Brief Report

CLINICAL INVESTIGATION

A comparative clinical trial to assess a standardized escalation dose strategy of interleukin-1 blockade in Kawasaki disease: The ANACOMP trial

Abstract

Background: Based on the auto-inflammatory pattern of Kawasaki Disease (KD), the most frequent and heart threatening vasculitis in children before five years, we hypothesize that anti-IL-1 blocking agents could bring a rapid and sustained effect on systemic and coronary inflammation in patients with KD.

Aims and primary objective: To compare the efficacy of anakinra (IL-1R1 receptor antagonist) with second IVIG infusion, in the second line, on fever in patients with KD, who failed to respond to the first infusion of IVIG.

Methods: A multicenter national, 60-day, the randomized controlled open-labeled trial of superiority running in two parallel groups in a 1:1 ratio to arm A: experimental strategy (anakinra) or arm B: control strategy (IV IG+standard care). In arm A, patients will receive anakinra, at a starting dose of 4 mg/kg. Up to H36, the dose of anakinra will be increased every 12 h if the patients have fever>38°C, and up to a maximum of 8 mg/kg. The main criterion-evaluating efficacy in both groups is an abatement of fever<38°C within 2 days after initiation of treatment, a decrease of the CRP values from baseline to day 30, reduction in physician and patient's parent's assessment of disease activity of at least to 50% between baseline and day 14, and treatment tolerability. In addition, we will assess the resolution of coronary abnormalities; i.e. worst Z score<2.5, by echocardiogram if present on day 45.

Conclusion: Anakinra treatment is expected to enhance more frequently than IVIG retreatment a rapid and sustained effect on vascular inflammation

Keywords: Kawasaki disease • anakinra • interleukin-1 • comparative trial • intravenous immunoglobulin

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Introduction

Kawasaki Disease (KD) is a systemic vasculitis that affects children before the age of 5 years. Clinical symptoms start as an acute febrile illness associated with mucous and cutaneous signs together with strong biological inflammation [1]. Coronary aneurysms may develop during the acute phase with a frequency of 25 percent and represent a major issue on long-term morbidity and mortality. The cause of KD is unknown but the early age of onset combined with its occurrence following an infectious trigger suggests deregulation of the innate immune system. Genetic susceptibility factors play a role in the Japanese population, which remains the most affected, and provide some hypothesis on the aberrant inflammatory response and the variation in response to treatment [2]. A single infusion

2 g/kg of Intravenous Immunoglobulins (IVIG) together with 30-50 mg/kg of aspirin represents the standard treatment [3]. Rapid and sustained abatement of fever and inflammatory symptoms occurs in 80% of cases, and early treatment before 10 days after disease onset decreases the occurrence of a coronary aneurysm to 5% [4]. The limits of this effective therapeutic strategy are that 40% of children younger than 1-year-old already have cardiac complications at the time of diagnosis and that up to 30% of patients do not respond spontaneously to IVIG treatment with an increased risk of coronary aneurysms [5]. The common practice is to administer a second dose of IVIG (2 g/kg) to patients who fail to become afebrile within 24 to 48 hours after completion of the first infusion, even though the benefits of this approach is currently unknown, especially in terms of cardiac complications, therefore, finding effective treatment strengthening or alternatives represents a major unmet need. The strategy of adding steroids to initial treatment with IVIG has shown a decrease occurrence of coronary aneurysms in comparison to IVIG alone in a meta-analysis of six clinical trials [6-11]. However, enrolled patients were stratified by IVIG resistance risk factors; i.e. the Kobayashi score, which lacks sensitivity in non-Asian ethnic groups [12]. The addition of TNFα blockers; i.e. Infliximab and etanercept, failed to demonstrate superiority to IVIG alone on coronary aneurysms, essentially because the trials were not enough powered [13]. Anakinra is a recombinant selective interleukin-1 receptor antagonist (IL-1Ra) which blocks the action of both IL-1α and IL-1β treatment and is a powerful antipyretic. It has first been developed for the treatment of symptoms of moderate to severely active rheumatoid arthritis. The aim of the ANACOMP study is to compare anakinra, which has shown early experimental proof of efficacy in KD, to a second IVIG infusion for the treatment of persistent or recrudescent fever in children with KD who fail to become afebrile after the first IVIG infusion. The chosen design allows evaluating the experimental treatment of the escalation dose.

