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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)

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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

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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.

Table 3
Dose escalation decision rules.

Subjects with a DLT at a given dose	Escalation decision rule
0 out of 3	Enter 3 patients at the next dose level until maximum tolerated dose.
1 out of 3	Enter a total of 6 patients at this dose level. • If 0 of these additional patients experience a DLT, proceed to the next dose level. • If 1 of these additional patients experiences a DLT, then dose escalation is stopped (see below).
≥2	At least 3 additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose. This lower dose level will be declared the MTD.

DLT = dose limiting toxicity; A DLT is defined as any of the following at the 2 or 6 week time point: (1) Serious infection qualifying as a serious adverse event and requiring intervention; (2) a decrease in the white blood cell count to $<1500/mm^3$ (Grade 3 severity by NIH/NIAID) [33]; (3) an anaphylactoid reaction to an injection of anakinra. MTD = maximum tolerated dose; the MTD is defined as the highest dose of anakinra studied at which no more than on in six subjects experiences a DLT during the 6 weeks of treatment.

4. Inclusion and exclusion criteria

Infants and children at least 8 months of age (age limited by Food and Drug Administration) within the first 20 days after fever onset who meet American Heart Association criteria for KD and have a Z

Table 4
Inclusion and exclusion criteria.

Inclusion criteria:

1. Infant or child aged 8 months to 17 years, who meets clinical criteria for KD according to American Heart Association guidelines: Fever (T ≥ 38 °C or 100.4 °F) ≥ 3 days and ≥2 clinical criteria with left anterior descending (LAD) and/or right coronary artery (RCA) Z score ≥ 3.0 or an aneurysm (≥1.5 × the adjacent segment) of one of the coronary artery segments
   a. Clinical criteria for KD include: (1) Bilateral conjunctival injection, (2) changes of the mucous membranes of the upper respiratory tract: injected pharynx, injected, fissured lips, strawberry tongue; (3) changes of the peripheral extremities: peripheral edema, peripheral erythema, periungual desquamation; (4) polymorphous rash; and (5) cervical adenopathy >1.5 cm
2. Patient presents within the first 20 days after fever onset
3. Parent or legal guardian able and willing to provide informed consent; adolescent or child assent as appropriate
4. Post-menarchal females: Negative pregnancy test at screening and willing to use two forms of contraception during the study
5. Males engaging in sexual activity that could lead to pregnancy willing to use a condom.

Exclusion criteria:

1. Use of an IL-1 antagonist within the 3 months prior to enrollment
2. History of chronic disease, except asthma, atopic dermatitis, autism or controlled seizure disorder
3. History of hypersensitivity to anakinra
4. History of tuberculosis (TB) or TB exposure
5. Active, culture-positive bacterial infection

