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Evaluating a novel treatment for coronary artery inflammation in acute Kawasaki disease: A Phase I/IIa trial of atorvastatin

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Abstract

Introduction—Since the 1980s, the primary treatment of acute Kawasaki disease (KD) has been intravenous immunoglobulin and aspirin. However, 5-10% of children with acute KD will develop coronary artery abnormalities despite treatment within the first ten days after fever onset. There is no approved adjunctive therapy to prevent progression of coronary artery damage in these patients

Areas covered—The rationale and study design of a Phase I/IIa trial of atorvastatin in children with acute KD and coronary artery inflammation is presented. The studies of host genetics and KD pathogenesis leading up to this trial are reviewed.

Expert opinion—The repurposing of well-studied drugs used in the adult population is a cost-effective and efficient strategy to identify new therapies for pediatric diseases. Exploiting the anti-inflammatory, non-lipid-lowering effects of statins may open up new applications for this class of drugs for the pediatric age group.

Keywords

atorvastatin; repurposing; intravenous immunoglobulin; Kawasaki disease

1. Introduction

Kawasaki disease (KD) is a self-limited vasculitis of unknown etiology. The current recommended treatment for acute KD is a single dose of intravenous immunoglobulin

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(IVIG, 2 g/kg) with high-dose aspirin [1]. This approach, if implemented within the first 10 days after fever onset, reduces the incidence of coronary artery aneurysms from 25% to 5%. 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 transmural inflammation destroys the normal architecture and the vessel is never functionally normal again, even in remodeled vessels with a normal lumen [2]. Without a new therapeutic approach the number of young adults with a history of KD and coronary artery abnormalities (CAA) is expected to grow by 1,400 individuals each year [3]. 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 [4]. Clearly, aneurysm prevention is a primary goal of treatment during the acute phase of the disease. This article outlines the rationale for a dose-escalation Phase I/IIa clinical trial of atorvastatin for patients with acute KD and CAA.

2. Rationale for atorvastatin treatment in KD

The pleiotropic anti-inflammatory and anti-oxidant effects of the HMG co-A reductase inhibitors promote healing of the endothelium and have been credited with much of the cardiovascular risk reduction in adults taking this class of drugs [5]. Several lines of evidence have led us to consider statins as a potential therapy to halt the progression of arterial wall damage in CAA in KD:

2.1 Inhibition of matrix metalloproteinases (MMPs)

Genetic studies have shown an impact of genetic variation in MMP genes on both KD susceptibility and aneurysm formation [6]. In a mouse model of KD, atorvastatin inhibited MMP-9 secretion in the vessel wall [7]. Atorvastatin has been shown to attenuate MMP-9 gene expression and activity *in vitro* in human endothelial cells [8].

2.2 Expansion of regulatory T-cells

Characterization of regulatory T cells in acute KD provides strong evidence that IVIG reduces inflammation in part by expanding this pool of cells and by increasing expression of IL-10 [9]. Atorvastatin has been shown to increase the number and suppressive function of regulatory T-cells in adults with rheumatoid arthritis [10].

2.3 Inhibition of endothelial/epithelial to mesenchymal transition

Genetic studies in KD patients have underscored the importance of the TGFβ signaling pathway in the pathogenesis of CAA [11]. Immunohistochemical studies of the coronary arteries from KD autopsy cases demonstrated α-smooth muscle actin+/smoothelin- infiltrating cells that have a myofibroblast phenotype and secrete both IL-17 and MMP-9 [12], which could potentially be inhibited by statins [13].

Thus, the goal of the study outlined here is to translate the findings on the role of MMPs, regulatory 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 acute KD.

3. Phase I/IIa KD atorvastatin study

3.1 Study overview and objectives

This is an open-label, two-center, Phase I/IIa dose escalation study repurposing atorvastatin to determine its safety, pharmacokinetics (PK) and activity in children with acute KD and CAA (NCT00367458) (Tables 1 **and** 2). All patients will have received IVIG, aspirin, and infliximab (5 mg/kg) prior to study entry. The primary outcome measure of the study is the safety and tolerability of atorvastatin in the study population. The secondary outcome measures include the PK, change in markers of inflammation including levels of inflammatory biomarkers (C-reactive protein (CRP), α-1-antitrypsin and fibrinogen), white blood cell count (WBC), erythrocyte sedimentation rate (ESR), pro-inflammatory cytokines (IFN-γ, MMP-9, IL-17, sIL6r, sTNFR1 and sTNFR2), and markers of oxidant and anti-oxidant capacity (superoxide dismutase, glutathione, and catalase). The internal diameter of the coronary arteries adjusted for body surface area (Z-score) from 2-D echocardiograms at baseline, two and six weeks will be determined by the Core Echo Lab at the University of California San Diego. For comparison, laboratory data from historical control KD subjects matched for age, sex, and coronary artery Z-score on the first echocardiogram will be used in the analysis.

3.2 Dose escalation protocol

Subjects will receive daily, oral atorvastatin for six weeks at either the dose determined by the dose escalation study or by the maximally tolerated dose (MTD) once that is determined. The dose-escalation protocol is designed to enroll a minimum of three subjects per dose level (Dose Level, dose (mg/kg/day); 1, 0.125 mg/kg/day; 2, 0.25 mg/kg/day; 3, 0.5 mg/kg/day; 4, 0.75 mg/kg/day). Based on the adult maximum dose, no patient will receive a dose greater than 80 mg/day. The “3+3 dose escalation design” uses the numbers of DLTs to set the MTD (Table 2) and is frequently used in oncology Phase I studies [14]. Once the MTD is reached, subjects will continue to enroll at this dose until a total of 32 subjects have enrolled in the study.