Methods

Study design: ANACOMP is a 60-day, phase III, randomized, open-label, and multicentre study in 84 patients with KD and persistence or recrudescence of fever ≥ 38°C, 48 hours after the infusion of 2 g/kg of IV Ig. The study will run globally in accordance with the declaration of Helsinki and applicable local laws/regulation; all participants (patient's parents) will give written informed consent. The institutional review board and an independent ethics committee will review the study protocol. Patient with KD according to the American Heart Association definition for complete or incomplete KD will be randomized using a web-based application and secured access (Cleanweb) in a 1:1 ratio to arm A: experimental strategy (involving anakinra) or arm B: control strategy (IV IG+standard care), according to a computer-generated list of randomly permuted blocks of a random size. Randomization and concealment will use a centralized, secure, computer-generated, interactive, web-response system accessible from each study center. Randomization will be stratified on age (group<2 years old and group ≥ 2 years old), sex, and drug status matching. The randomization list and the list of treatment's numbers will be performed using the statistical software SAS © 2002-2012 by SAS Institute Inc., Cary, NC, USA, version 9.4 for Windows.

The first step of the study: will last 48 hours, and will end with the measurement of the primary endpoint, the body temperature (axillary, tympanic, oral), for all intention to treat the population. The second step of the study will last from D3-D60 (57-day total duration) while during this period all the secondary endpoints will be collected/measured by the investigators and analyzed by the end of the study for the all intention-to-treat population.

Study objectives and endpoints: To compare the efficacy of anakinra (IL-1R1 receptor antagonist) with second IVIG infusion, in the second line, on fever in patients with KD, who failed to respond to one infusion of IVIg (standard treatment). The main efficacy evaluation criterion will be; i.e. the patient must reach a body (axillary, tympanic, oral) temperature<38°C within 2 days (48 hours) after initiation of treatment by anakinra (i.e. a binary outcome: success/failure), and from the beginning of the IVIG infusion. Secondary objectives will compare anakinra with IVIG retreatment in terms of temperature <38°C within 3 days (H72) after initiation of treatment. They include a binary outcome success/failure, decrease of the CRP values measured in mg/L from baseline to day 30, reduction in physician assessment of disease activity of at least to 50% between baseline and day 14, reduction in patient's parent's assessment of disease activity, of at least 50% between baseline and day 14. In addition, we will assess the resolution of

coronary abnormalities; i.e. worst Z score<2.5, by echocardiogram if present on day 45.

Eligibility criteria: The ANACOMP study will enroll children, male and female, from 3 months to<18 years old, weighing at least 5 kg. Patients will have KD according to the American Heart Association definition for complete or incomplete KD, which include fever ≥ 5 days or at least 3 days if KD with AHA criteria since the third days of fever and ≥ 4 of 5 main clinical signs among modification of the extremities, polymorphic exanthema, and bilateral bulbar not exudative conjunctivitis, erythema of the lips or oral cavity, and cervical lymph nodes usually unilateral>1.5 cm in diameter. Patients who failed to respond to the standard therapy of KD, e.g. Persistence or recrudescence of fever ≥ 38°C, 48 hours after the infusion of 2 g/kg of IVIG. The screening period will occur 24 hours after the end of the first infusion if the patient remains febrile 24 hours after the end of the first infusion. Patient, parents or legal guardian's written informed consent is required and patients with health insurance. Table 1 summarizes the inclusion and exclusion criteria.

Experimental arm A

Experimental treatment rationale: The innate immune system plays a pivotal role inducing the inflammatory phenotype of KD, which is mostly interleukin 1 driven [14]. Unknown trigger(s) such as viruses, bacteria, and HSP may activate the inflammatory cascade in genetically predisposed individuals and induce endothelial cell activation and subsequent coronary damage. Important clinical evidence, increasing biological data, and mouse model experiments suggest a critical role for IL-1β. IL-1β is released from Peripheral Blood Mononuclear Cells (PBMCs) of KD patients and present at high concentrations in their serum together with IL-18 [15]. In addition in case of severe inflammation, endothelial cells in apoptotic bodies release IL-1α as an alarmin, and mononuclear cells and macrophages release IL-1β in membrane microvesicles, suggesting that both IL-1α and IL-1β are involved in KD vasculitis [16]. Increased transcript abundance of the neutrophil-associated calcium-binding proteins; S100A8 and A9 confirms the role of activated neutrophils in acute KD, as these proteins regulate adhesion of neutrophils and monocytes to the endothelial cell; S100A8/9 proteins have been shown to be elevated in patients who develop coronary aneurysms [17]. A mouse model of KD vasculitis, induced by lactobacillus cell wall injection, has demonstrated a crucial involvement of the NLRP3 inflammasome and efficacy of IL-1 blockade by anakinra in preventing vascular aneurysms and myocarditis [18]. During the past 3 years, there is an increasing number of case reports describing the effect of anakinra in children with IGIV resistance and serious complications, in which, acute myocarditis-related shock, and macrophage activation syndrome [19-23]. To explore further the role of IL-1 in KD, we have conducted a phase IIa open-label exploratory study (Kawakinra NCT 02390596,) in a small cohort of patients with IVIG resistance to assess the efficacy and safety of anakinra for abatement of fever as a primary objective. Seventy-five percent in the ITT group and 87% in the PP group of patients attained fever<38°C within 48 h of anakinra treatment, and six (with coronary abnormalities at screening visit) of 12 patients in the ITT group and 6/8 patients in the PP group with the resolution of coronary abnormalities at d45 [24].