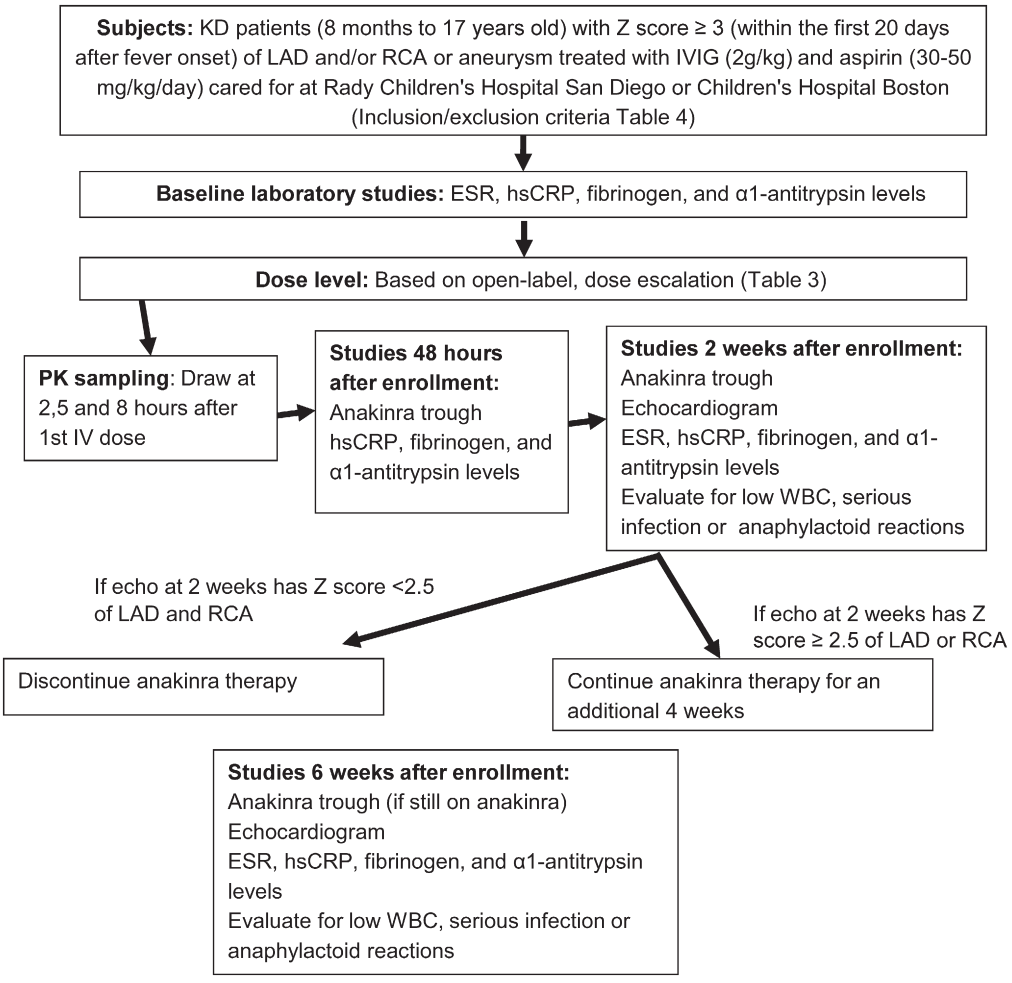

Fig. 1. Legend: Study design and flow LAD, left anterior descending coronary artery; RCA, right coronary artery; IVIG, intravenous immunoglobulin; WBC, white blood cell count; hsCRP, high sensitivity C-reactive protein; ESR, erythrocyte sedimentation rate; PK, pharmacokinetic.

score of ≥3.0 of the LAD and/or RCA or an aneurysm are study eligible (Table 4). Subjects with an active, culture-positive bacterial infection will be excluded.

5. Primary and secondary endpoints

The primary endpoint of the study is safety and tolerability of anakinra in the study population. The pre-specified secondary endpoints are the pharmacokinetics of anakinra, the changes in echocardiographic assessment of the internal diameters of the coronary arteries expressed as Z scores over the course of the study, and the change in biomarkers of inflammation including levels of hsCRP, α1-antitrypsin and fibrinogen, and the WBC and ESR. Innate immune cells and T cells will be studied prior to therapy and 2 and 6 weeks after therapy. Plasma and transcript levels of relevant cytokines and IL-1 pathway molecules, including IL-17, tumor necrosis factor (TNF)αR1 and R2, IL-8, IL-27, IFNg, sIL-1R1 and R2, IL-6, sIL-6R, and IL-10 will be assessed.

6. Ethics and informed consent

The study protocol was reviewed and approved by the Institutional Review Board at the University of California San Diego and Boston Children's Hospital. Written informed consent will be obtained from the parents or legal guardians and assent, when appropriate, will be obtained from the patient. This trial is registered with clinicaltrials.gov (NCT02179853).

7. Statistical methods

7.1. Data analysis

All enrolled subjects at the maximum tolerated dose will be included in a case:control study and matched with historical controls from each center for age, sex, illness day, adjunctive therapies in addition to IVIG, and the worst coronary artery Z score for the RCA and LAD on the initial, pre-treatment echocardiogram. Measures of inflammation, including hsCRP, ESR and WBC, at two weeks will be compared to that of matched controls via paired statistical tests (e.g. McNemar's test for categorical outcomes or the paired *t*-test for continuous outcomes). Non-parametric alternatives will be considered only if distributional assumptions are violated. Each marker will be initially summarized descriptively and analyzed individually. Separate multivariable mixed models repeated measures for clustered data (to account for the case-control paired nature of samples and repeated measures over time) will be used to characterize the markers of anakinra-treated subjects versus matched controls to adjust for any known confounders and additional time points (baseline, 48 h, 2 weeks, and 6 weeks).

7.2. Sample size

This Phase I/IIa trial is not powered to show a difference in coronary artery dimensions or treatment response compared to controls. Instead, the sample size was determined based on detectable differences in inflammatory markers. A sample size of 30 KD patients treated with anakinra and 30 matched controls will have 80% power based on a two-sided, paired *t*-test with alpha set to 0.05 to compare the change from baseline to two weeks in several inflammatory markers, including α-1-antitrypsin and hsCRP.

