Multi-centre, randomised, open-label, blinded endpoint assessed, trial of corticosteroids plus intravenous immunoglobulin (IVIG) and asperin, versus IVIG and asperin for prevention of coronary artery aneurysm (CAA) in Kawasaki disease (KD)

Published: 25-08-2021
Last updated: 16-11-2024

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Ethical review	Approved WMO
Status	Completed
Health condition type	Coronary artery disorders
Study type	Interventional

Summary

ID

NL-OMON50876

Source
ToetsingOnline

Brief title
KD CAAP

Condition

- Coronary artery disorders
- Aneurysms and artery dissections

Synonym

Kawasaki disease

Research involving
Human

Sponsors and support

Primary sponsor: University college London
Source(s) of monetary or material Support: EU geld

Intervention

Keyword: Coronary artery aneurysm, Corticosteroids, Diagnostic biomarker, Kawasaki disease

Outcome measures

Primary outcome

KD-CAAP will have two co-primary outcome measures based on repeat

echocardiography

undertaken at weeks 1, 2, 6 and 12 weeks:

(i) 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)

(ii) 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

Efficacy secondary outcomes

(i) At each of weeks 1, 2, 6 and 12 individually, the maximum coronary Z-score

(ii) CAA defined solely by a luminal internal diameter z-score of >=2.5

(iii) Receipt of rescue treatment

(iv) Receipt of second dose of IVIG

(v) Duration of fever after enrolment (time to temperature <38 °C)

(vi) Daily serum concentrations of CRP from days 1-5, and at 1 and 2 weeks after

enrolment, and time to normalisation of CRP (<=10 mg/L)

(vii) Duration of hospitalisation

Safety secondary outcomes

(viii) Serious adverse events including deaths

(ix) Grade 3 or 4 adverse events

(x) Clinical adverse events of any grade judged related to IVIG, aspirin or

corticosteroids

Study description

Background summary

Kawasaki disease (KD) is an acute self-limiting inflammatory vasculitis affecting predominantly
medium-sized arteries, particularly the coronary arteries causing coronary artery aneurysms (CAA). KD is currently the commonest cause of acquired heart disease in children in high-income countries. KD causes CAA in 15-25% of untreated patients while 2-3% of untreated cases die
as a result of coronary vasculitis [1, 5-7]. Coronary artery vasculitis can cause acute myocardial events
in the early stages of the disease leading to myocardial infarction or even death [1, 5-7]. Late morbidity
can also arise from late KD vasculopathy, a process involving remodelling following the acute
inflammatory event, distinct from atherosclerosis, but ultimately leading to coronary vascular
insufficiency and late cardiac events [1, 5-7]. Notably, as more children with KD survive into adulthood,

the disease remains an important cause of long-term cardiac disease in adulthood and requires
rigorous follow-up, particularly for those with CAA, to reduce risk of myocardial ischaemia and
infarction.
The disease has a world-wide distribution with a male preponderance (male: female ratio of 1.5:1,
seasonality and occasional epidemics. KD is more prevalent in Japanese children (308/100,000
under the age of five years) [8]. An increased incidence of KD is also observed in Japanese and other
Asian children resident in North America and Europe, suggesting a genetic contribution [8-10]. In the
UK, a recent direct British Paediatric Surveillance Unit epidemiological survey (2013-2015) showed
that the incidence of KD in the UK and Ireland was 4.55/100,000 children under 5 years, which
represents a slight increase since the last survey in 1990 [7, 11]. Whilst the majority of cases were
Caucasian, KD in the UK is over-represented in Chinese or Japanese Asians and Black Africans [7]. Other
recent studies have demonstrated a higher incidence of KD of 25/100,000 children <5 years in the US
[1]; and 5.5/100,000 children < 5 years in Skane, Sweden [12]. Mortality of KD varies by population:
0.015% in Japan; 0.17% in the USA and 0.36% in the UK .

Study objective

The overarching goal is to optimise the treatment of KD in children/adolescents across Europe.
KD-CAAP will test the hypothesis that adding immediate adjunctive corticosteroid treatment to IVIG
and aspirin will reduce CAA rates in unselected KD patients across Europe compared with IVIG and
aspirin alone.
The primary aim of the KD-CAAP trial is therefore to establish:
1. the effectiveness and efficacy of adjunctive corticosteroid therapy combined with IVIG/aspirin for
prevention of CAA in unselected patients with KD across Europe;
Secondary aims are to establish:
2. the safety of adjunctive corticosteroid therapy combined with IVIG/aspirin for prevention of CAA
in KD;
3. whether adjunctive corticosteroid therapy reduces the duration of fever and length of
hospitalisation for patients with KD;

4. the incremental cost-effectiveness ratio for corticosteroid therapy, expressed as the cost per
QALY gained, from cost and utility data measured via resource use forms and the Child Health
Utility 9D questionnaire.
5. the utility of the Paediatric Glucocorticoid Toxicity (pGTI) tool to assess corticosteroid toxicity.
KD-CAAP will therefore develop an evidence-base that will directly and definitively inform European
guidelines for the treatment of KD, which at the moment only target corticosteroids at patients
deemed high-risk based on pragmatic, consensus, but non evidence-based clinical features that were
formulated as an interim measure pending clinical trials outside of Japan (such as KD-CAAP) [5].
Therefore, beyond the trial, the results will directly influence European clinical guidelines for the
treatment of KD, and additionally will likely have international impact beyond Europe as well since
data from Russia and the US also suggest poor outcomes with IVIG alone.