Table 1. List of the participating centers in France.

Pediatrics hospital name
APHP, Bicêtre, Le Kremlin-Bicêtre
APHP, Robert Debré, Paris
APHP, Necker, Paris
APHP, Jean-Vendier, Bondy
APHP, Louis Mourier, Colombes
André Mignot, Versailles
CHU de Toulouse
Lyon, Hôpital Mère Enfant
APHM, Hôpital Nord, Marseille
CHRU de Lille
Groupe Hospitalier de l'Est, Meaux
CHI de Créteil
CH Delafontaine, Saint-Denis

Experimental treatment properties**:** Anakinra is a recombinant selective interleukin-1 receptor antagonist (IL-1Ra) which blocks the action of both IL-1α and IL-1β treatment and is a powerful antipyretic. Its safety should be good, as the drug has a very short half-life, which allows its rapid withdrawal in case of serious adverse events [25]. The use of anakinra is not associated with the risk of contamination by infectious agents, which remain even minimal, a possibility with the use of IVIG. As demonstrated in the animal model and previous proof of concept study; clinical trials NCT02390596, we expect a dramatic response on clinical symptoms and cardiac complications, when compared with second IVIG injection (still recommended by the AHA outside any level of evidence) [24].

Experimental strategy: In Arms A, patients will receive anakinra, at a starting dose of 4 mg/kg. If patients are still febrile with 12 hours (H12) of treatment, they will receive a supplementary dose of 2 mg/kg; otherwise, they will remain at a starting dose of 4 mg/kg. If they are still febrile at H24, they will receive a dose of 8 mg/kg; otherwise, they will maintain their dose of 6 mg/kg. Patients with temperature<38°C at any point between initiation and day 14, but who develop secondary fever due to KD could have further escalation dose of anakinra until a maximum dose of 8 mg/kg. In the case, that clinician's clinical impression creates the suspicion of uncontrolled disease, even if the patient is not febrile, the physician has the possibility to increase the anakinra dose at H12 or H24 until a maximum dose of 8 mg/kg. After the last escalation dose, if any necessary, we will assess the primary criteria at H48. Patients not responding to anakinra will follow the usual standard care and will complete information related to the study visits. Figure 1 shows the study design, for the group receiving anakinra.

Dosing rationale: Anakinra is a recombinant selective interleukin-1 receptor antagonist (IL-1Ra), which also blocks IL1α and IL-1β. One mL prefilled glass syringe contains: 0.67 mL (100 mg) of anakinra in a solution (pH 6.5) containing sodium citrate (1.29 mg), sodium chloride (5.48 mg), disodium EDTA (0.12 mg), and polysorbate 80 (0.70 mg) in Water for Injection, USP. The drug is injected once daily subcutaneously at regular intervals because of its short half-life. Anakinra is labeled in the USA and Europe for patients with CAPS and systemic JIA from the age of 8 months (10 kg) [25]. The recommended starting dose is 2 mg/kg for CAPS and 4 mg/kg for systemic JIA, but the dose can be increased up to 8 mg/kg. Anakinra has been also used in younger children, especially those