8. Discussion

Despite timely treatment with high dose IVIG and aspirin, some infants and children with KD develop CAA. However, there is no recommended therapy to halt the progression of arterial wall damage and prevent aneurysm formation. Thus, aneurysm prevention is a primary goal of treatment during the acute phase of the disease and is the focus of this trial. Data from both animal studies and evaluation of the IL-1 pathway in patients with acute KD support IL-1 blockade as a therapeutic option.

Studies in the LCWE-induced mouse model of KD vasculitis have shown that the NLRP3 inflammasome, caspase 1 activation and IL-1β and IL-1α are important in KD vasculitis [19–21,41]. The IL-1 R antagonist, anakinra, which blocks both IL-1α and IL-1β, significantly blocked coronary arteritis, aortitis and myocarditis in this experimental model [19,20].

In KD, the interleukin (IL)-1 pathway is upregulated, as demonstrated by increased transcript abundance by microarray and by increased levels of pathway proteins in the plasma [11,23,26,37]. In a microarray study of acute and convalescent whole blood samples (PAXgene®) from 141 KD subjects, transcript abundance profiles from KD patients were compared to those of pediatric subjects with different acute infectious diseases and to pediatric healthy controls [11]. Differentially expressed transcripts were analyzed according to their participation in different biologic pathways. Common features of the top three pathways for KD were the abundance of transcripts related to the activation of the NLRP3 inflammasome, including IL-1α and β and caspase-1- related transcripts. The upregulation of key genes in the IL-1 pathway was validated using qRT-PCR in an independent cohort of 20 KD patients and 10 healthy controls [11]. IL-1α also plays a critical role in chronic inflammation, and recent studies suggest that IL-1α may regulate IL-1β secretion [6–8,14]. It is intriguing that, IL-1 signaling drives proliferation of smooth muscle cells (SMC) and myofibroblast formation [2,3,44], a pathologic hallmark of subacute arteriopathy seen in KD.

Recent genome wide association studies have identified several risk loci and polymorphisms in patients with KD. Among, these, the SNPs in the inositol-trisphosphate 3-kinase C (ITPKC) gene were the most strongly associated polymorphisms with KD in both Japanese and US children [17,24,34]. Importantly, ITPKC regulates Ca^{2+} influx in the cell, and this mutation leads to sustained elevation of intracellular Ca^{2+}, which is known to induce NLRP3 inflammasome activation [13,18,29,38]. The convergence of emerging genetic data with the findings that IL-1 signaling plays a crucial role in the experimental mouse model of KD, as well as the IL-1 pathway being upregulated in KD patients, provide a strong rationale for our hypothesis that IL-1 signaling plays a key role in KD vasculitis and coronary arteritis.

Anakinra is currently used in several inflammatory diseases in infants and children, including systemic juvenile idiopathic arthritis and many of the autoinflammatory syndromes including cryopyrin-associated periodic syndromes (CAPS) and tumor necrosis factor receptor-associated periodic syndrome (TRAPS) [9,12,40]. In a recent study of 26 patients with the autoinflammatory syndrome neonatal-onset multisystem inflammatory disease (NOMID), treatment with anakinra for 36 months had a low adverse event rate, with upper respiratory infection as the most commonly reported complication [47]. A similar study using anakinra in another autoinflammatory disorder, Muckle Wells syndrome, did not demonstrate any serious adverse events in the 12 patients treated with anakinra for a median of 11 months (range 5–14 months), of whom 5 were children [16].

At least 52 pregnant women, infants and children <2 years of age have been treated with anakinra with doses ranging from 1 to 20 mg/kg without serious adverse events [1,4,5,12,25,28,30,32,36,39,42,43,46–48]. In addition, through an informal survey of rheumatologists belonging to the Childhood Arthritis and Rheumatology Research Alliance (CARRA) Network, I was notified of an additional 10 infants (2 to 11 months old) who received anakinra (maximum dose ranging from 3 to 9 mg/kg) for inflammatory disorders without major adverse events. Thus, given the established safety of anakinra in young infants and children with inflammatory disorders, a Phase I/IIa study that evaluates safety, tolerability, and immunomodulatory effects in infants and children with acute KD and CAA is justified.

