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Phase I/IIa Trial of Atorvastatin in Patients with Acute Kawasaki Disease with Coronary Artery Aneurysm

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Objectives To determine the safety, tolerability, pharmacokinetics, and immunomodulatory effects of a 6-week course of atorvastatin in patients with acute Kawasaki disease with coronary artery (CA) aneurysm (CAA).

Study design This was a Phase I/IIa 2-center dose-escalation study of atorvastatin (0.125-0.75 mg/kg/day) in 34 patients with Kawasaki disease (aged 2-17 years) with echocardiographic evidence of CAA. We measured levels of the brain metabolite 24(S)-hydroxycholesterol (24-OHC), serum lipids, acute-phase reactants, liver enzymes, and creatine phosphokinase; peripheral blood mononuclear cell populations; and CA internal diameter normalized for body surface area before atorvastatin treatment and at 2 and 6 weeks after initiation of atorvastatin treatment.

Results A 6-week course of up to 0.75 mg/kg/day of atorvastatin was well tolerated by the 34 subjects (median age, 5.3 years; IQR, 2.6-6.4 years), with no serious adverse events attributable to the study drug. The areas under the curve for atorvastatin and its metabolite were larger in the study subjects compared with those reported in adults, suggesting a slower rate of metabolism in children. The 24-OHC levels were similar between the atorvastatin-treated subjects and matched controls.

Conclusions Atorvastatin was safe and well tolerated in our cohort of children with acute Kawasaki disease and CAA. A Phase III efficacy trial is warranted in this patient population, which may benefit from the known anti-inflammatory and immunomodulatory effects of this drug. *(J Pediatr 2019;■:1-11)*.

Despite the fact that more than 40 million adults in the US use statin medications on a daily basis for their lipid-lowering and anti-inflammatory effects, this class of drugs has not been studied systematically in young children.[1] Statin therapy is Food and Drug Administration (FDA)-approved for use in children at least 8 years of age for familial hypercholesterolemia.[2] Statins are also commonly used following heart transplantation in infants and young children and are recommended in the 2010 International Society of Heart and Lung Transplantation Guidelines for pediatric heart transplant patients with coronary allograft vasculopathy.[3-5] However, no data are available to guide dosing in the pediatric age group.

24-OHC	24(S)-hydroxycholesterol	LAD	Left anterior descending coronary artery
AE	Adverse event		
ALT	Alanine aminotransferase	LCWE	*Lactobacillus caseii* cell wall extract
ASA	Aspirin		
AST	Aspartate aminotransferase	mDC	Myeloid dendritic cell
CA	Coronary artery	MMP	Matrix metalloproteinase
CAA	Coronary artery aneurysm	MTD	Maximum tolerated dose
CK	Creatine kinase	nTreg	Natural T regulatory cell
C_{max}	Maximum plasma concentration	PBMC	Peripheral blood mononuclear cell
CRP	C-reactive protein		
DLT	Dose-limiting toxicity	PK	Pharmacokinetics
DSMB	Data Safety Monitoring Board	RCA	Right coronary artery
ELISA	Enzyme-linked immunosorbent assay	RCHSD	Rady Children's Hospital–San Diego
FDA	Food and Drug Administration	SAE	Serious adverse event
HUVEC	Human umbilical vein endothelial cell	Treg	T regulatory cell
		T_{max}	Time to maximum plasma concentration
IL	Interleukin		
iTreg	Peripherally induced T regulatory cells	TNF	Tumor necrosis factor
		Zmax	Maximal z-score
IVIG	Intravenous immunoglobulin		

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Statins have pleotropic antioxidant and anti-inflammatory effects that help promote endothelial cell homeostasis and block myofibroblast transformation, making this class of drugs potentially useful in the treatment of vascular inflammation.[6-8] Studies have also shown that the statins induce autophagy and mitophagy and thus inhibit NRLP3 inflammasome activation and inflammatory cytokines, such interleukin (IL)-1β, which is linked to the pathogenesis of Kawasaki disease.[9-11] The leading cause of acquired heart disease in children, Kawasaki disease is a pediatric vasculitis that can lead to coronary artery (CA) aneurysm (CAA) resulting from oxidative stress, immune activation, and vessel wall infiltration by cells of the innate and adaptive immune system associated with secretion of proinflammatory cytokines, elastases, and matrix metalloproteinases (MMPs).[10,12-16] Based on the new American Heart Association definition of aneurysms in Kawasaki disease, in a single-center study, 6.4% of patients with Kawasaki disease developed new CAA despite standard treatment with intravenous immunoglobulin (IVIG; 2 g/kg) and aspirin (ASA) within the first 10 days after fever onset.[17,18] The prognosis is even worse for infants younger than 6 months of age, more than one-half of whom have persistent CAA despite timely IVIG therapy.[19] The rationale for using statins as adjunctive therapy for acute Kawasaki disease was based on their inhibition of MMP secretion and myofibroblast transformation, both of which have been implicated in the formation of CAA in Kawasaki disease.[10,15,20,21]

In the US, the number of young adults with a history of Kawasaki disease and CAA is projected to increase by 1400 individuals annually without a new therapeutic approach to intervene in this process.[22] Atorvastatin was chosen for this study because it is FDA-approved for children at least 8 years of age with FH in the United States and data support its anti-inflammatory role in pathways critical to CAA formation in Kawasaki disease.[23-29] To study the safety and tolerability, to generate pharmacokinetics (PK) data, and to understand the immunomodulatory effects of atorvastatin in young children, we performed a Phase I/IIa dose-escalation study of atorvastatin to treat patients with acute Kawasaki disease with CAA.

Methods

This study recruited patients from Rady Children's Hospital San Diego (RCHSD) and Children's Hospital Colorado between October 1, 2012, and December 31, 2017. Children aged 2-17 years who had at least 3 days of fever with at least 2 clinical signs of Kawasaki disease in accordance with American Heart Association guidelines and a CA internal diameter normalized for body surface area (z-score) of the left anterior descending CA (LAD) or right CA (RCA) of at least 2.5 within the first 20 days after onset of fever were eligible for enrollment. Children with a chronic disease, with a screening creatine phosphokinase level >3 times the upper limit of normal, or who had taken a CYP3A4 inhibitor (ie, cyclosporine, clarithromycin, or doxycycline) in the previous 7 days were excluded. The IND issued by the FDA for this study limited enrollment to subjects with Kawasaki disease at least 2 years of age, owing to a lack of juvenile toxicity data in infant rats submitted by Pfizer at the time of initial atorvastatin licensing.

