Contemporary Clinical Trials 48 (2016) 70–75

Contents lists available at ScienceDirect

Contemporary Clinical Trials

journal homepage: www.elsevier.com/locate/conclintrial

Rationale and study design for a phase I/IIa trial of anakinra in children with Kawasaki disease and early coronary artery abnormalities (the ANAKID trial)

Adriana H. Tremoulet [a,b,*], Sonia Jain [c], Susan Kim [d], Jane Newburger [e,f], Moshe Arditi [g,h], Alessandra Franco [i], Brookie Best [i,j], Jane C. Burns [a,b]

[a] Kawasaki Disease Research Center, Department of Pediatrics, University of California San Diego, La Jolla, CA, USA
[b] Rady Children's Hospital San Diego, San Diego, CA, USA
[c] Biostatistics Research Center, Department of Family Medicine and Public Health, University of California San Diego, La Jolla, CA, USA
[d] Rheumatology Program, Division of Immunology, Boston Children's Hospital, Boston, MA, USA
[e] Department of Cardiology, Harvard Medical School, Boston, MA, USA
[f] Department of Pediatrics, Children's Hospital of Boston, Boston, MA, USA
[g] Department of Pediatrics, Cedars Sinai Medical Center, USA
[h] UCLA School of Medicine, USA
[i] Department of Pediatrics, University of California San Diego, La Jolla, CA, USA
[j] Skaggs School of Pharmacy, La Jolla, CA, USA

ARTICLE INFO

Article history:
Received 16 December 2015
Received in revised form 27 March 2016
Accepted 5 April 2016
Available online 11 April 2016

Keywords:
Anakinra
Interleukin 1
Kawasaki disease
Coronary artery aneurysm

ABSTRACT

Background: Although Kawasaki disease (KD) is the most common cause of acquired heart disease in children and may result in coronary artery aneurysms (CAA) with an attendant risk of myocardial infarction, there is no recommended therapy to halt progression of arterial wall damage and prevent aneurysm formation in the acute phase of the vasculitis. While intravenous immunoglobulin (IVIG) reduces the risk of CAA, up to 20% of KD patients are IVIG resistant and have a higher risk for developing CAA. The IL-1 pro-inflammatory pathway is upregulated in children with acute KD and plays a critical role in the experimental animal model of KD. Thus, IL-1 is a logical therapeutic target.
Objectives: The goal of this study is to determine the safety, tolerability, pharmacokinetics, and immunomodulatory effects of anakinra, a recombinant human IL-1 receptor antagonist, in acute KD patients with coronary artery abnormalities on the baseline echocardiogram.
Design: This is a two-center dose-escalation Phase I/IIa trial in 30 acute KD patients ≥8 months old with a coronary artery Z score ≥ 3.0 in the right coronary artery and/or left anterior descending artery or an aneurysm. Subjects will receive a 2- to 6-week course of anakinra by daily subcutaneous injection and will be assessed for resolution of inflammation and dose limiting toxicities (leukopenia, anaphylactoid reaction, or severe infection).
Conclusion: The safety and tolerability of blocking both IL-1α and Il-1β by anakinra will be evaluated as a strategy to prevent or attenuate coronary artery damage in infants and children with acute KD.
Trial registration: Clinical Trials.gov # NCT02179853, registered June 28, 2014

1. Introduction and rationale

Kawasaki disease (KD), the most common cause of acquired heart disease in children in Western developed countries and Asia, is a systemic vasculitis of unknown etiology. KD causes both a myocarditis and a vasculitis that damages the coronary arteries and other medium-sized muscular arteries leading to the formation of aneurysms [49,53]. The major sequelae of aneurysms include thrombosis, late coronary artery stenosis, myocardial ischemia, myocardial infarction, and death [10,15,27]. Treatment with intravenous immunoglobulin (IVIG) reduces the risk of aneurysm formation from 25% to 5% [31]. However, for patients with IVIG-resistance, the risk of aneurysms increases 3- fold [51]. Currently, there is no recommended therapy beyond IVIG to halt the progression of arterial wall damage and prevent aneurysm formation. Since aneurysm prevention is a primary goal of treatment during the acute phase of KD, we have focused on intensification of therapy for patients with early coronary artery abnormalities (CAA) detected by transthoracic echocardiography.

In the KD mouse model, in which a coronary artery vasculitis, aortitis, and myocarditis are induced with an intraperitoneal injection

* Corresponding author at: Department of Pediatrics, UCSD School of Medicine, 9500 Gilman Dr. Mail Code 0641, La Jolla, CA 92093-0641, USA.
E-mail address: atremoulet@ucsd.edu (A.H. Tremoulet).

http://dx.doi.org/10.1016/j.cct.2016.04.002
1551-7144/

of a cell wall extract from *Lactobacillus casei* (LCWE), mice exhibit systemic inflammation, increased body temperature, and elevated levels of IL-1β [22,45,52]. This LCWE-induced vasculitis occurs through the IL-1R signaling pathway via MyD88 in wild-type C57BL/6 but not IL-1R knockout mice [19,20,41]. Studies to evaluate the effects of IL-1 blockade with anakinra in the LCWE KD mouse model have demonstrated clear benefit with reduction in inflammation. In addition, IL-1 related genes are upregulated in KD peripheral blood during acute phase of illness [11].

Given the data supporting the role of IL-1 in the systemic inflammatory response in KD, we have chosen to pursue blocking of the IL-1 pathway in children with acute KD with anakinra, which competitively inhibits IL-1 binding to the IL-1 type 1 receptor. The rationale for choosing anakinra over other agents includes the rapid onset of IL-1 blockade, the ability to block both IL-1α and β, the excellent safety profile in young infants and children, and the short half-life in case of infectious disease complications (Table 1).