Anakinra has been used to treat three severe KD patients who were resistant to IVIG treatment [5,46,50]. A 2 year old with giant aneurysms

who failed therapy with IVIG and steroids was treated with a 6 week course of anakinra at 1 mg/kg [5]. She suffered no adverse effects and at 6 months coronary angiography demonstrated resolution of the aneurysms, which was unexpected in such a severe case of KD. An 11 week old with KD and giant aneurysms was refractory to three doses of IVIG, steroids and a dose of infliximab [46]. She was treated with anakinra initially at 6 mg/kg/day and then increased to 9 mg/kg/day. She too did not suffer any adverse effects and at an 8 month follow up visit her coronary artery status had also significantly improved. At our center, we treated a 2 month old White female infant who presented with a one week history of fever, classic signs of KD, and dilation of the left main coronary artery and left anterior descending coronary artery as well as an aneurysm of the right coronary artery (Z score max 8.2) by echocardiography. Given the severity of this infant's illness, we added anakinra (2 mg/kg/day) on the eighth day of illness for five days. Unexpectedly, tissue remodeling, evidenced by decreasing Z score of the RCA, was documented within a month following anakinra treatment. In these three KD patients with CAA, treatment with anakinra did not result in any adverse events and coincided with a decrease in systemic inflammation and coronary artery dimensions.

The 3 + 3 study design allows a rapid escalation through three dosage levels while providing valuable data for PK analysis to inform the choice of dose for a subsequent Phase III efficacy trial. No assumptions are made about the dose/toxicity relationship and the design avoids exposing too many subjects to sub-optimal doses while preserving safety considerations for the toxicity endpoint. This adaptive study design is particularly well-suited to Phase I/II trials enrolling patients with rare or uncommon diseases for which the numbers of study-eligible subjects are limited but the trial requires rapid accrual. This dose finding scheme is a common approach in Phase I oncology trials given its simple design with defined stopping rules for escalation.

There are several strengths and limitations of this study. This is the first clinical trial to target the innate immune response to block progression of arterial wall damage in acute KD patients.

Although enrollment can frequently be a major issue in KD clinical trials, our experience is that families in this setting are interested in participating in research that might help improve the future treatment and understanding of this uncommon condition. Obtaining permission from parents for phlebotomy is always a potential hurdle in any clinical trial. We have timed the research phlebotomy to coincide, as much as possible, with clinically-indicated phlebotomy to improve parent acceptance. The choice of a Z score of 3.0 as entrance criterion was based on our experience with 103 KD patients with CAA at Rady Children's Hospital San Diego. Of these patients, 8 of 43 (or approximately 1 in 6 patients) with a Z score ≥ 3 went on to develop an aneurysm. This cut-point had a higher proportion of KD patients with an aneurysm than a Z score of 2.5 for which only 11 of 103 (or approximately 1 in 10 patients) developed an aneurysm. Thus, in order to capture a large proportion of the children who would develop an aneurysm yet limit the number of children treated with anakinra, we chose a cut-point Z score of 3. There is currently no robust biomarker to identify patients at risk for aneurysm development.

9. Conclusion

Thus, this dose-escalation Phase I/IIa trial will determine the safety, tolerability and immunomodulatory effects of anakinra in KD patients at least 8 months of age.

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References

[1] I. Aksentijevich, S.L. Masters, P.J. Ferguson, P. Dancey, J. Frenkel, A. van Royen-Kerkhoff, R. Laxer, U. Tedgard, E.W. Cowen, T.H. Pham, M. Booty, J.D. Estes, N.G. Sandler, N. Plass, D.L. Stone, M.L. Turner, S. Hill, J.A. Butman, R. Schneider, P. Babyn, H.I. El-Shanti, E. Pope, K. Barron, X. Bing, A. Laurence, C.C. Lee, D. Chapelle, G.I. Clarke, K. Ohson, M. Nicholson, M. Gadina, B. Yang, B.D. Korman, P.K. Gregersen, P.M. van Hagen, A.E. Hak, M. Huizing, P. Rahman, D.C. Douek, E.F. Remmers, D.L. Kastner, R. Goldbach-Mansky, An autoinflammatory disease with deficiency of the interleukin-1-receptor antagonist, N. Engl. J. Med. 360 (23) (2009) 2426–2437.

[2] M.R. Alexander, C.W. Moehle, J.L. Johnson, Z. Yang, J.K. Lee, C.L. Jackson, G.K. Owens, Genetic inactivation of IL-1 signaling enhances atherosclerotic plaque instability and reduces outward vessel remodeling in advanced atherosclerosis in mice, J. Clin. Invest. 122 (1) (2012) 70–79.

[3] P.D. Bonin, G.J. Fici, J.P. Singh, Interleukin-1 promotes proliferation of vascular smooth muscle cells in coordination with PDGF or a monocyte derived growth factor, Exp. Cell Res. 181 (2) (1989) 475–482.

[4] Z. Chang, C.Y. Spong, A.A. Jesus, M.A. Davis, N. Plass, D.L. Stone, D. Chapelle, P. Hoffmann, D.L. Kastner, K. Barron, R.T. Goldbach-Mansky, P. Stratton, Anakinra use during pregnancy in patients with cryopyrin-associated periodic syndromes (CAPS), Arthritis Rheum. 66 (11) (2014) 3227–3232.