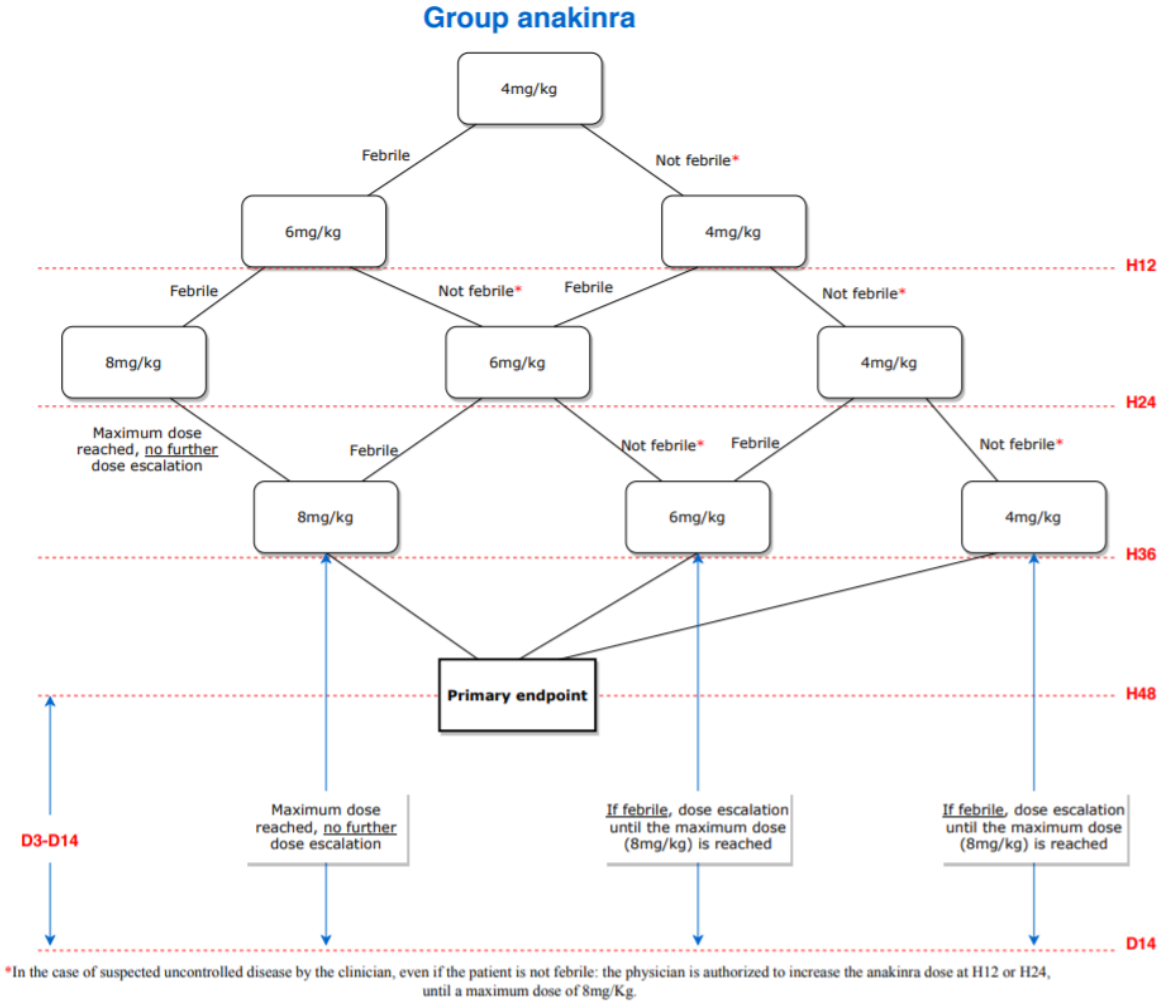

Figure 1: Study design, for the group receiving anakinra (arm A: experimental treatment).

with CAPS without specific safety warning, and the KAWAKINRA study has included patients since 3 months of age and 5 kg, to be in accordance with the KD-observed study population [25,26]. Preliminary data suggest that median effective doses in KD could be 4 mg/kg whatever the age of the patient; higher doses of anakinra (e.g. 8 mg/kg) could be occasionally required, especially in younger patients. This drug has a short delay of action and half-life (around 6 hours) ensuring both a rapid assessment of its efficacy and an early withdrawal in case of a serious adverse event. Like in the Kawakinra study, we intend to give anakinra during 14 consecutive days, independently of the period of escalation dose if any. For the moment, it is unjustifiable neither to shorten nor to pursue anakinra on a longer duration. Injection-site reaction (pain, erythema) is the most frequent side effect partially preventable by the use of local anesthetics and the application of ice. Neutropenia and hepatitis need to be monitored. The long-term use of anakinra is associated with an increased risk for serious bacterial infections. As a whole, the expected safety of anakinra, used on short-term treatment, appears very good. The use of anakinra is not associated with the risk of contamination by infectious agents, which remain even minimal, a possibility with the use of IVIG (Figure 2).

Control arm: In arm B, patients will be assigned to receive a control therapy, IVIg infusion of 2 g/kg, and their treatment will follow usual standard care. All patients, responding or not responding to IVIG treatment, will complete information related to the study visits.