All patients received IVIG (2 g/kg), ASA (30-50 or 80-100 mg/kg/day while hospitalized; lowered to 3-5 mg/kg/day, maximum 81 mg at discharge), and infliximab (5 or 10 mg/kg IV) before study entry. The primary outcome measure was the safety and tolerability of atorvastatin. The secondary outcome measures included PK; changes in markers of inflammation, including levels of C-reactive protein (CRP), white blood cell count, and erythrocyte sedimentation rate; change in protein carbonyl level; and change in CA z-score. Peripheral blood mononuclear cell (PBMC) population was quantified at the 2-week visit and compared with a cohort of age- and z-score–matched historical controls—patients with Kawasaki disease treated with IVIG, ASA, and infliximab at RCHSD.

Five of the patients treated with atorvastatin (0.5-0.75 mg/kg/day) were age-matched with 5 patients treated with only IVIG and infliximab and their PBMCs were separated by Ficoll-Hypaque at the subacute stage (days 15-30). Phenotyping of innate and adaptive immune cells in these 10 subjects was performed using the antibodies described below.

As measures of oxidative stress, plasma carbonyl levels were measured in 9 patients treated with atorvastatin (0.125-0.75 mg/kg/day) and age- and Illness day- matched 1:2 with 18 control subjects with Kawasaki disease treated only with IVIG and infliximab. Details of Kawasaki disease and control subjects are given in **Table I** (available at www.jpeds.com).

The study protocol was reviewed and approved by the University of California San Diego's Institutional Review Board and the Colorado Multiple Institutional Review Board. Written informed consent was obtained from a parent or legal guardian, and assent, when appropriate, was obtained from the patient. This study has been registered with ClinicalTrials.gov (identifier NCT01431105). The FDA-issued IND number is 113304.

Administration of Study Drug

Atorvastatin was provided for this study by Pfizer. The study drug was readily and rapidly dissolved by combining one 10-mg atorvastatin tablet with either 2.5 or 5.0 mL of water and equal volumes of Ora-Sweet syrup (Perrigo Company, Allegan, Michigan) to produce a final concentration of 1-2 mg/mL. Immediately after mixing, the appropriate volume (weight-based dosing) was drawn up in a syringe and administered orally before breakfast. An additional 2.5-5 mL of water was then drawn up in the syringe and administered to deliver any residual drug.

Dose Escalation Protocol

Details of the study protocol and planned analysis have been published previously.[30] In brief, the dose-escalation protocol

was designed to enroll a minimum of 3 subjects per dose level (dose level 1, 0.125 mg/kg/day; dose level 2, 0.25 mg/kg/day; dose level 3, 0.5 mg/kg/day; dose level 4, 0.75 mg/kg/day). Based on the adult maximum dose, no subject received a dose >80 mg/day. The "3+3 dose escalation design" used the number of dose-limiting toxicities (DLTs) to determine the maximum tolerated dose (MTD).[31] A DLT was defined as any of the following at the 2-week or 6-week time point: creatine kinase (CK) elevation >10 times the upper limit of normal or symptoms of muscle pain due to myositis; a decrease in total cholesterol level that was at least 10% lower than entry level and <100 mg/dL (~2.5th percentile for children age 2 years); or an alanine aminotransferase (ALT) or aspartate aminotransferase (AST) level >3 times the upper limit of the age- and sex-adjusted normal range. In subjects who experienced DLT, atorvastatin was discontinued immediately and monitoring for resolution of toxicity was maintained as medically appropriate.

Dose escalation depended on the number of subjects with a DLT at a given dose level. If 0 of 3 subjects had a DLT, then 3 subjects were enrolled at the next dose level; if 1 of 3 subjects had a DLT, then an additional 3 subjects were enrolled at that dose level, and further dose escalation was dependent on the number of DLTs in those additional 3 subjects; and if 2 of 3 subjects had a DLT, then 3 additional subjects were enrolled at the next-lowest dose. The MTD was defined as the highest dose of atorvastatin studied at which no more than 1 in 6 patients experienced a DLT during the 6 weeks of treatment. Once the MTD was determined, the remaining subjects were enrolled in the "dose expansion" phase of the study at the MTD to further assess the safety and activity of atorvastatin at the MTD.

Monitoring Drug Toxicity

The main side effects of statins are elevated serum aminotransferase concentrations and myopathy. The following laboratory studies were obtained at baseline, 2 weeks (±4 days), and 6 weeks (±4 days) after enrollment: complete blood count, fasting lipid panel, CRP, ALT, AST, and CK. Given the importance of cholesterol in brain development and to ensure that brain cholesterol levels were not significantly affected by atorvastatin therapy, the plasma concentrations of the brain-specific cholesterol metabolite, 24(S)-hydroxycholesterol (24-OHC), were measured at 2 and 6 weeks in a subset of the subjects (9 patients with Kawasaki disease on atorvastatin and 7 controls matched for age, illness day, and infliximab treatment not treated with atorvastatin). The cartridges to isolate lipids from the serum (Supelco, Bellefonte, Pennsylvania; catalog no. 57012) were equilibrated by passing 3 mL of 100% methanol, followed by 3 mL of distilled water. Serum samples (100 μL) were mixed with 200 μL of 100% methanol and 150 μL of isopropanol. The solution was vortexed for 1 minute and then centrifuged for 10 minutes at 12,000 × *g*. The supernatant was then loaded onto the cartridges. After washing, the analyte was eluted using 3 mL of 85% methanol. The eluate was then dried by passing nitrogen gas over the collection tube. Dried samples were kept at 4 °C until analysis by enzyme-linked immunosorbent assay (ELISA). 24-OHC was measured using a commercially available kit (Enzo 24-OHC ELISA Kit, catalog no. ADI-900-210; Enzo Life Sciences, Farmingdale, New York), following the manufacturer's instructions.