3.3 Monitoring side effects

The main side effects of statins are elevated serum aminotransferase concentrations and myopathy. The following laboratory studies will be obtained at baseline, 2 weeks, and 6 weeks after enrollment: complete blood count, lipid panel, CRP, ALT, aspartate aminotransferase (AST), and CK. As cholesterol is important in the development of neuronal myelin, a lower threshold has been set for plasma cholesterol and the plasma concentrations of the brain-specific cholesterol metabolite, 24S-hydroxysterol, and the peripheral metabolite, 27-hydroxycholesterol will be measured at 2 and 6 weeks. All subjects will be monitored for both adverse events and serious adverse events during the 6 weeks of the study.

3.4 Statistical analyses

Incidence rates of adverse events and the proportion of subjects prematurely withdrawn from the study due to adverse events will be compiled. Measures of inflammation and oxidative

stress will be compared to that of historical matched controls via paired statistical tests. Non-parametric alternatives will be considered only if distributional assumptions are violated or if sample sizes are limiting. Separate multivariable mixed effects regression modeling for clustered data (to account for the case-control paired nature of samples) will be used to characterize the markers of atorvastatin-treated subjects versus matched controls to adjust for any known confounders and additional time points (baseline, 2 weeks, and 6 weeks). In addition, any covariate at the individual level that is simultaneously unbalanced and associated with the outcome will be included in the model. Covariates of interest include demographic variables (e.g., ethnicity, Illness Day at diagnosis, response to IVIG therapy). Statistical analyses will be performed using the statistical software R (version 3.1.1) (http://www.r-project.org). Analyses will be performed following the intent-to-treat principle. No adjustments for multiple comparisons will be made for secondary analyses, and a p-value of 0.05 will be considered statistically significant.

4. Atorvastatin in late convalescent KD patients

As compared to this Phase I/IIa study of atorvastatin for acute KD, atorvastatin in KD patients with CAA months to years after their initial KD has been reported [15]. Twenty patients with CAA after KD (median CAA z-score ≥ 25) were treated with 5 or 10 mg of atorvastatin daily for a median of 2.5 years (range 0.5–6.8) starting at a median of 2.3 years (range 0.3–8.9) after acute KD (median age 9.3 years [range 0.7–14.3]). Of the twenty patients, two required dose lowering because of hypocholesterolemia and one experienced a reversible increase in the creatine kinase. The authors concluded that atorvastatin is safe to use in very young children but should be closely monitored.

5. CONCLUSIONS

This Phase I/IIa trial will determine the safety, tolerability and activity of atorvastatin in children with acute KD and CAA. If an anti-inflammatory effect of atorvastatin is suggested, this will be followed by a larger, Phase III efficacy trial. If successful, this will be the first use of statins to modulate acute inflammation in a pediatric disease.

6. EXPERT OPINION

Despite timely treatment with IVIG and aspirin, a subset of patients with KD will develop aneurysms. There are no clinical trial data in Western children to guide treatment of these patients. In Japan, patients at increased risk of IVIG resistance were selected with a scoring system and treated with oral methylprednisolone for 3-5 weeks in addition to standard IVIG and aspirin therapy [16]. The steroid-treated cohort had a reduced incidence of CAA. However, this study excluded patients with initial CAA by echocardiogram, which includes over 80% of the patients who will ultimately go on to develop CAA.

Finding new therapies for children with KD and CAA is critical to reducing the morbidity and mortality from this disease. Given the intense destructive process in the arterial wall at the time of diagnosis, intensification of initial therapy is the only way to improve outcomes.

Repurposing drugs is a faster and more cost-effective path to new therapies for rare, pediatric diseases as compared to traditional new drug development.

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Article highlights box

- 5-10% of KD patients develop coronary artery abnormalities (CAA) despite timely treatment with IVIG and aspirin
- In order to improve the outcome of children with KD the field must move towards optimizing primary therapy and rescue therapy for KD patients with early CAA.
- An open-label, two-center, Phase I/IIa, dose escalation study repurposing atorvastatin in children with acute KD and CAA is described (NCT00367458).

Table 1

Inclusion and Exclusion Criteria

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°C or 100.4°C) ≥ 3 days and ≥ 2 clinical criteria with LAD/RCA z-score ≥ 2.5 or an aneurysm (≥ 1.5 × 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
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) ≥ 3× 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

Table 2

"3+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 MTD.
1 out of 3	Enter up to 3 more patients at this dose level. • If 0 of these additional 3 patients experience a DLT, proceed to the next dose level. • If 1 of these additional 3 patients experience a DLT, then dose escalation is stopped
≥ 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 timepoint: (1) creatine kinase (CK) elevation > 10 times the upper limit of normal or symptoms of muscle pain due to myositis; (2) a decrease in total cholesterol level that is at least 10% lower than entry level AND below 100 mg/dl (~2.5th percentile for children age 2 yrs.); (3) ALT or AST more than 3× the upper limit of age and sex-adjusted normal. A subject who experiences a DLT will discontinue atorvastatin immediately, will be monitored for resolution of the toxicity as medically appropriate, and will be removed from the study.

MTD = maximum tolerated dose; The MTD is defined as the highest dose of atorvastatin studied at which no more than one in six patients experiences a DLT during the 6 weeks of treatment.