Study Proposal & Statistical Analysis Plan

Phase I/IIa Study of Pharmacokinetics and Safety of Atorvastatin in Children with Coronary Artery Abnormalities Secondary to Kawasaki Disease

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I. Study Overview

OVERALL OBJECTIVE
The goal of this study is to determine the safety, pharmacokinetics and activity of atorvastatin in children with acute Kawasaki disease (KD) and coronary artery abnormalities. The goal will be to find a treatment that could prevent or attenuate coronary artery damage in acute KD.

HYPOTHESIS
We postulate that atorvastatin will be safe in children ≥ 2 years old with acute KD.

STUDY TYPE
This is a Phase I/IIa dose escalation study

STUDY POPULATION
Children ≥2 years to 17 years with acute KD who have a Z-score ≥ 2.5 or aneurysm (≥ 1.5 x the adjacent segment) of one of the coronary arteries.

STUDY DURATION
4 years

PRIMARY OUTCOME
Safety of atorvastatin in the study population.

SECONDARY OUTCOMES
1. Pharmacokinetics of atorvastatin
2. Activity of atorvastatin
    a. Biomarkers and measures of inflammation
    b. Echocardiographic assessment of coronary artery abnormalities

II. Background & Significance

IIA. Significance:

KD, the most common cause of acquired heart disease in children in Western developed countries and Asia, is a systemic vasculitis of unknown etiology. In the United States, there are 5-6,000 new cases each year [1]. However, without a specific diagnostic test, the true burden of disease is unknown. At Rady Children's Hospital San Diego, we cared for over 90 new KD cases in 2010 and follow over 1,200 families in our outpatient KD Clinic (350 outpatient visits/yr.), of whom 9% developed aneurysms and 25% developed dilated coronary arteries. In Japan, the country of highest incidence (>215/100,000 children < 5 yrs), there are more than 12,000 new cases each year and rates continue to rise [2]. KD causes both a myocarditis and a vasculitis that damages the coronary arteries and other medium-sized muscular arteries [3, 4]. The major sequelae of aneurysms include thrombosis, late coronary artery stenosis, myocardial ischemia, myocardial infarction, and death [5, 6]. **Clearly, aneurysm prevention is a primary goal of treatment during the acute phase of the disease, which leads us to focus on treatment of patients with early signs of coronary artery abnormalities (CAAs) in this application.**

Intravenous immunoglobulin (IVIG) in combination with aspirin is the only approved therapy for KD and no clinical trials have focused on blocking the progression of coronary artery dilatation or aneurysm formation in the subset of KD patients who develop this complication. The major acute risk of aneurysm formation is thrombosis, which can be prevented with systemic anti-coagulation with warfarin or enoxaparin in addition to antiplatelet therapy with aspirin or clopidogrel in patients with large aneurysms

(>6 mm). However, there is no recommended therapy to halt the progression of arterial wall destruction and prevent aneurysm formation. In KD, CD8+ T-cells infiltrate the arterial wall and data from the Franco lab suggest that T-cell regulation is a key factor in reducing the acute inflammation[7, 8] **The proposed studies will determine if atorvastatin is safe to use in young children and has demonstrable anti-inflammatory activity at a well-tolerated dose so that future studies can address the efficacy of atorvastatin in attenuating vascular wall damage and preventing aneurysms in KD patients.**

IIB. Importance of the problem

Once aneurysms have formed, there is no way to turn back the biologic clock and undo them. The transmural inflammation destroys the normal architecture and even in children who remodel the aneurysm to form a more normal lumen, the vessel is never functionally normal again. The remodeled segment cannot dilate normally during increased myocardial oxygen demand and thus serves as a functional stenosis. It has been estimated that there are currently over 24,000 young adults in the United States with a history of KD, including over 8,000 with a history of coronary artery abnormalities. Without a new therapeutic approach this number is expected to grow by 1,400 individuals each year [6]. A recent study found that over 5% of all young adults (<40 years) evaluated by cardiac catheterization for suspected myocardial ischemia have aneurysms compatible with antecedent KD[9].

IIC. Validity of the approach

A Phase I/IIa trial will generate sufficient data to determine if a full-scale Phase III trial is warranted. The trial will also establish if the anti-inflammatory effects of statins can be measured in children with an acute vasculitis.