All subjects were monitored for both adverse events (AEs) and serious adverse events (SAEs) during the 6 weeks of the study. These were classified according to severity and relationship to the study drug. A Data Safety Monitoring Board (DSMB) reviewed the clinical data at the end of each dose level, granted permission for escalation to the next dose level, and determined the MTD at the end of enrollment in the Phase I study.

PK Analyses

Samples were collected before the first dose of oral atorvastatin and then at 1, 2, 6, 12, and 24 hours after the dose. Trough levels were drawn just before giving an observed oral dose in the clinic at 2 and 6 weeks after enrollment. The samples were analyzed for levels of atorvastatin, the parent drug, as well as the ortho-hydroxyatorvastatin metabolite (Q^2 Solutions, Morrisville, North Carolina). For concentrations below the limit of detection, the value was set to 0.125 ng/mL or 1.25 ng/mL, depending on the detection limit of the assay. The maximum plasma concentration (C_{max}), corresponding time (T_{max}), half-life ($t_{1/2}$), and area under the curve $(AUC)_{0\text{-last}}$ for atorvastatin and the ortho-hydroxyatorvastatin metabolite were calculated as described previously.[32] The noncompartmental oral clearance rate (Cl/F_{NC}) was calculated as the ratio of dose to $AUC_{0\text{-}\infty}$. Apparent volume of distribution (V_d/F_{NC}) was calculated as Cl/F_{NC} over λ_z. Half-life ($t_{1/2}$) was calculated as $0.693/\lambda_z$. Plasma atorvastatin trough concentrations collected at weeks 2 and 6 were compared with the 24-hour postdose concentration collected during the acute phase (study day 1).

Genotyping

Samples from 10 subjects with Kawasaki disease enrolled in this study were available for both PK and genetic analysis. DNA was collected from either whole blood or mouthwash samples as described previously,[33] and genotyping for rs4149056 in SLCO1B1 (solute carrier organic anion transporter family, member 1B1) was performed using TaqMan SNP genotype assays (Life Technologies, Carlsbad, California) following the manufacturer's instructions. This locus was chosen because this polymorphism in SLCO1B1 has been associated with reduced activity of the OATP1B1 pathway and increased levels of atorvastatin and have been associated with statin myopathy.[34]

Protein Carbonyls

As a measure of oxidative stress, plasma carbonyl levels were measured in 9 patients treated with atorvastatin (0.125-0.75 mg/kg/day) and age- and illness day–matched 1:2 with 18 control subjects with Kawasaki disease treated only with IVIG and infliximab. We measured the concentration of plasma protein carbonyl groups by ELISA (Cell Biolabs,

San Diego, California) as instructed by the vendor. The results for all samples fell within the standard curve of 0.375-7.5 nmol of protein carbonyl/mg protein using 4-parameter curve fitting.

Echocardiographic Evaluation

Two-dimensional transthoracic echocardiograms were obtained in all subjects with Kawasaki disease according to a strict predetermined protocol. All echocardiographic images from the 2 sites were evaluated by a single cardiologist (B.P.) at the Core Echo Lab at RCHSD, who was blinded to patient clinical status. The CA internal diameter was adjusted for body surface area (*z*-score) from 2-dimensional echocardiograms at baseline, 2 weeks, and 6 weeks. Analyses included comparison across dose levels for Zmax, defined as the maximum *z*-score of either the LAD or RCA measured on any echocardiogram during the 6 weeks of the study, and the change in *z*-scores between baseline and 2 and 6 weeks after study entry.

Immune Phenotyping

Given the role of T cells and myeloid dendritic cells (mDCs) in the proinflammatory and anti-inflammatory pathways in Kawasaki disease, we focused on immune phenotyping these cell populations. mDC populations were characterized and enumerated by flow cytometry using the following monoclonal antibodies: anti-human CD11c-APC, mouse IgG1κ, clone B-ly6; anti-human CD11b-APC-Cy7, mouse IgG1κ, clone ICRF44; anti-human CD14-PE Cy7, mouse IgG2aκ, clone M5E2; and anti-human CD86-FITC, mouse IgG1κ, clone 2331 (FuN-1) (all from eBioscience, San Diego, California).

T-cell populations were characterized and enumerated by flow cytometry using the following monoclonal antibodies: CD25 BV421, mouse IgG1 k, clone M-A251 (BD Biosciences, San Jose, California); anti-human CD4-percp-Cy5.5, mouse IgG1k, clone RPA-T4; anti-human CD8, Alexa Fluor 700, clone RPA-T8, mouse IgG1k; anti-human CD45RA APC, mouse IgG2b k, clone HI100, anti-human CD127 FITC, mouse IgG1 k, clone eBioRDR5; and anti-human HLA-DR APC-H7 clone G46-6, mouse IgG2a k (eBioscience). Data were acquired with a FACSAria II flow cytometer and analyzed using FACSDiva (BD Biosciences).

Statistical Analyses

Incidence rates of AEs and the proportion of subjects who withdrew from the study prematurely due to AEs was compiled. For continuous variables, the Kruskal-Wallis test was performed to compare the 4 dose levels. For categorical variables, the Fisher exact test was used. Statistical analyses were performed using 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 .05 was considered statistically significant.

Results

Clinical and Laboratory Profiles of Study Patients

The participant flow, as well as the baseline demographic and clinical characteristics for the study population overall (n = 34) and by dose level, are summarized in **Figure 1** (available at www.jpeds.com) and **Table II**. Except for race, for which there were more white subjects at dose levels 2 and 4 (P = .01), there were no significant differences in baseline characteristics across the 4 dose levels. There were no significant differences in the change in laboratory values by dose level between baseline and weeks 2 and 6 across dose levels (**Table III**; available at www.jpeds.com).