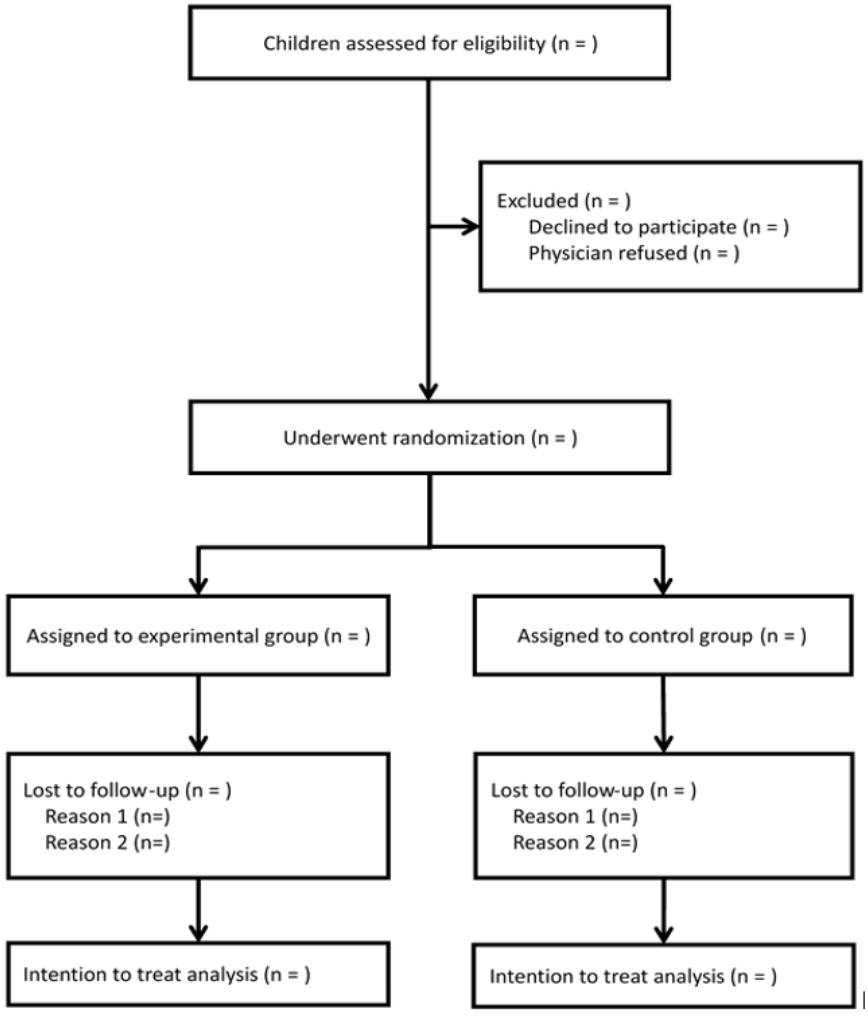

Figure 2: Flow chart of the trial based on the CONSORT Statement.

Prohibited and concomitant medications: The following treatments are not allowed at baseline and during the entire study: preventative antipyretics (paracetamol, NSAIDs other than aspirin), as long as the patient receives the study medication. Immunosuppressive medications will not be given in a period less than twice of their half-life prior to the patient receives the study medication (systemic steroids, cyclosporine, tacrolimus, azathioprine, cyclophosphamide, interferon, mycophenolate, other anti-IL-1, anti-IL-6, anti CD20, and anti-TNF), plasmapheresis.

Assessment of efficacy: Primary outcome: Fever will be measured in °C accordingly, by oral, tympanic, rectal, or axillary (+0.5°C).

Secondary outcomes: The serum CRP will be measured in mg/L, normal value<6 mg/L. Global evaluation of disease activity by the physician and the parents will use a 10 points visual analog scale. Evaluation of KD signs is reported with exploratory objectives and related endpoints in Table 2. Coronary arteries measurements will be reported in Z scores according to the method of Dallaire et al., which includes the use of the Haycock method to calculate the Body Surface Area (BSA), uses regression with the square root of body surface area to predict coronary arteries diameter, and includes the evaluation of the circumflex artery [27]. Coronary abnormalities will be classified in z scores, according to the AHA recommendations:<2, normal, 2 to<2.5, dilatation; ≥2.5 to<5: aneurysm; ≥ 5 to<10: small aneurysm; ≥ 10 giant aneurysm. The analyzed segments will be the left coronary artery LMCA and LAD, the circumflex, and the proximal right coronary artery RCA. The ST junction of the Aorta will be assessed by the method of Pettersen and al [28]. We will also assess changes in z scores between the baseline, day 14, and day 45. Anakinra and IVIG retreatment will be also compared regarding the abatement of KD symptoms and study drug tolerability (Table 3).

Assessment of safety: Safety and side effect profiles will be evaluated by using the Medical Dictionary for Regulatory Activities reporting criteria for clinical trials for Adverse Events (AEs) and Serious AEs (SAEs) upon study treatments. Adverse Events (AEs) of special interest will be in the anakinra group: tolerability at the injection site, hematologic: leukopenia and macrophage activation syndrome, hepatitis, and bacterial infections. In the IVIG group, we will monitor infusion reactions headaches, rash, chills, malaise, hypersensitivity reaction, renal insufficiency (TA, creatinine, diuresis), and hemolytic anemia.

