighted in recent European consensus SHARE guideline.

Note that patients with KD can still be included in KD-CAAP if they have started IVIG treatment, as long as they are randomised no more than 24 hours after the IVIG infusion is initiated (see exclusion criteria below).

Test results must be from tests done on the calendar day of randomisation or the day before.

Participant type(s)
Patient

Age group
Child

Lower age limit
30 Days

Upper age limit
15 Years

Sex
Both

Target number of participants
Planned Sample Size: 262; UK Sample Size: 46

Total final enrolment
103

Key exclusion criteria
Current exclusion criteria as of 19/02/2025:

Disease-related exclusions:
1. This diagnosis is a second or further episode of KD
2. Already established CAA at screening
3. Severe Congestive Heart Failure or cardiogenic shock defined as the presence of hypotension and shock requiring the initiation of volume expanders
4. Known congenital coronary artery abnormality that would impair assessment of the primary endpoint
5. Suspected macrophage activation syndrome

Exclusions related to medications:
6. Started IVIG more than 24 hours prior to randomisation
7. Known hypersensitivity to prednisolone or methylprednisolone or known phenylketonuria to aspartame used in a formulation in an infant less than 12 weeks.
8. Current oral, intravenous or intramuscular corticosteroid treatment for more than 3 days in previous 7 days prior to randomisation
9. History of previous severe reaction to any human immune globulin preparation

Exclusions related to general health or other issues:
10. Active varicella zoster virus or influenza infection; or known exposure to a case of varicella within the previous 21 days prior to randomisation if known to be non-immune
11. Co-enrolment in another study/trial of an investigative medicinal product

12. Pregnant or/and breastfeeding adolescents

Disease-related exclusions relate to those (rare) patients who already have severe fulminant inflammation and/or shock when they are diagnosed with KD, in whom recent European consensus suggests corticosteroids and/or other immunosuppression are required. Such exceptional cases
represent a small minority and therefore will not substantial impact on recruitment targets.

A blood or urine pregnancy test must be completed on the day or day before randomisation for adolescents who have begun menstruation.

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Previous exclusion criteria:

Disease-related exclusions:
1. This diagnosis is a second or further episode of KD
2. Already established CAA at screening
3. Severe Congestive Heart Failure or cardiogenic shock defined as the presence of hypotension and shock requiring the initiation of volume expanders
4. Known congenital coronary artery abnormality that would impair assessment of the primary endpoint
5. Suspected macrophage activation syndrome

Exclusions related to medications:
6. Started IVIG more than 24 hours prior to randomisation
7. Known hypersensitivity to prednisolone or methylprednisolone
8. Current oral, intravenous or intramuscular corticosteroid treatment for more than 3 days in previous 7 days prior to randomisation
9. History of previous severe reaction to any human immune globulin preparation

Exclusions related to general health or other issues:
10. Active varicella zoster virus infection; or known exposure to a case of varicella within the previous 21 days prior to randomisation if known to be non-immune
11. Co-enrolment in another study/trial of an investigative medicinal product

Date of first enrolment
01/09/2020

Date of final enrolment
31/07/2024

Locations

Countries of recruitment
Austria

Belgium

Czech Republic

England

Estonia

Finland

France

Germany

Greece

Ireland

Italy

Netherlands

Northern Ireland

Poland

Scotland

Spain

Sweden

United Kingdom

Wales

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Funder(s)

Funder type
Other

Funder Name
Innovative Medicines Initiative 2 Joint Undertaking (JU), under grant agreement No 777389 that supports the Conect4children (c4c) research consortium

Results and Publications

Publication and dissemination plan
The protocol will be made available at the following link: https://www.ctu.mrc.ac.uk/studies/all-studies/k/kd-caap/

The publication of the primary results will be submitted to a peer-reviewed journal which enables Open Access. The current planned date of submission is for November 2023. The researchers will also produce a lay summary of results which will be disseminated through patient organisations included in the trial, in particular Soceiti.

Intention to publish date
31/07/2025

Individual participant data (IPD) sharing plan

Anonymised data will be available for sharing after the publication of the primary trial results, and consent was obtained for this. Sharing will follow the MRC CTU at UCL's controlled access approach, based on the following principles:
1. No data should be released that would compromise an ongoing trial or study
2. There must be a strong scientific or other legitimate rationale for the data to be used for the requested purpose
3. Investigators who have invested time and effort into developing a trial or study should have a period of exclusivity in which to pursue their aims with the data, before key trial data are made available to other researchers
4. The resources required to process requests should not be under-estimated, particularly successful requests which lead to preparing data for release. Therefore adequate resources must be available in order to comply in a timely manner or at all, and the scientific aims of the study must justify the use of such resources
5. Data exchange complies with Information Governance and Data Security Policies in all of the relevant countries.
Those wishing to access data will be asked to complete a short request form covering these areas

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article		26/01/2023	27/01/2023	Yes	No
HRA research summary			28/06/2023	No	No