[5] S. Cohen, C.E. Tacke, B. Straver, N. Meijer, I.M. Kuipers, T.W. Kuijpers, A child with severe relapsing Kawasaki disease rescued by IL-1 receptor blockade and extracorporeal membrane oxygenation, Ann. Rheum. Dis. 71 (12) (2012) 2059–2061.

[6] C.A. Dinarello, A. Simon, J.W. van der Meer, Treating inflammation by blocking interleukin-1 in a broad spectrum of diseases, Nat. Rev. Drug Discov. 11 (8) (2012) 633–652.

[7] A. Fettelschoss, M. Kistowska, S. LeibundGut-Landmann, H.D. Beer, P. Johansen, G. Senti, E. Contassot, M.F. Bachmann, L.E. French, A. Oxenius, T.M. Kündig, Inflammasome activation and IL-1β target IL-1α for secretion as opposed to surface expression, Proc. Natl. Acad. Sci. U. S. A. 108 (44) (2011) 18055–18060.

[8] S. Freigang, F. Ampenberger, A. Weiss, T.D. Kanneganti, Y. Iwakura, M. Hersberger, M. Kopf, Fatty acid-induced mitochondrial uncoupling elicits inflammasome-independent IL-1α and sterile vascular inflammation in atherosclerosis, Nat. Immunol. 14 (10) (2013) 1045–1053.

[9] R. Goldbach-Mansky, N.J. Dailey, S.W. Canna, A. Gelabert, J. Jones, B.I. Rubin, H.J. Kim, C. Brewer, C. Zalewski, E. Wiggs, S. Hill, M.L. Turner, B.I. Karp, I. Aksentijevich, F. Pucino, S.R. Penzak, M.H. Haverkamp, L. Stein, B.S. Adams, T.L. Moore, R.C. Fuhlbrigge, B. Shaham, J.N. Jarvis, K. O'Neil, R.K. Vehe, L.O. Beitz, G. Gardner, W.P. Hannan, R.W. Warren, W. Horn, J.L. Cole, S.M. Paul, P.N. Hawkins, T.H. Pham, C. Snyder, R.A. Wesley, S.C. Hoffmann, S.M. Holland, J.A. Butman, D.L. Kastner, Neonatal-onset multisystem inflammatory disease responsive to interleukin-1beta inhibition, N. Engl. J. Med. 355 (6) (2006) 581–592.

[10] J.B. Gordon, A.M. Kahn, J.C. Burns, When children with Kawasaki disease grow up myocardial and vascular complications in adulthood, J. Am. Coll. Cardiol. 54 (21) (2009) 1911–1920.

[11] L.T. Hoang, C. Shimizu, L. Ling, A.N. Naim, C.C. Khor, A.H. Tremoulet, V. Wright, M. Levin, M.L. Hibberd, J.C. Burns, Global gene expression profiling identifies new therapeutic targets in acute Kawasaki disease, Genome Med. 6 (11) (2014) 541.

[12] H.M. Hoffman, Therapy of autoinflammatory syndromes, J. Allergy Clin. Immunol. 124 (6) (2009) 1129–1138 quiz 1139-1140.

[13] T. Horng, Calcium signaling and mitochondrial destabilization in the triggering of the NLRP3 inflammasome, Trends Immunol. (2014).

[14] Y. Kamari, A. Shaish, S. Shemesh, E. Vax, I. Grosskopf, S. Dotan, M. White, E. Voronov, C.A. Dinarello, R.N. Apte, D. Harats, Reduced atherosclerosis and inflammatory cytokines in apolipoprotein-E-deficient mice lacking bone marrow-derived interleukin-1α, Biochem. Biophys. Res. Commun. 405 (2) (2011) 197–203.

[15] H. Kato, T. Sugimura, T. Akagi, N. Sato, K. Hashino, Y. Maeno, T. Kazue, G. Eto, R. Yamakawa, Long-term consequences of Kawasaki disease. A 10- to 21-year follow-up study of 594 patients, Circulation 94 (6) (1996) 1379–1385.

[16] J.B. Kuemmerle-Deschner, P.N. Tyrrell, I. Koetter, H. Wittkowski, A. Bialkowski, N. Tzaribachev, P. Lohse, A. Koitchev, C. Deuter, D. Foell, S.M. Benseler, Efficacy and safety of anakinra therapy in pediatric and adult patients with the autoinflammatory Muckle-Wells syndrome, Arthritis Rheum. 63 (3) (2011) 840–849.