Safety of Atorvastatin

According to the 3+3 protocol, the number of DLTs dictated the minimum number of subjects enrolled at each dose level. Because there were no DLTs in dose levels 1 and 3, the minimum of 3 subjects were enrolled in each of these dose levels. One DLT occurred at dose level 2, requiring a minimum of 6 subjects at that dose level. Overall, we enrolled 6 subjects in dose level 1 (3 more than were needed as we awaited DSMB approval to open the next dose level), 7 subjects in dose level 2 (1 more than needed as we awaited DSMB approval to open the next dose level), 3 subjects in dose level 3, and 18 subjects in dose level 4, as the latter also included subjects in the dose expansion cohort. Two subjects had laboratory abnormalities during the dose escalation phase of the study that met the criteria for a DLT. The first subject was receiving 0.25 mg/kg/day of atorvastatin and had a total cholesterol level of 95 mg/dL after 6 weeks of study drug, and thus qualified as a DLT because the cholesterol was <100 mg/dL and >10% below the initial cholesterol level of 140 mg/dL. Because this was the end of the study, atorvastatin was discontinued in accordance with the study protocol, and the cholesterol level increased to 148 mg/dL by 4 weeks later. The second subject was receiving 0.75 mg/kg/day of atorvastatin and had an ALT of 82 IU/L that had decreased from 114 IU/L at the time of diagnosis of Kawasaki disease. However, because this ALT level after 2 weeks of atorvastatin treatment was still 3 times above the upper limit of normal for age, the study drug was discontinued in accordance with the study protocol. The ALT decreased to within the normal range (26 IU/L) 4 weeks later.

During the expansion phase, a subject receiving 0.75 mg/kg/day of atorvastatin had a total cholesterol level of 95 mg/dL after 2 weeks of study drug administration. The study drug was discontinued because the cholesterol level was <100 mg/dL and >10% below the initial cholesterol level of 139 mg/dL. The cholesterol level increased to 113 mg/dL by 4 weeks after discontinuation of study drug. Thus, atorvastatin was discontinued because of low total cholesterol in 1 of 7 subjects (14.3%) at the second dose level (0.25 mg/kg/day) and because of either low total cholesterol or elevated ALT in 2 of 18 subjects (11.1%) at the highest dose level (0.75 mg/kg/day).

Table II. Baseline demographic and clinical characteristics of the study population

Characteristics	All dose levels (N = 34)	Dose 1 (0.125 mg/kg/d) (N = 6)	Dose 2 (0.25 mg/kg/d) (N = 7)	Dose 3 (0.5 mg/kg/d) (N = 3)	Dose 4 (0.75 mg/kg/d) (N = 18)	*P* value (across doses)
Age, y, median (range)	4 (2.1–16.5)	7.3 (2.5-12.8)	3.3 (2.2-16.5)	5.3 (3.9-11.9)	3 (2.1-14.5)	.19
Male sex, n (%)	24 (70.6)	2 (33.3)	5 (71.4)	3 (100)	14 (77.8)	.18
Race, n (%)						
White	21 (61.8)	1 (16.7)	5 (71.4)	1 (33.3)	14 (77.8)	.01
Asian	3 (8.8)	0 (0)	0 (0)	2 (66.7)	1 (5.6)	
African American	1 (2.9)	1 (16.7)	0 (0)	0 (0)	0 (0)	
Other*	1 (2.9)	1 (16.7)	0 (0)	0 (0)	0 (0)	
Multiple	8 (23.5)	3 (50)	2 (28.6)	0 (0)	3 (16.7)	
Hispanic ethnicity, n (%)	13 (38.2)	1 (16.7)	4 (57.1)	1 (33.3)	7 (38.9)	.62
Days of illness at study enrollment, median (range)†	8 (4-21)	8 (4-17)	10 (4-21)	7 (5-9)	7.5 (5-15)	.62
WBC count, $\times 10^9$/L, median (range)	12.9 (4.7-36.7)	11.9 (6-26.7)	14.2 (8.7-36.7)	12 (6.2-16.8)	13.6 (4.7-23.5)	.72
zHgb, median (range)‡	−1.6 (−3.8 to 2.67)	−1.3 (−3.5 to 1.2)	−2.6 (−3.8 to −0.8)	−2.7 (−2.8 to −1.7)	−1.3 (−3.7 to 2.7)	.14
Platelet count, $\times 10^9$/L, median (range)	356 (66-624)	385 (184-624)	389 (308-550)	283 (201-429)	346 (66-554)	.56
CRP, mg/dL, median (range)	8.8 (0.5-36.3)	6.5 (0.5-21.7)	17.2 (4-36.3)	17.7 (6.9-25.9)	8.6 (3.5-31.7)	.38
ESR, mm/h, median (range)	68 (10->140)	60 (38-72)	80 (37->140)	99 (45->140)	69 (10->140)	.40
ALT, U/L, median (range)	62 (15-473)	55 (19-191)	49 (19-268)	62 (25-166)	68 (15-473)	.81
GGT, U/L, median (range)	62 (11-270)	128 (16-211)	84 (13-270)	95 (25-136)	31 (11-249)	.58
Albumin, g/dL, median (range)	3.5 (2.4-5.9)	3.5 (3.3-5.9)	3.6 (2.9-4.2)	3.5 (3.3-3.8)	3.6 (2.4-4.4)	.97
Z-scores, median (range)§						
Proximal LAD	2.7 (0.4-9.1)	2.6 (0.6-4.2)	5.2 (0.4-9.1)	3.3 (3.2-3.5)	2.5 (1.4-6.2)	.36
Proximal RCA	2.3 (−0.7-8.9)	2.4 (0.8-3.7)	2.7 (0.8-8.9)	3.3 (2.4-4.1)	1.9 (−0.7-5.3)	.30

GGT, gamma glutamyl transferase.
*Other: Afghani.
†One subject was enrolled on day 21 of illness rather than within the first 20 days of illness.
‡zHgb, SD units from the mean for age-adjusted hemoglobin values.[35]
§*Z*-scores were calculated as described previously.[36]

Table IV. AEs during the 6-week study period stratified by dose level

Parameters	All dose levels (N = 34)	Dose 1 (0.125 mg/kg/d) (N = 6)	Dose 2 (0.25 mg/kg/d) (N = 7)	Dose 3 (0.5 mg/kg/d) (N = 3)	Dose 4 (0.75 mg/kg/d) (N = 18)	*P* value
Total AEs, n	87	11	14	6	56	
Subjects experiencing ≥1 AE, n (%)	24 (70.6)	4 (66.7)	4 (57.1)	2 (66.7)	14 (77.8)	.754
Subjects experiencing ≥2 AEs, n (%)	20 (58.8)	2 (33.3)	3 (42.9)	2 (66.7)	13 (72.2)	.263
AE–study drug relationship						
Probably related to study drug, n (%)	3 (3.5)	0 (0)	1 (7.1)	0 (0)	2 (3.6)	>.99
Possibly related to study drug, n (%)	6 (6.9)	0 (0)	0 (0)	0 (0)	6 (10.7)	.16
SAEs, n	4	0	0	1	3	
Subjects experiencing SAEs, n (%)	4 (11.8)	0 (0)	0 (0)	1 (33.3)	3 (16.7)	.369
Recrudescent fever, n*	2	0	0	1	1	
Worsening CAA, n*	2	0	0	0	2	

*These events led to prolonged hospitalization and thus qualified as an SAEs.