IID. Critical barriers to improving care

Barriers to improving treatment for children with KD include the lack of a validated predictive score to identify those children at highest risk of aneurysm formation and lack of a therapeutic intervention that can prevent progression of CAAs once they have been detected.

IIE. Potential to effect change in clinical practice

The current clinical practice is to give every patient the same standard therapy (IVIG 2g/kg with aspirin 80-100mg/kg) and to monitor for CAA. The mechanism of action of this immunomodulatory therapy remains unknown, but is being addressed by other research by the PI in collaboration with Dr. Franco (RO1 HL103536 and RO1 FD003514). In the unfortunate child who carries the genetic risk for CAA, no intervention to modify vessel wall inflammation is currently recommended [10].

In a recent article entitled “Mining for therapeutic gold”, Director of the NIH, Dr. Francis Collins, stated that “drug repurposing” should be a strategy “to translate research into clinically useful products” [11] . Our goal is to translate our findings on the role of matrix metalloproteinases (MMPs), T-cells, and myofibroblasts in KD aneurysm formation and “repurpose” the drug atorvastatin to test the hypothesis that the pleiotropic anti-inflammatory properties of this drug will prevent or attenuate coronary artery aneurysms in children with KD.

IV. Specfic Aims

Specific Aim 1 will test the hypothesis that a 6-week course of atorvastatin will be safe and well-tolerated in children with KD and early CAAs.

The safety of atorvastatin will be assessed. A dose escalation design will be used to find a dose in subjects that is tolerated with limited side effects.

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V. Human subjects

VA. Inclusion criteria:

1. Age ≥ 2 years to 17 years old
2. Meets clinical criteria for KD according to AHA guidelines (Table 2): Fever (T≥38^{o}C or 100.4^{o}C by oral or rectal route; if measured by a non-core route (i.e. Axillary, ear, temporal artery), then add 0.5 ^{o}C to temperature; by history acceptable) ≥ 3 days and ≥ 2 clinical criteria with LAD/RCA z-score ≥ 2.5 or an aneurysm (≥ 1.5 x the adjacent segment) of one of the coronary arteries
3. Patient presents within the first 20 days after fever onset
4. Parent or legal guardian able and willing to provide informed consent and subject willing and able to provide assent when appropriate.
5. Post-menarchal females: Negative pregnancy test at screening and willing to use two forms of contraception during the study
6. Males engaging in sexual activity that could lead to pregnancy must use a condom.

VB. Exclusion Criteria:

1. Use of a statin, fibrate, or niacin within the 3 months prior to enrollment
2. Have any chronic disease, except asthma, atopic dermatitis, autism or controlled seizure disorder
3. Screening creatine phosphokinase (CK) ≥ 3x upper limit of normal for age
4. Patient taking a CYP3A4 inhibitor (i.e. cyclosporine, clarithromycin or doxycycline) in the last 7 days
5. Patient has a history of allergy to atorvastatin or its derivatives

VC. Data Collection: The following data will be recorded for all patients:

1. **Demographic data**:

- Patient's age at KD onset, sex, self-reported ethnicity of each biologic parent

2. **Clinical data:**

- Physical findings confirming the KD case definition (**Table 2**)[10]
- Illness day at study entry
- Response to IVIG (IVIG-resistance will be defined as persistent or recrudescent fever (T≥38.0˚C rectally) ≥36 h and < 7d following the end of the IVIG infusion (2g/kg)[14].) -
- Name, dose and indication of concomitant medications taken from enrollment until study completed
- Complete blood count, C-reactive protein (CRP), high sensitivity CRP (hsCRP), erythrocyte sedimentation (ESR), aspartate aminotransferase (AST), ALT, and GGT at baseline, 2 weeks and 6 weeks
- CK and fasting lipid panel at baseline (after enrollment), 2 weeks and 6 weeks

VI. Statistical analyses

Incidence rates of adverse events and the proportion of subjects prematurely withdrawn from the study due to adverse events was compiled. For continuous variables, the Kruskal Wallis Test was performed to compare the four dose levels. For categorical variables, Fisher's Exact Test was performed. Statistical analyses were performed using the statistical software R (version 3.4.4) (http://www.r-project.org). Analyses were performed following the intent-to-treat principle. No adjustments for multiple comparisons were made for secondary analyses, and a p-value of 0.05 was considered statistically significant.