Study conduction: Patients (parents) will receive information on the ANACOMP study as soon as they have recrudescence of fever after the initial IVIG infusion of 2 g/kg. As soon as they have given their written informed consent, they will undergo screening tests ensuring fulfillment of inclusion and exclusion criteria. The inclusion visit may be done the same day and will take place since day 5 and no later than 11 days of illness to expect the full clinical effect of the study treatment. For randomization, the investigating doctor will connect to clean WEB and then will be assigned an anonymous number to the patient (refer to the patient identifier on the CRF). The experimental and control arm will be distributed in a 1:1 ratio. After the assignment, patients will

Table 2. ANACOMP study: the inclusion/exclusion criteria.

Inclusion criteria	Exclusion criteria
Children, male and female, from 3 months to<18 years old	Preterm and neonates, pregnancy
Patient ≥ 5 kg	Suspicion of another diagnosis
Patient with KD according to the American Heart Association definition for complete or incomplete KD	Patient with an overt concomitant bacterial infection
Patients who failed to respond to the standard therapy of KD, e.g. Persistence or recrudescence of fever ≥ 38°C, 48 hours after the infusion of 2g/kg of IV Ig	Patient previously treated with steroids and/or another biotherapy
Patient, parents, or legal guardian's written informed consent is required	Patient with increased risk of TB infection
Patient with health insurance	Recent tuberculosis infection or with active TB
	Patient with any type of immunodeficiency or cancer
	Patient with end-stage renal disease: patients with severe renal impairment (CLcr<30 ml/minute)
	Patient with hepatic insufficiency
	Patients with neutropenia (ANC<1.5 × 109/l)

Table 3. The related secondary objectives and endpoints for the evaluation of KD.

Secondary objectives	Secondary endpoints
Efficacy on fever at 72 h	Compare the Anakinra group with IVIG retreatment in terms of the temperature<38°C within 3 days (72 h) after initiation of treatment and the decrease of the CRP values from baseline to day 30
Efficacy on disease activity and on KD symptoms	Reduction in physician and patient's parent's assessment of disease activity, on a 10 points scale, of at least to 50% between baseline and day 14
Efficacy on KD symptoms	Assessment of malaise and other symptoms related to KD
Efficacy on coronary lesions (e.g.: dilatation and aneurysm)	Resolution of coronary abnormalities; i.e. worst Z score<2.5, by echocardiogram if present on day 45.
Efficacy on inflammation/Safety and tolerability	Monitoring of adverse events:
	Physical examination: Complete clinical exam will be performed at each visit to detect symptoms of KD (rash, cervical nodes, mucous lesions, extremities, GI, pulmonary, CV, neurologic, and muscular/joint evaluation) and possible associated morbidity: e.g. concomitant infection
	Local tolerability of injections: will be evaluated by a physician from V2 to V8: pain, redness, swelling, induration, itching, hemorrhage, (and quoted from none, mild, moderate, severe)
	Vital signs and body measurements: at each visit: V1 to V9. The body temperature will be measured daily until d30. Parents will receive a booklet.
	Laboratory evaluations: hematologic, hepatic, and renal assessment will be followed

receive either anakinra (4 mg/kg) sub cut or 2 g/kg of IVIG i. If the patient becomes again febrile after 12 hours interval of anakinra treatment, the investigator may increase the dose of 2 mg/kg, the same day if appropriate. During visits D1 and D2, if patients are still febrile with 12 hours* (H12) of treatment they will receive a supplementary dose of 2 mg/kg; otherwise, they will remain at a starting dose of 4 mg/kg. If they are still febrile at H24, they will receive a dose of 8 mg/kg; otherwise, they will maintain their dose of 6 mg/kg. Patients with temperature<38°C at any point between initiation and day 14, but who develop secondary fever due to KD could have further escalation dose of anakinra until a maximum dose of 8 mg/kg. The last administration of anakinra will occur at visit 7 (day 14). Evaluation of disease activity and tolerability of treatment will be evaluated in both groups. Patients can be discharged from the hospital at D4 in both groups if they are still afebrile (for at least 48 hours), CRP has decreased by at least 50% of the pre-treatment value, PGA has decreased by at least 50% of the pre-treatment value (by the parents and the physician) and upon agreement of the investigator. Either by parents or by a private nurse will administer the study treatment (anakinra) at home. The last visit will occur at D60 (± 5 days). In case of early termination, the patient will follow all the visits planned by the ANACOMP trial.

Sample size calculation and statistical analysis: We are expecting a 30% difference in the response rate between the experimental and control group (i.e. 80% response rate in the anakinra group and 50% response rate in the control group). Under the research hypothesis of 80% response rate versus a 50% and an equal allocation ratio of 1:1, we require 38 patients in each group (76 patients in total) in order to achieve 80% power. Since lost to follow are expected, the sample size was increased by 10%. Thus, 84 is the total number of scheduled patients in 13 French centers.