AEs

The AEs are summarized in Table IV. No patient experienced an elevation in plasma CK level. Of the 34 subjects, 24 (70.6%) experienced at least 1 AE. There was no difference in the proportion of subjects with at least 1 AE across dose levels. The most common AEs included fever, due to either treatment resistance or concomitant viral illness, and bruising due to antiplatelet or anticoagulant therapy for CAA (Table V; available at www.jpeds.com). No SAE was related to the study drug. Four SAEs occurred necessitating either readmission or prolonged hospitalization, including recurrence of fever in 2 subjects (1 receiving 0.5 mg/kg/day and 1 receiving 0.75 mg/kg/day) and worsening CAA in 2 subjects at the highest dose level of 0.75 mg/kg/day (Table IV). There was no difference in the proportion of subjects with at least 1 SAE across the dose levels.

24-OHC

Detection of 24-OHC using extracted serum samples was tested in linearity assays (82.3% recovery), and the intra-assay coefficient of variation for the ELISA was 0-11.7%. Compared with control subjects who received standard therapy with IVIG but no atorvastatin, there was no difference in 24-OHC levels after 6 weeks of treatment with atorvastatin regardless of dose (Figure 2, A). Across all subjects, the serum levels of 24-OHC were elevated before IVIG treatment and decreased by 6 weeks later, irrespective of whether atorvastatin was administered (Figure 2, B).

PK of Atorvastatin

Of the 21 subjects in whom PK samples were collected during the dose escalation phase of the study, 15 had sufficient data for PK evaluation. Increasing the weight-based dose of atorvastatin led to increases in the median C_{max} and AUC of atorvastatin, as well as of the ortho-hydroxyatorvastatin metabolite (Figure 3 and Table VI [available at www.jpeds.com]). The median T_{max} was reached at 1 hour for atorvastatin (range, 1-2 hours) and at 2 hours for ortho-hydroxyatorvastatin (range, 1-6 hours) (Table VI).

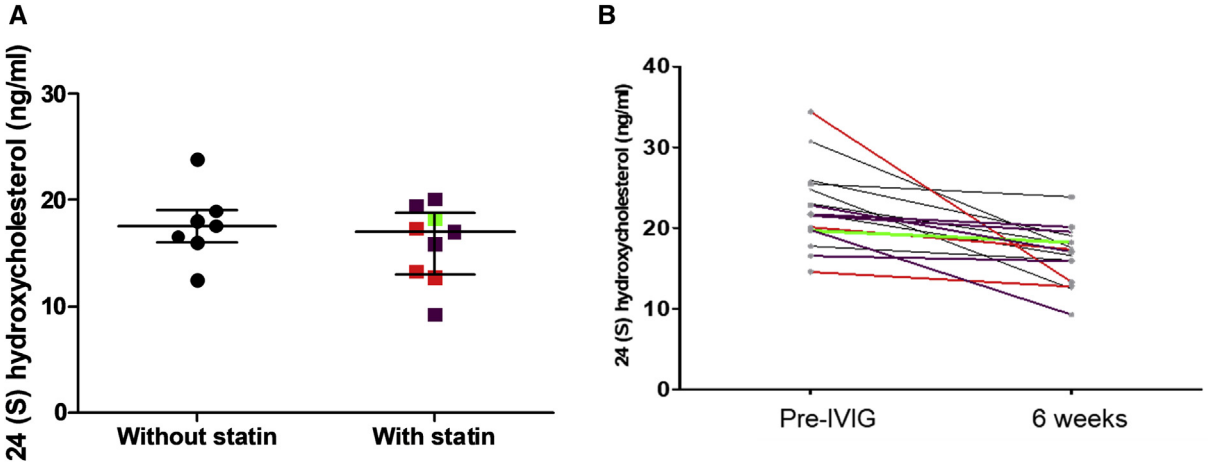

Figure 2. Levels of 24(S)-hydroxycholesterol with and without atorvastatin therapy and across dose levels. **A,** 24(S)-hydroxycholesterol levels after 6 weeks of diagnosis of Kawasaki disease in subjects who received IVIG and infliximab vs those who received IVIG, infliximab, and atorvastatin. **B,** Individual 24(S) hydroxycholesterol levels for each Kawasaki disease subject treated with atorvastatin shown by dose level. *Red*, 0.25 mg/kg; *green*, 0.5 mg/kg; *purple*, 0.75 mg/kg; *black*, without atorvastatin treatment.