[17] H.-C. Kuo, Y.-W. Hsu, M.-H. Lo, Y.-H. Huang, S.-C. Chien, W.-C. Chang, Single-nucleotide polymorphism rs7251246 in ITPKC is associated with susceptibility and coronary artery lesions in Kawasaki disease, PLoS One 9 (3) (2014), e91118.

[18] G.-S. Lee, N. Subramanian, A.I. Kim, I. Aksentijevich, R. Goldbach-Mansky, D.B. Sacks, R.N. Germain, D.L. Kastner, J.J. Chae, The calcium-sensing receptor regulates the NLRP3 inflammasome through Ca(2+) and cAMP, Nature (2012).

[19] Y. Lee, D.J. Schulte, K. Shimada, S. Chen, T.R. Crother, N. Chiba, M.C. Fishbein, T.J. Lehman, M. Arditi, Interleukin-1beta is crucial for the induction of coronary artery inflammation in a mouse model of Kawasaki disease, Circulation 125 (12) (2012) 1542–1550.

[20] Y. Lee, D.J. Schulte, K. Shimada, S. Chen, T.R. Crother, N. Chiba, M.C. Fishbein, T.J. Lehman, M. Arditi, Interleukin-1β is crucial for the induction of coronary artery inflammation in a mouse model of Kawasaki disease, Circulation 125 (12) (2012) 1542–1550.