VII. Literature Cited

1. Kaneko, K., et al., *Prediction of the Risk of Coronary Arterial Lesions in Kawasaki Disease by Brain Natriuretic Peptide.* Pediatr Cardiol.
2. Nakamura, Y., et al., *Epidemiologic Features of Kawasaki Disease in Japan: Results of the 2007-2008 Nationwide Survey.* J Epidemiol, 2010.
3. Yonesaka, S., et al., *Endomyocardial biopsy in children with Kawasaki disease.* Acta Paediatr Jpn, 1989. **31**(6): p. 706-11.
4. Yutani, C., et al., *Histopathological study on right endomyocardial biopsy of Kawasaki disease.* Br Heart J, 1980. **43**(5): p. 589-92.
5. Kato, H., et al., *Long-term consequences of Kawasaki disease. A 10- to 21-year follow-up study of 594 patients.* Circulation, 1996. **94**(6): p. 1379-85.
6. Gordon, J.B., A.M. Kahn, and J.C. Burns, *When children with kawasaki disease grow up myocardial and vascular complications in adulthood.* J Am Coll Cardiol, 2009. **54**(21): p. 1911-20.
7. Franco, A., et al., *Memory T-cells and characterization of peripheral T-cell clones in acute Kawasaki disease.* Autoimmunity, 2010. **43**(4): p. 317-24.
8. Franco, A., et al., *Endoplasmic reticulum stress drives a regulatory phenotype in human T-cell clones.* Cell Immunol, 2010. **266**(1): p. 1-6.
9. Daniels, L.B., Tjajadi, MS, Walford, HH, Fernandez S, Trofimenko V, Fick DB, Phan, HAL, Linz PE, Nayak, K, Kahn AM, Burns, JC, Gordon JB., *Prevalence of Kawasaki Disease in Young Adults with Suspected Myocardial Ischemia.* Submitted.
10. Newburger, J.W., et al., *Diagnosis, treatment, and long-term management of Kawasaki disease: a statement for health professionals from the Committee on Rheumatic Fever, Endocarditis and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association.* Circulation, 2004. **110**(17): p. 2747-71.
11. Collins, F.S., *Mining for therapeutic gold.* Nature reviews. Drug discovery, 2011. **10**(6): p. 397.
12. Sato, Y.Z., et al., *Cardiovascular biomarkers in acute Kawasaki disease.* Int J Cardiol, 2011.
13. Tremoulet, A.H., et al., *Evolution of Laboratory Values in Patients With Kawasaki Disease.* Pediatr Infect Dis J, 2011.
14. Tremoulet, A.H., et al., *Resistance to intravenous immunoglobulin in children with Kawasaki disease.* J Pediatr, 2008. **153**(1): p. 117-21.
15. Manlhiot, C., et al., *Improved Classification of Coronary Artery Abnormalities Based Only on Coronary Artery z-Scores After Kawasaki Disease.* Pediatr Cardiol, 2009.
16. *Guidelines for diagnosis and management of cardiovascular sequelae in Kawasaki disease (JCS 2008)--digest version.* Circ J. **74**(9): p. 1989-2020.
17. Printz, B.F., et al., *Noncoronary cardiac abnormalities are associated with coronary artery dilation and with laboratory inflammatory markers in acute kawasaki disease.* J Am Coll Cardiol. **57**(1): p. 86-92.
18. Kato, T., et al., *Coronary arterial ectasia in a 2-year-old boy showing two symptoms of Kawasaki disease without manifesting fever.* Rheumatol Int.
19. Ravekes, W.J., et al., *Aortic root dilation in Kawasaki disease.* Am J Cardiol, 2001. **87**(7): p. 919-22.
20. Chaudhuri, K., et al., *Polymorphism in the promoter of the CCL5 gene (CCL5G-403A) in a cohort of North Indian children with Kawasaki disease. A preliminary study.* Clin Exp Rheumatol.