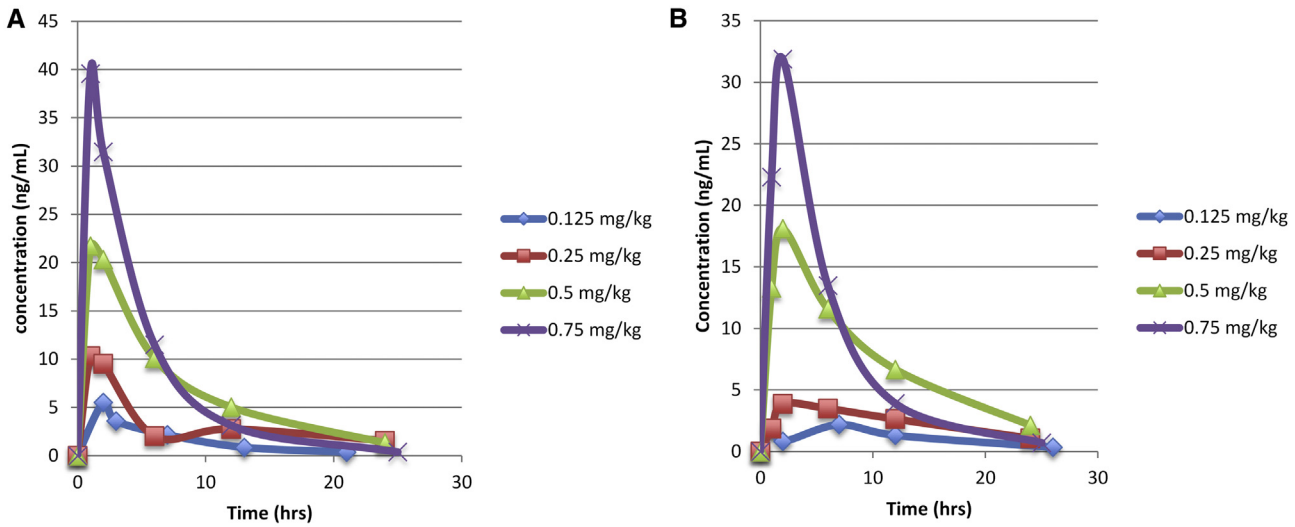

Figure 3. Median concentrations of **A,** atorvastatin and **B,** ortho-hydroxyatorvastatin metabolite vs time by dose (in mg/kg), showing increasing doses over time. *Blue*, 0.125 mg/kg/day; *red*, 0.25 mg/kg/day; *green*, 0.5 mg/kg/day; *purple*, 0.75 mg/kg/day.

Genotyping of SLCO1B1

In the 10 subjects for whom both DNA and PK data were available, 2 were heterozygous for the C risk allele for SLCO1B1 at rs4149056. One of these subjects had the highest C_{max} and AUC of all subjects (**Figure 3**).

Protein Carbonyls

There was no difference in plasma protein carbonyl concentration between the atorvastatin-treated and matched control subjects with Kawasaki disease at either baseline (pre-IVIG) or 2 weeks after initiation of treatment (**Figure 4**; available at www.jpeds.com). However, there was a significant decrease in plasma protein carbonyl concentration from baseline to 2 weeks in both the atorvastatin-treated and matched control subjects (P = .0078 and .0005, respectively), although there was no difference in the change between the 2 groups.

Echocardiographic Evaluation

The baseline z-score of the LAD or RCA did not differ significantly by dose level (**Table II**). The maximum z-scores for each coronary artery segment at any time point (Zmax) and the difference in z-scores from baseline to 2 weeks and 6 weeks were similar across all 4 dose levels based on the Echo Core Lab readings (**Table VII**; available at www.jpeds.com). The evolution of z-scores is outlined for subjects who had a Zmax ≥5 in **Table VIII** (available at www.jpeds.com). Two subjects treated with 0.75 mg/kg/day had progression of CAA while on the study drug (**Figure 5**; available at www.jpeds.com).

Immune Phenotyping

The phenotype of innate and adaptive PBMCs at the subacute phase (illness days 15-30) was compared between 5 patients treated with IVIG, ASA, infliximab, and atorvastatin (0.5-0.75 mg/kg/day) and 5 patients treated with IVIG, ASA, and infliximab alone (**Figure 6**; available at www.jpeds.com). The groups did not differ with respect to median age. The predominant innate PBMCs were mDCs defined by the expression of CD11c and CD11b. Within the mDC population, a large percentage expressed CD14 as a marker of tolerogenic mDCs that have been previously described in Kawasaki disease.[37] These $CD14^+$ cells expressed CD86 as a maturation and activation marker. There was no significant difference in the distribution of mDC populations between the 2 treatment groups.

T-cell lineages were compared between the 2 groups using markers for activation (DR), expansion (IL7R), and regulation ($CD25^{high}$). $CD4^+CD25^{high}$ T cells were further characterized as peripherally induced T regulatory cells (iTregs: $IL\text{-}7R^+CD45RA^+$) and natural Tregs (nTregs: $IL\text{-}7R^-CD45RA^-$). The only consistent difference between the patients treated with or without atorvastatin was a lower percentage of circulating $CD8^+$ T cells in patients who received atorvastatin (P = .03) (**Figure 7**; available at www.jpeds.com). However, the percentage of activated (DR^+) $CD8^+$ T cells was similar in the 2 groups. Although iTregs have been described as induced by atorvastatin treatment in adults, these cells are not abundant in the circulation in children in general,[38] and were a minor cell population in both groups of subjects with Kawasaki disease regardless of treatment. nTregs that were previously reported to downregulate inflammation in acute Kawasaki disease were equally represented in the 2 treatment groups.[39]

Discussion

This study assessed the safety and tolerability of a 6-week course of atorvastatin in children with acute Kawasaki disease

and CAA and to determine the PK around the first dose. Atorvastatin at doses ranging from 0.125-0.75 mg/kg/day was safe and well tolerated in this young patient population. Based on this study in a multiethnic population, 0.75 mg/kg/day of atorvastatin for a 6-week period was well tolerated in patients with acute Kawasaki disease with CAA.

Because cholesterol is important for brain development in the pediatric age group, a conservative lower threshold of 100 mg/dL was set for plasma cholesterol concentration as a DLT. Although cholesterol did drop to 95 mg/dL in 2 subjects, it improved after atorvastatin was discontinued. To assess whether a 6-week course of atorvastatin decreased the levels of brain cholesterol metabolite 24-OHC in children with Kawasaki disease, we compared 24-OHC levels in our subjects treated with atorvastatin and those treated without atorvastatin. The lack of significant change in 24-OHC levels in the 2 groups reaffirms the safety of a 6-week course of atorvastatin in patients with acute Kawasaki disease. We were also reassured by the lack of increase in CK levels in our subjects after a 6-week course of atorvastatin. There were no signs of myopathy on physical examination or by parental report. Although it is sometimes difficult to assess muscle tenderness in young children, data from adult clinical trials show that true myopathy is rare and consistently associated with CK elevation.[40]

The PK data from this study may help guide dosing in other pediatric populations, although the acute inflammatory state of our subjects with Kawasaki disease may have altered both drug absorption and metabolism. The C_{max} and $AUC_{0-\infty}$ values of atorvastatin and ortho-hydroxyatorvastatin were higher in our study population compared with values reported in similar weight-based dosing using an average adult weight of 70 kg.[41,42] In contrast, the T_{max} values in our subjects were similar to published data in adults,[43] suggesting that in children, the rate of absorption of atorvastatin is similar, but the extent of absorption is greater and/or overall metabolism is slower.