For each group and at each assessment date, qualitative variables will be described as number and percentage, and quantitative variables as a number, mean and standard deviation. Quantitative variables with skewed distribution will be presented as median and Interquartile Range (IQR). Comparison of outcome variables between the two groups such as proportions of the primary outcome, nature, and frequency of side effects or quality of life will be performed using parametric or non-parametric tests according to nature and the distributions of the variables. Categorical variables will be compared using the chi-square test or Fisher's exact test, and continuous variables will be compared using student's t-test or a non-parametric Wilcoxon-Mann-Whitney test, depending on their distribution. For the primary endpoint analysis, the response rate will be calculated after 48 hours of treatment and compared between the two groups. The univariate model will be performed using respectively demographics, clinical and biological variables as independent variables and body temperature less than 38°C within 3 days (yes/no) as the dependent variable. A multiple logistic regression analysis will then be performed using the backward analysis to risk factors of fever at 3 days. The multivariate logistic regression model will be

constructed using the parameters of the univariate analysis, which showed at least a trend toward significance, with a cut-off of p=0.2. Backward elimination will start with all candidate risk factors in the model and runs a sequence of statistical tests to remove them from or keep them in the model based on a nominal p-value (<0.05). All the other secondary analyses will be done on the ITT basis. Unless otherwise specifies, the statistical significance level is defined as p<0.05.

Expected results

As demonstrated in the animal model and previous proof of concept study; clinical trials NCT02390596, we expect a dramatic response on clinical symptoms and cardiac complications, when compared with second IVIG injection (still recommended by the AHA outside any level of evidence). Our study confirms these results; anakinra could be tested in the first line, where intensifying primary therapy is warranted. This will participate in the future in reducing early mortality and in improving global cardiac prognosis.

Discussion

KD is on many points an intriguing and potentially serious disease. Even almost endemic in certain parts of Asia, its incidence seems to increase in Western countries where disease diagnosis, predictability of prognosis, and response to standard treatment, remain challenging. IVIG in association with anti-inflammatory aspirin has considerably changed the cardiac outcome. Their immunomodulatory effects are diverse and the exact ways by which they rapidly control inflammation in KD are still misunderstood. In addition, as they are human plasma-derived products from thousands of healthy donors then, the composition of IVIG batches may vary in terms of antibodies repertory of interest, IVIG inhibits activation of monocytes and macrophages in both mice and humans and induces anti-inflammatory cytokines like IL-1 receptor antagonist (IL-1RA), TGF-β and IL-10 [29]. The mechanisms of response to IVIG, although poorly understood, could involve a dose effect, which would justify the interest of repeating a dose in case of initial unresponsiveness. Indeed, a retrospective Japanese study has shown that pre-IVIG and post-IVIG IgG levels correlated well with non-responders with statistical significance, suggesting that higher IgG levels have more immunomodulatory action [30]. Despite this observation, we do not have a valid clinical trial justifying IVIG retreatment is effective on KD's outcome. However, in clinical practice IVIG retreatment is widely used, and recommended by the AHA, justifying our choice to challenge it as standard therapy to compare with anakinra [3]. Kawasaki disease is an acute disease that can damage the vessels and heart tissue very quickly and for the long term, which requires prompt and effective treatment for all patients. Resistance to IVIG poses a major problem because it is not foreseeable in all cases, in particular, Japanese scores do not apply to other populations, and that it exposes to more cardiac complications [5,12]. Several therapeutic alternatives have been attempted added either to the first IVIG in selected high-risk patients in most cases or added after unresponsiveness to a first IVIG. Among them, the RAISE study in Japan demonstrated that in high-risk selected patients with KD, the addition of prednisolone to initial IVIG reduced the occurrence of coronary aneurysms to 3%, in comparison to 23% (CI 0.12-0.28, p<0.001), in patients treated with the standard therapy with IVIG alone [7]. None of the studies performed in unselected patients and using either corticoids or infliximab have demonstrated efficacy on coronary aneurysms. Interleukin 1 is a major cytokine of the innate immune system and data given from a mouse model of Lactobacillus casei induced vasculitis and immunologic studies, have evidence that it could be a robust therapeutic target in KD. Indeed, IL-1β together with IL-18 and TNF increase in the serum during the acute phase of KD [31]. In addition, increased transcript abundance of the neutrophil-associated calcium-binding proteins; S100A8 and A9 have confirmed the role of activated neutrophils in acute KD, as these proteins regulate adhesion of neutrophils and monocytes to the endothelial cell, a critical process in KD vasculitis [31]. Of interest, the human vasculature expresses the IL-1α precursor, which participates in neutrophils activation in KD. The mouse model of KD demonstrated a major role of the NLRP3 inflammasome as a source of IL-1β, and anakinra given 3 to 5 days prevented the vasculitis. In line with these experimental data, a number of patients with severe KD settings (myocarditis, macrophage activation syndrome, coronary aneurysms with IVIG, and corticoids resistance) evolved successfully under treatment with anakinra [18]. Taken together, all these data encourage pursuing investigational studies with anakinra in KD.