[21] Y. Lee, D. Wakita, J. Dagvadorj, K. Shimada, S. Chen, G. Huang, T.J. Lehman, M.C. Fishbein, H.M. Hoffman, T.R. Crother, M. Arditi, IL-1 signaling is critically required in stromal cells in Kawasaki disease vasculitis mouse model: role of both IL-1alpha and IL-1beta, Arterioscler. Thromb. Vasc. Biol. 35 (12) (2015) 2605–2616.
[22] T.J. Lehman, S.M. Walker, V. Mahnovski, D. McCurdy, Coronary arteritis in mice following the systemic injection of group B *Lactobacillus casei* cell walls in aqueous suspension, Arthritis Rheum. 28 (6) (1985) 652–659.
[23] D.Y. Leung, R.S. Cotran, E. Kurt-Jones, J.C. Burns, J.W. Newburger, J.S. Pober, Endothelial cell activation and high interleukin-1 secretion in the pathogenesis of acute Kawasaki disease, Lancet 2 (8675) (1989) 1298–1302.
[24] J. Lou, S. Xu, L. Zou, R. Zhong, T. Zhang, Y. Sun, X. Lu, L. Liu, C. Li, L. Wang, G. Xiong, W. Wang, F. Gong, J. Wu, A functional polymorphism, rs28493229, in ITPKC and risk of Kawasaki disease: an integrated meta-analysis, Mol. Biol. Rep. (2012).
[25] T. Matsubara, M. Hasegawa, M. Shiraishi, H.M. Hoffman, T. Ichiyama, T. Tanaka, H. Ueda, T. Ishihara, S. Furukawa, A severe case of chronic infantile neurologic, cutaneous, articular syndrome treated with biologic agents, Arthritis Rheum. 54 (7) (2006) 2314–2320.
[26] C.P. Maury, E. Salo, P. Pelkonen, Circulating interleukin-1 beta in patients with Kawasaki disease, N. Engl. J. Med. 319 (25) (1988) 1670–1671.
[27] B.W. McCrindle, Kawasaki disease: a childhood disease with important consequences into adulthood, Circulation 120 (1) (2009) 6–8.
[28] K. Minkis, I. Aksentijevich, R. Goldbach-Mansky, C. Magro, R. Scott, J.G. Davis, N. Sardana, R. Herzog, Interleukin 1 receptor antagonist deficiency presenting as infantile pustulosis mimicking infantile pustular psoriasis, Arch. Dermatol. 148 (6) (2012) 747–752.
[29] T. Murakami, J. Ockinger, J. Yu, V. Byles, A. McColl, A.M. Hofer, T. Horng, Critical role for calcium mobilization in activation of the NLRP3 inflammasome, Proc. Natl. Acad. Sci. (2012).
[30] B. Neven, I. Marvillet, C. Terrada, A. Ferster, N. Boddaert, V. Couloignier, G. Pinto, A. Pagnier, C. Bodemer, B. Bodaghi, M. Tardieu, A.M. Prieur, P. Quartier, Long-term efficacy of the interleukin-1 receptor antagonist anakinra in ten patients with neonatal-onset multisystem inflammatory disease/chronic infantile neurologic, cutaneous, articular syndrome, Arthritis Rheum. 62 (1) (2010) 258–267.
[31] J.W. Newburger, M. Takahashi, J.C. Burns, A.S. Beiser, K.J. Chung, C.E. Duffy, M.P. Glode, W.H. Mason, V. Reddy, S.P. Sanders, et al., The treatment of Kawasaki syndrome with intravenous gamma globulin, N. Engl. J. Med. 315 (6) (1986) 341–347.
[32] P.A. Nigrovic, M. Mannion, F.H. Prince, A. Zeft, C.E. Rabinovich, M.A. van Rossum, E. Cortis, M. Pardeo, P.M. Miettunen, G. Janow, J. Birmingham, A. Eggebeen, E. Janssen, A.I. Shulman, M.B. Son, S. Hong, K. Jones, N.T. Ilowite, R.Q. Cron, G.C. Higgins, Anakinra as first-line disease-modifying therapy in systemic juvenile idiopathic arthritis: report of forty-six patients from an international multicenter series, Arthritis Rheum. 63 (2) (2011) 545–555.
[33] NIH and DAIDS. (2009). "Division of AIDS table for grading the severity of adult and pediatric adverse events." from http://www.niaid.nih.gov/LabsAndResources/resources/DAIDSClinRsrch/Documents/daidsaegradingtable.pdf.
[34] Y. Onouchi, T. Gunji, J.C. Burns, C. Shimizu, J.W. Newburger, M. Yashiro, Y. Nakamura, H. Yanagawa, K. Wakui, Y. Fukushima, F. Kishi, K. Hamamoto, M. Terai, Y. Sato, K. Ouchi, T. Saji, A. Nariai, Y. Kaburagi, T. Yoshikawa, K. Suzuki, T. Tanaka, T. Nagai, H. Cho, A. Fujino, A. Sekine, R. Nakamichi, T. Tsunoda, T. Kawasaki, Y. Nakamura, A. Hata, ITPKC functional polymorphism associated with Kawasaki disease susceptibility and formation of coronary artery aneurysms, Nat. Genet. 40 (1) (2008) 35–42.
[35] S.M. Opal, C.J. Fisher Jr., J.F. Dhainaut, J.L. Vincent, R. Brase, S.F. Lowry, J.C. Sadoff, G.J. Slotman, H. Levy, R.A. Balk, M.P. Shelly, J.P. Pribble, J.F. LaBrecque, J. Lookabaugh, H. Donovan, H. Dubin, R. Baughman, J. Norman, E. DeMaria, K. Matzel, E. Abraham, M. Seneff, Confirmatory interleukin-1 receptor antagonist trial in severe sepsis: a phase III, randomized, double-blind, placebo-controlled, multicenter trial. The interleukin-1 receptor antagonist sepsis investigator group, Crit. Care Med. 25 (7) (1997) 1115–1124.
[36] Y. Paccaud, G. Berthet, A. Von Scheven-Gete, B. Vaudaux, Y. Mivelaz, M. Hofer, M. Roth-Kleiner, Neonatal treatment of CINCA syndrome, Pediatr. Rheumatol. Online J. 12 (2014) 52.