The absorption and metabolism of oral atorvastatin also may be affected by changes in gastrointestinal permeability that appear to occur in acute Kawasaki disease. In the *Lactobacillus caseii* cell wall extract (LCWE) mouse model of Kawasaki disease, the mice exhibit intestinal leakage, associated with increased serum levels of zonulin, a protein marker of intestinal permeability.[44] Although the enzymes required to metabolize atorvastatin are nearing adult activity by 1 year of age, pediatric liver weight lags behind total body weight, and thus the mass of the liver in proportion to the body smaller in children.[45,46] This developmental detail could contribute to these findings. Host genetics also influence statin metabolism, and the subject with the highest C_{max} value was heterozygous for the C risk allele for SLCO1B1 at rs4149056.[47] This polymorphism can potentially reduce the metabolism and first-pass loss of atorvastatin via the OATP1B1 pathway and lead to higher circulating concentrations. Another subject who was heterozygous for the C risk allele had the third-highest C_{max} value among the genotyped subjects. Neither subject experienced any toxicity from these high levels of atorvastatin.

The transmural inflammation occurring in the coronary arteries during CAA formation in acute Kawasaki disease destroys the normal architecture, and the arterial wall most likely is never functionally normal again, even in remodeled vessels with a normal lumen.[48,49] Proinflammatory cytokines, including IL-1β and tumor necrosis factor α, and MMPs circulate at high levels in patients with acute Kawasaki disease, and these aspects of systemic vasculitis have been recapitulated in a murine model using intraperitoneal injection of LCWE.[50-53] Genetic studies have suggested that allelic variants in MMP genes are associated with susceptibility to Kawasaki disease and CAA.[14] Using mouse splenocytes incubated with LCWE, Blankier et al demonstrated that T cell proliferation, MMP-9 secretion, and tumor necrosis factor α production were reduced in a dose-dependent manner in response to ex vivo exposure to atorvastatin.[54] These observations lend support to the potential beneficial role of statins in protecting the arterial wall during the acute vasculitis of Kawasaki disease.

The importance of cytotoxic T cells in mediating the destruction of the arterial wall in Kawasaki disease is well documented. Immunohistochemistry studies have shown infiltration of $CD8^+$ T cells into the media, and gene expression studies from autopsies of the arterial walls of deceased patients with Kawasaki disease have shown increased transcripts associated with activated $CD8^+$ T cells.[55,56] In a mouse model of myocarditis, statin treatment of $CD8^+$ T cells ameliorated disease induction.[57] The exploratory immunophentoyping in our cohort suggests that circulating $CD8^+$ T cells may be reduced in children on atorvastatin therapy, but these preliminary findings remain to be validated in a larger cohort. This type of immune monitoring, available as a routine laboratory test in many hospital clinical laboratories, could be incorporated into a future Phase III trial.

In previously published work, blood samples from several subjects in this study were evaluated in an in vitro model of endothelial-to-mesenchymal transition using human umbilical vein endothelial cells (HUVECs).[58] Incubation of pretreatment serum incubated with HUVECs initiated a molecular cascade involving KLF4, mir-483, and CTGF that resulted in transition of the HUVECs to a mesenchymal phenotype. In contrast, Kawasaki disease patient sera after six weeks of atorvastatin therapy induced higher levels of mir-483, an inhibitor of CTGF, and endothelial-to-mesenchymal transition in the HUVEC cultures compared with serum from age-, illness day– and *z*-score–matched patients with Kawasaki disease who had been treated only with IVIG and infliximab. These in vitro data support the potential benefit of atorvastatin therapy in patients with acute Kawasaki disease with early signs of CA damage. Additional support comes from analysis of autopsies of patients with acute Kawasaki disease. Immunohistochemistry of the arterial wall demonstrated α-smooth muscle actin–positive, smoothelin-negative myofibroblast-like cells in the thickened

intima coexpressing IL-17, lending more support to the injurious role of myofibroblasts in acute Kawasaki disease.[15]

Autopsy studies from the late convalescent phase have demonstrated luminal myofibroblastic proliferation in the arterial wall, resulting in significant stenosis.[59] For this reason, the convalescent use of statins in older patients with Kawasaki disease with CAA has been widely adopted. A report from Japan described a significant reduction in high-sensitivity CRP in 11 patients with Kawasaki disease with CAA treated with fluvastatin for 12 months at an average of 12.4 years after the acute phase.[60] In a Canadian study of 20 patients with Kawasaki disease with giant CAA, atorvastatin at a dose of either 5 or 10 mg/day administered for a median of 2.5 years beginning at least 2 years after the acute phase was determined to be safe, but no PK studies were performed.[61] Another study of 13 patients with Kawasaki disease with CAA at least 1 year after the acute phase demonstrated improved flow-mediated dilation of the brachial artery and lower high-sensitivity CRP levels after 6 months of pravastatin therapy.[62] In 2 case reports of adults with Kawasaki disease with giant CAA and inflammation in the arterial wall demonstrated by fluorodeoxyglucose–positron emission tomography, the inflammation signal was greatly attenuated after the initiation of statin therapy but returned in the 1 patients with Kawasaki disease in whom the statin was discontinued.[63,64]

We recognize both strengths and weaknesses of this study. This is the first dose-escalation PK study of a statin in children with acute cardiovascular inflammation and the first study to demonstrate the safety of atorvastatin in children with acute Kawasaki disease. However, rare AEs related to atorvastatin could have been missed owing to the small sample size. As a Phase I/IIa study, this clinical trial was neither placebo-controlled nor powered to determine the effectiveness of atorvastatin in reducing laboratory measures of inflammation or change in Zmax. In this study, only children aged ≥2 years were eligible for the trial, given the lack of juvenile toxicity data in infant rats submitted to the FDA at the time of initial drug approval. Thus, the safety of atorvastatin in children age <2 years, who are at the greatest risk for CAA, remains unanswered. The limited number of patients studied for immune phenotyping limited the strength of the conclusions that we could draw. The standard clinical laboratory values that were compared between atorvastatin-treated subjects and controls are likely insensitive measures of statin effect. With respect to the protein carbonyl studies, treatment with IVIG and infliximab alone was likely sufficient to reduce reactive oxygen species. Measurement of specific MMP and proinflammatory cytokines within a shorter time frame (eg, 24-72 hours after initiation of statin therapy) might have been more informative and should be considered in future trial designs.