The ANACOMP study aims to confirm the results

of the KAWAKINRA study (https://clinicaltrials.gov/ct2/show/NCT02390596) which was an open-label single-arm study designed for patients with unresponsiveness to IVIG, and intended to provide a proof of concept, establishing an optimal effective dose and verifying the tolerability. Our study had shown that a median dose of 4 mg/kg could result in the abatement of fever in ¾ of patients in the ITT group and 87% in the PP group within 48 h of treatment by anakinra. In addition, the median CRP levels were 10 mg/L at day 7 and 5 mg/L at day 14 and were present, coronary abnormalities normalized in 50% of patients at day 45 [24]. The tolerability of anakinra was satisfactory and we did not observe any serious infection or death. This study had limitations due to the limited number of patients included, and essentially, because it was not comparative. To date, therapeutic trials aimed at improving the cardiac fate of KD have mainly added corticosteroids or biotherapies (essentially anti TNF) to the initial IVIG. The main part of these studies held in Japan in patients predefined at risk of resistance according to the Kobayachi criteria, which are not reliable in non-Asian populations [12]. Thus, comparing anakinra as an alternative to IVIG retreatment seemed to us the most suitable scheme for investigating its effectiveness and in line with the requirements of the ethics committee. In addition, such a study design allows for evaluating the efficacy of anakinra alone. The feasibility of the study will be ensured by the coordinating centers in Kremlin Bicêtre Hospital, which acts as a reference center in a living basin of 12 million inhabitants, and by the enrollment of 13 centers most of which have already participated in clinical studies on KD. With a large uncertainty on the percentage of response to IVIG retreatment that we evaluated 50%, we expect a superiority of 30% in the anakinra arm versus the IVIG arm. The primary and secondary objectives will be comparable to the KAWAKINRA study and the outcome measures as well.

Conclusion

Even the cause(s) and pathogenesis of KD are still unclear, it becomes evident that the innate immune system plays a pivotal role inducing the inflammatory phenotype, which is mostly interleukin 1 driven. Anakinra is a drug of choice because it can block both the IL-1α, the IL1β, and the IL receptor; its security profile is reasonable for short-term treatment and its short half-life allows it to be effectively and quickly suspended in case of a serious adverse event. The KAWAKINRA studies have shown effectiveness in reducing systemic inflammation and coronary dilatation but it will have a little practical impact if we do not go forward a comparative study. The ANACOMP trial will not only validate anakinra as second-line treatment after unresponsiveness to IVIG but will also open the window of comparative studies with IVIG on the first line in all patients.

Anakinra treatment is expected to enhance more frequently than IVIG retreatment a rapid and sustained effect on vascular inflammation.

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Executive summary

Background: Based on the auto-inflammatory pattern of Kawasaki Disease (KD), the most frequent and heart threatening vasculitis in children before five years, we hypothesize that anti-IL-1 blocking agents could bring a rapid and sustained effect on systemic and coronary inflammation in patients with KD.

Aims and primary objective: To compare the efficacy of anakinra (IL-1R1 receptor antagonist) with second IVIG infusion, in the second line, on fever in patients with KD, who failed to respond to the first infusion of IVIG.

Methods: A multicenter national, 60-day, the randomized controlled open-labeled trial of superiority running in two parallel groups in a 1:1 ratio to arm A: experimental strategy (anakinra) or arm B: control strategy (IV IG + standard care). In arm A, patients will receive anakinra, at a starting dose of 4 mg/kg. Up to H36, the dose of anakinra will be increased every 12h if the patients have fever >38°C, and up to a maximum of 8 mg/kg. The main criterion-evaluating efficacy in both groups is an abatement of fever <38˚C within 2 days after initiation of treatment, a decrease of the CRP values from baseline to day 30, reduction in physician and patient's parent's assessment of disease activity of at least to 50% between baseline and day 14, and treatment tolerability. In addition, we will assess the resolution of coronary abnormalities; i.e. worst Z score <2.5, by echocardiogram if present on day 45.

Conclusion: Anakinra treatment is expected to enhance more frequently than IVIG retreatment a rapid and sustained effect on vascular inflammation.

References

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