[37] S.J. Popper, C. Shimizu, H. Shike, J.T. Kanegaye, J.W. Newburger, R.P. Sundel, P.O. Brown, J.C. Burns, D.A. Relman, Gene-expression patterns reveal underlying biological processes in Kawasaki disease, Genome Biol. 8 (12) (2007) R261.
[38] B. Rada, J.J. Park, P. Sil, M. Geiszt, T.L. Leto, NLRP3 inflammasome activation and interleukin-1β release in macrophages require calcium but are independent of calcium-activated NADPH oxidases, Inflamm. Res. (2014).
[39] J.L. Record, T. Beukelman, R.Q. Cron, Combination therapy of abatacept and anakinra in children with refractory systemic juvenile idiopathic arthritis: a retrospective case series, J. Rheumatol. 38 (1) (2011) 180–181.
[40] S. Ringold, P.F. Weiss, T. Beukelman, E.M. DeWitt, N.T. Ilowite, Y. Kimura, R.M. Laxer, D.J. Lovell, P.A. Nigrovic, A.B. Robinson, R.K. Vehe, 2013 update of the 2011 American College of Rheumatology recommendations for the treatment of juvenile idiopathic arthritis: recommendations for the medical therapy of children with systemic juvenile idiopathic arthritis and tuberculosis screening among children receiving biologic medications, Arthritis Rheum. 65 (10) (2013) 2499–2512.
[41] M.E. Rosenkranz, D.J. Schulte, L.M. Agle, M.H. Wong, W. Zhang, L. Ivashkiv, T.M. Doherty, M.C. Fishbein, T.J. Lehman, K.S. Michelsen, M. Arditi, TLR2 and MyD88 contribute to *Lactobacillus casei* extract-induced focal coronary arteritis in a mouse model of Kawasaki disease, Circulation 112 (19) (2005) 2966–2973.
[42] L. Rossi-Semerano, M. Piram, C. Chiaverini, D. De Ricaud, A. Smahi, I. Kone-Paut, First clinical description of an infant with interleukin-36-receptor antagonist deficiency successfully treated with anakinra, Pediatrics 132 (4) (2013) e1043–e1047.
[43] A. Ruiz Gomez, M.L. Couce, J. Garcia-Villoria, A. Torres, A. Bana Souto, J. Yague, M.A. Vilaseca, A. Ribes, J.I. Arostegui, Clinical, genetic, and therapeutic diversity in 2 patients with severe mevalonate kinase deficiency, Pediatrics 129 (2) (2012) e535–e539.
[44] S. Sasu, D. Beasley, Essential roles of IkappaB kinases alpha and beta in serum- and IL-1-induced human VSMC proliferation, Am. J. Physiol. Heart Circ. Physiol. 278 (6) (2000) H1823–H1831.
[45] D.J. Schulte, A. Yilmaz, K. Shimada, M.C. Fishbein, E.L. Lowe, S. Chen, M. Wong, T.M. Doherty, T. Lehman, T.R. Crother, R. Sorrentino, M. Arditi, Involvement of innate and adaptive immunity in a murine model of coronary arteritis mimicking Kawasaki disease, J. Immunol. 183 (8) (2009) 5311–5318.
[46] A. Shafferman, J.D. Birmingham, R.Q. Cron, High dose anakinra for treatment of severe neonatal Kawasaki disease: a case report, Pediatr. Rheumatol. Online J. 12 (2014) 26.
[47] C.H. Sibley, N. Plass, J. Snow, E.A. Wiggs, C.C. Brewer, K.A. King, C. Zalewski, H.J. Kim, R. Bishop, S. Hill, S.M. Paul, P. Kicker, Z. Phillips, J.G. Dolan, B. Widemann, N. Jayaprakash, F. Pucino, D.L. Stone, D. Chapelle, C. Snyder, J.A. Butman, R. Wesley, R. Goldbach-Mansky, Sustained response and prevention of damage progression in patients with neonatal-onset multisystem inflammatory disease treated with anakinra: a cohort study to determine three- and five-year outcomes, Arthritis Rheum. 64 (7) (2012) 2375–2386.
[48] M. Stenerson, K. Dufendach, I. Aksentijevich, J. Brady, J. Austin, A.M. Reed, The first reported case of compound heterozygous IL1RN mutations causing deficiency of the interleukin-1 receptor antagonist, Arthritis Rheum. 63 (12) (2011) 4018–4022.
[49] N. Tanaka, Pathological study of Kawasaki disease (MCLS): with special reference to sequelae, Jpn. J. Med. Sci. Biol. 32 (4) (1979) 245–246.
[50] A. Tremoulet, J. Burns, Anakinra treatment for IVIG-resistant Kawasaki disease patient with coronary artery aneurysms, Clin. Exp. (2015).
[51] A.H. Tremoulet, B.M. Best, S. Song, S. Wang, E. Corinaldesi, J.R. Eichenfield, D.D. Martin, J.W. Newburger, J.C. Burns, Resistance to intravenous immunoglobulin in children with Kawasaki disease, J. Pediatr. 153 (1) (2008) 117–121.
[52] R.S. Yeung, Lessons learned from an animal model of Kawasaki disease, Clin. Exp. Rheumatol. 25 (1 Suppl 44) (2007) S69–S71.
[53] S. Yonesaka, T. Nakada, Y. Sunagawa, K. Tomimoto, S. Naka, T. Takahashi, T. Matubara, I. Sekigami, Endomyocardial biopsy in children with Kawasaki disease, Acta Paediatr. Jpn. 31 (6) (1989) 706–711.
[54] S. Urien, C. Bardin, B. Bader-Meunier, R. Mouy, S. Compeyrot-Lacassagne, F. Foissac, B. Florkin, C. Wouters, B. Neven, J.M. Treluyer, P. Quartier, Anakinra pharmacokinetics in children and adolescents with systemic-onset juvenile idiopathic arthritis and autoinflammatory syndromes, BMC Pharmacol. Toxicol. 14 (1) (2013) 40.