Study design

Multi-centre, randomised, open-label, blinded endpoint assessed parallel group trial

Intervention

All patients will receive intravenous immunoglobulin (IVIG) at 2g/kg given as per local
standard of care; and aspirin at a dose of 40 mg/kg/day until the patient is afebrile for at
least 48 hours, thereafter at 3-5 mg/kg/day for at least 21 days after the fever resolves as
per standard of care.
Patients will be randomised to
* Control group: no additional initial treatment
* Experimental group: additional 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:
(i) 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.
(ii) If CRP>10 mg/L (regardless of temperature) or T>=38 °C rescue treatment should be
considered at discretion of local investigator.

Study burden and risks

1. IVIG is safe and standard of care. Side effects are generally rare, reversible and mild. Risk of
blood product derived infection are minimal with modern screening and processing of IVIG,
and since patients receive this for KD anyway, no extra risk from the trial exists. Benefit is
prevention of coronary artery aneurysms which would have lifelong consequences, as proven
by meta-analyses.
2. Aspirin is safe and standard of care. Side effects are generally rare, reversible and mild. Risk
of Gastrointestinal bleeding is minimal in children at dose and duration used for KD, and since
patients receive this for KD anyway, no extra risk from the trial exists. Benefit is prevention of
coronary artery aneurysms when given with IVIG, which would have lifelong consequences,
as proven by meta-analyses.
3. Prednisolone is standard of care for high-risk cases in Europe as highlighted in the European
consensus SHARE guideline [5] and many patients receive this for KD, even though there is
some degree of equipoise (and hence the need for the trial). Any side effects at the doses and
duration used are minimal and a detailed commentary is provided in the Information Sheet.
Mitigation of these is use of proton pump inhibitors, and close monitoring for side effects
using the Paediatric Glucocorticoid Toxicity Index. Clinicians already use prednisolone for
many paediatric indications, and are familiar with their therapeutic index.
4. Despite a number of comparative and non-comparative studies comparing the impact of
steroids in KD [54], this potentially highly effective treatment is not commonly used for the
treatment of KD. Several factors are likely to contribute - inability to identify high-risk children
early on in the disease course, when the meta-analysis suggests benefits will be greatest* lack

of clarity on wider benefits in terms of longer-term cardiovascular health in children without
overt vasculitis (coronary artery aneurysms, CAA))* relative weakness of the evidence base
with Randomised Controlled Trial evidence being relatively small* and concerns about
generalisability of findings from Japanese studies on Japanese populations in case ethnic
differences contribute to variable efficacy. The proposed trial would delineate the evidence
supporting adjunctive corticosteroids (or not), in all patients with KD, leading to a pragmatic
and easily implementable recommendation.
5. Epidemiological data suggest worse outcomes in terms of CAA for children under 1 year but
there remains significant equipoise about the use of corticosteroids in this age group,
therefore inclusion of these patients is still justified in this trial. Randomisation will be
stratified however, to ensure an equal balance of children < 1 year in each randomised group.
6. As there is no diagnostic test for KD the diagnosis relies on clinical criteria. The inclusion
criteria to the trial allows patients with incomplete cases of KD to be entered in to the trial
many patients (particularly infants under the age of 12 months) have some but not all of the
clinical features of KD, but may still be at high risk of CAA.
7. There is minimal risk of the overall protocol treatment above routine clinical care because all
patients are actively managed with IVIG and aspirin. In addition clear criteria for rescue
treatment are built into the trial design for both the control and experimental groups. Trial
sites have considerable experience with managing patients with KD which will minimise the
risks to the patients and the trial overall. We also established through a survey coordinated
by the national c4c hubs and PRINTO that the trial protocol is acceptable with no concerns
raised.
8. All children will be closely monitored so that side-effects are identified at the earliest
opportunity and appropriate action taken. A detailed risk assessment was conducted by the
MRC CTU at UCL prior to starting the trial which will inform the level of monitoring required