2. Objectives

The goal of this study is to determine the safety, pharmacokinetics, and activity of anakinra in acute KD patients at least 8 months of age with a coronary artery Z score (internal dimension of the coronary artery normalized for body surface area and expressed as standard deviations from the mean) ≥ 3.0 in the right coronary artery (RCA) and/or left anterior descending (LAD) artery. This study is viewed as preparatory to a Phase III trial of anakinra to prevent or attenuate coronary artery damage in acute KD.

3. Study design

This two-center dose-escalation Phase I/IIa trial (See Dose Levels Table 2) will determine the safety, tolerability and immunomodulatory effects of anakinra in 30 acute KD patients at least 8 months old with CAA. The enrollment age limit is a condition of our IND and was imposed by the FDA until safety data for KD could be reviewed after completion of this trial. Enrollment will occur at two study sites: Rady Children's Hospital San Diego and Children's Hospital of Boston.

All subjects will be treated with IVIG, 2 g/kg and aspirin (30–50 mg/kg/day divided every 6 h; lowered to 3–5 mg/kg/day at the time of discharge or when afebrile for 48 h, whichever comes first), which is the standard of care. The first two doses of anakinra will be administered intravenously (i.e. 4 mg/kg/day will be 2 mg/kg IV every 12 h for two doses) to ensure rapid drug effect and minimize discomfort related to medication administration in subjects. Anakinra will be administered intravenously by bolus over a 1 to 3 min period [35]. All subsequent doses will be administered once daily subcutaneously starting 24 h after the first dose of the medication. Treatment-resistance will be defined as persistent or recrudescent fever (T ≥ 38.0 °C orally or rectally) ≥36 h and <7 days following end of IVIG infusion ([51]. Subjects who meet criteria for treatment-resistance will be treated at the Center PI's discretion.

Table 2
Dose levels.

Dose cohort	Dose level	Number of subjects
1	4 mg/kg/day	3–6
2	6 mg/kg/day	3–6
3	8 mg/kg/day	3–6
Total		9–18[a]

[a] A total of 30 subjects will be enrolled in this study. Once the maximum tolerated dose (MTD) is determined, all remaining subjects will be enrolled at the MTD.

All subjects will receive at least 2 weeks of therapy. Only subjects with an echocardiogram at 2 weeks that shows either an LAD or RCA Z score ≥ 2.5 or an aneurysm (≥1.5 × the adjacent segment) of one of the coronary arteries will receive an additional 4-week course of anakinra. Although the inclusion criteria is a Z score ≥ 3.0, we consider a vessel with a Z score ≥ 2.5 two weeks after enrollment to be sufficiently abnormal to continue anakinra. All subjects will remain on study for the full 6 weeks whether or not they are receiving anakinra.

The dose-escalation protocol will enroll a minimum of three subjects per dose level (Table 2). A maximum of 100 mg/day will be administered. The 3 + 3 dose escalation design uses the number of dose limiting toxicities to determine the maximum tolerated dose (Table 3).

All patients will be evaluated at baseline as well as 48 h and 2 and 6 weeks after enrollment (Fig. 1). Relevant medical course, vital signs, and physical examination will be recorded. Pharmacokinetic samples will be taken at 2, 5 and 8 h after the first IV dose of the medication and trough samples will be collected at 48 h and 2 and 6 weeks (if still taking anakinra). Subjects will be monitored for adverse events and serious adverse events, and at 2 and 6 weeks will be assessed for a dose limiting toxicity, defined as a serious infection qualifying as a serious adverse event and requiring intervention, a decrease in the white blood cell count to $<1500/mm^3$ (Grade 3 severity by NIH/NIAID) [33] or an anaphylactoid reaction to an injection of anakinra. To assess for compliance with the study medication, the number of syringes dispensed as well as the remaining number of syringes at each study visit will be recorded. Echocardiograms will be performed at 2 and 6 weeks and read by a single cardiologist blinded to clinical and treatment status of the subjects. Additional echocardiograms for the clinical care of the subject will be at the discretion of the center investigator. The following testing will be performed on all subjects at baseline (pre-anakinra), 48 h, 2 and 6 weeks after study entry: levels of hsCRP, α1-antitrypsin and fibrinogen, and white blood cell count. The erythrocyte sedimentation rate (ESR) will be measured at baseline, 2 and 6 weeks. Subjects will be assessed for compliance with the study medication at the 2 and 6 week visit.

Table 1
Justification for selecting anakinra to block the IL-1 pathway in KD.

	Pros	Cons
Anakinra	• Blocks both IL-1α and IL-1β • Approved in infants with severe autoinflammatory diseases (no lower age limit) • Substantial use and proven safety in infants and young children • Rapid anti-inflammatory effect: peak plasma levels within hours of administration [54] • Short half-life and immunosuppression	• Daily subcutaneous injection
Rilonacept	• Blocks both IL-1α and IL-1β	• Approved only for children age 12 and older • Delayed response to treatment: median 4 weeks for clinical response in sJIA trial [54]
Canakinumab	• Requires only q 2–3 month SQ injections	• Only blocks IL-1β (IL-1α likely plays a role in KD pathogenesis) • Approved for children 2 years and older with sJIA and 4 years and older with severe autoinflammatory diseases • Prolonged immunosuppression

sJIA, systemic juvenile idiopathic arthritis.