and the proportion of on-site and central monitoring to ensure safety is being reliably
assessed. Safety issues will be explicitly considered by the independent Data Monitoring
Committee (DMC) who will review unblinded data regularly during the trial. The DMC will
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oversee all aspects of safety also taking into account any new data arising from other studies
worldwide. The DMC will have a charter clearly setting out their roles and responsibilities.
Serious adverse events will be reported to MRC CTU at UCL within 24 hours of becoming aware
of the event* this responsibility will lie with site PIs and co-PIs, but may also be delegated to
the Trial Physicians. The protocol contains a relatively short duration of corticosteroid
treatment (in the experimental arm). We will systematically screen for corticosteroid toxicity
using the newly formed Paediatric Glucocorticoid Toxicity Index, a variation of the adult tool
we helped develop.
9. As children will be involved (aged 30 days to 15 years inclusive) consent will be obtained from
parents or carers and assent from children (dependent the acuity of illness and local
requirements). They will be provided information on the purpose and nature of the research,
what it involves including the risks and benefits to make an informed decision of their child to
be involved. Due to the acute nature of KD consent will be required promptly after KD
diagnosis, a short trial introductory leaflet may initially be given to a potential patients parent
or carer after consideration and if requested the informed consent form will be given to the
parent/carer to provide consent.
10. For laboratory tests and storage samples collected within the trial the child/adolescent will
give blood. This may result in unwanted adverse effects. The blood drawn during the trial has
been limited and where possible will be taken at the same time as standard clinical
monitoring. Local anaesthetic creams or sprays routinely used for blood draws

may also be
used. Many children will be in hospital for the first 5-7 days when the majority of blood draws
will be made and will have a cannulae for medication through which the blood draws will be
made.
11. For children/adolescents randomised to receive corticosteroids, there will be a slight oral
medication burden in addition to/over standard of care. However, this is will be for a limited
time period as once the child/adolescent's fever has resolved and their CRP is equal to or less
than 10, after Day 5 the dosing of corticosteroids is tapered. A diary card will be completed by
parents to record doses taken by their children to determine their adherence.
COVID specific benefit-risk assessment
The safety of subjects participating in KD-CAAP is of primary importance to the sponsor. The risks of
subjects* involvement in KD-CAAP were specifically assessed in the context of the ongoing global
COVID-19 pandemic and the applicable precautionary response measures in place at the local or
national level. Risks to subjects were assessed against the anticipated benefit of KD-CAAP participation
for subjects in accordance with International Council for Harmonisation (ICH) Good Clinical Practice
(GCP) E6 (principle 2.2), and risks to quality were also assessed in accordance with ICH GCP E6 (Section
5). Clinical trial management requirements for KD-CAAP were also assessed against the European
Medicines Agency guidance on the management of clinical trials during the COVID-19 pandemic
(European Medicines Agency 2020).
The Sponsor have established measures to ensure that the conduct of KD-CAAP prioritizes the safety
of subjects and the integrity of clinical data. These measures were based on a risk assessment of the
impact of COVID-19 on subject safety and on clinical trial conduct. The specific measures established
for all subjects and investigative sites participating in KD-CAAP ar

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Children (2-11 years)
Babies and toddlers (28 days-23 months)

Inclusion criteria

1. Aged 30 days (post-natal age) to 15 years inclusive, and below the country-specific age of consent for the duration of the trial
2. KD defined in at least one of the three following ways
(a) as per American Heart Association (AHA) criteria [1]: namely fever for at least 5 days in addition to 4 of the following 5 clinical criteria:
i. bilateral non purulent conjunctivitis
ii. cervical lymphadenopathy
iii. polymorphous skin rash
iv. changes in lips or mucosa (strawberry tongue, red cracked lips, diffuse erythematous oropharynx)
v. extremity changes (erythema, oedema of palms and soles in initial phase, and at convalescent stage skin peeling)
(b) OR less than 5 days of fever but all 5 clinical criteria above
(c) OR incomplete KD cases, as per a modified*AHA definition [1], namely:
i. 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 greater than or equal to 7 days without other explanation;
AND for both age groups
ii. CRP >=30 mg/L or erythrocyte sedimentation rate (ESR) >=40 mm/hr (or both)
AND for both age groups
iii. 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*/L or <140 x10*/L; albumin <30 g/L; elevated ALT (> upper limit of normal reference range for local laboratory); white cell count >=15 x10*/L; urine >=10 white blood cells per high power field
iv. 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 and will not reach the age of consent for the duration of the trial 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 [5].

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

Exclusion criteria

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 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.
11.12. 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 [5]. 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.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Diagnostic

Recruitment

NL
Recruitment status: Completed

Start date (anticipated):	02-01-2021
Enrollment:	19
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	prednisolone
Generic name:	corticosteroids
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	25-08-2021
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-11-2021
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-01-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-05-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	30-05-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-07-2022
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-08-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-05-2024
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-08-2024
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2019-004433-17-NL
ISRCTN	ISRCTN71987471
CCMO	NL76277.018.21

Study results

Date completed: 16-07-2024

Summary results

Trial ended prematurely