In this study, we have established a range of safe doses of atorvastatin in children with acute Kawasaki disease and CAA. The potential benefit of the anti-inflammatory and immunomodulatory actions of atorvastatin warrant a Phase III efficacy trial to test the hypothesis that children with acute Kawasaki disease and early signs of CA damage will benefit from the addition of atorvastatin to standard therapy. ■

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Data statement

Data sharing statement available at www.jpeds.com.

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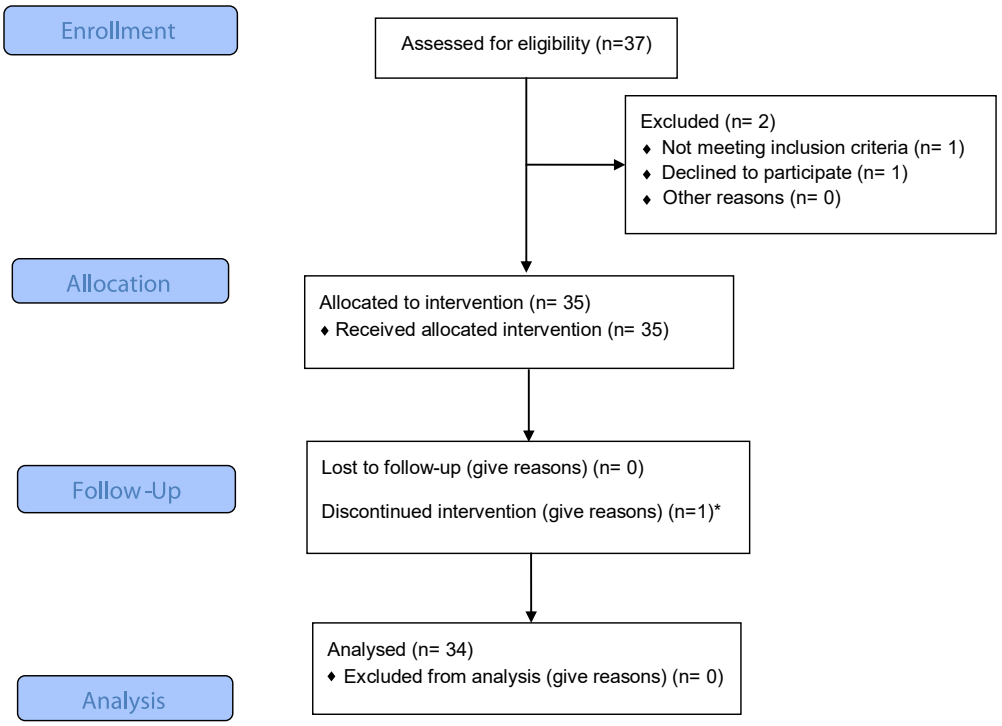


Figure 1. Participant CONSORT flow diagram. Of the 37 subjects assessed for eligibility, 1 did not meet the inclusion criteria (ie, had a chronic underlying disorder that excluded participation), 1 declined (ie, concerned about risks of atorvastatin), and 1 discontinued atorvastatin on discharge to home.

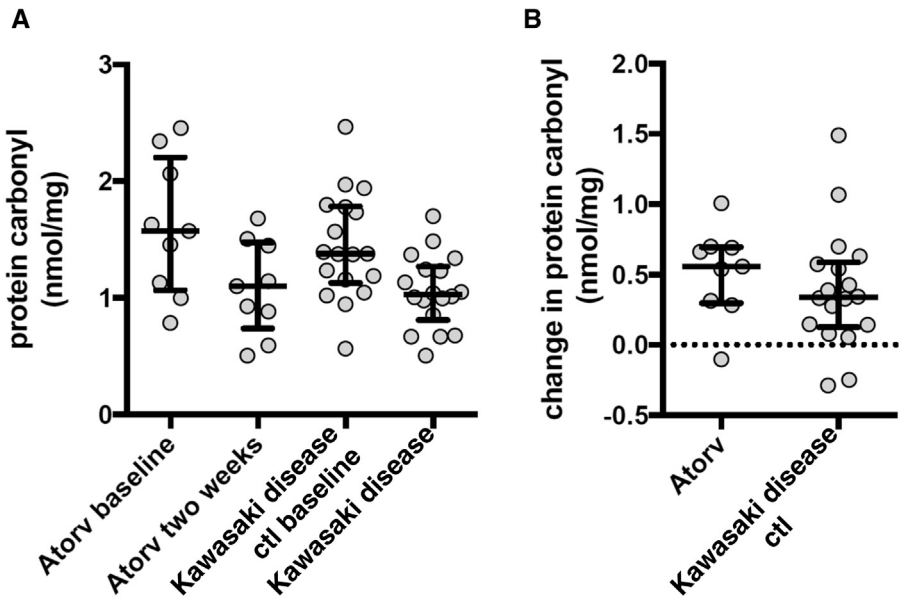


Figure 4. Plasma protein carbonyl concentration. **A,** Plasma protein carbonyl concentration (median and IQR) for samples acquired before IVIG administration (baseline) and after 2 weeks of atorvastatin compared with samples from matched Kawasaki disease control (ctl) patients. **B,** Difference in plasma protein carbonyl concentration (baseline minus 2 weeks) for study subjects and matched control Kawasaki disease patients (median and IQR).

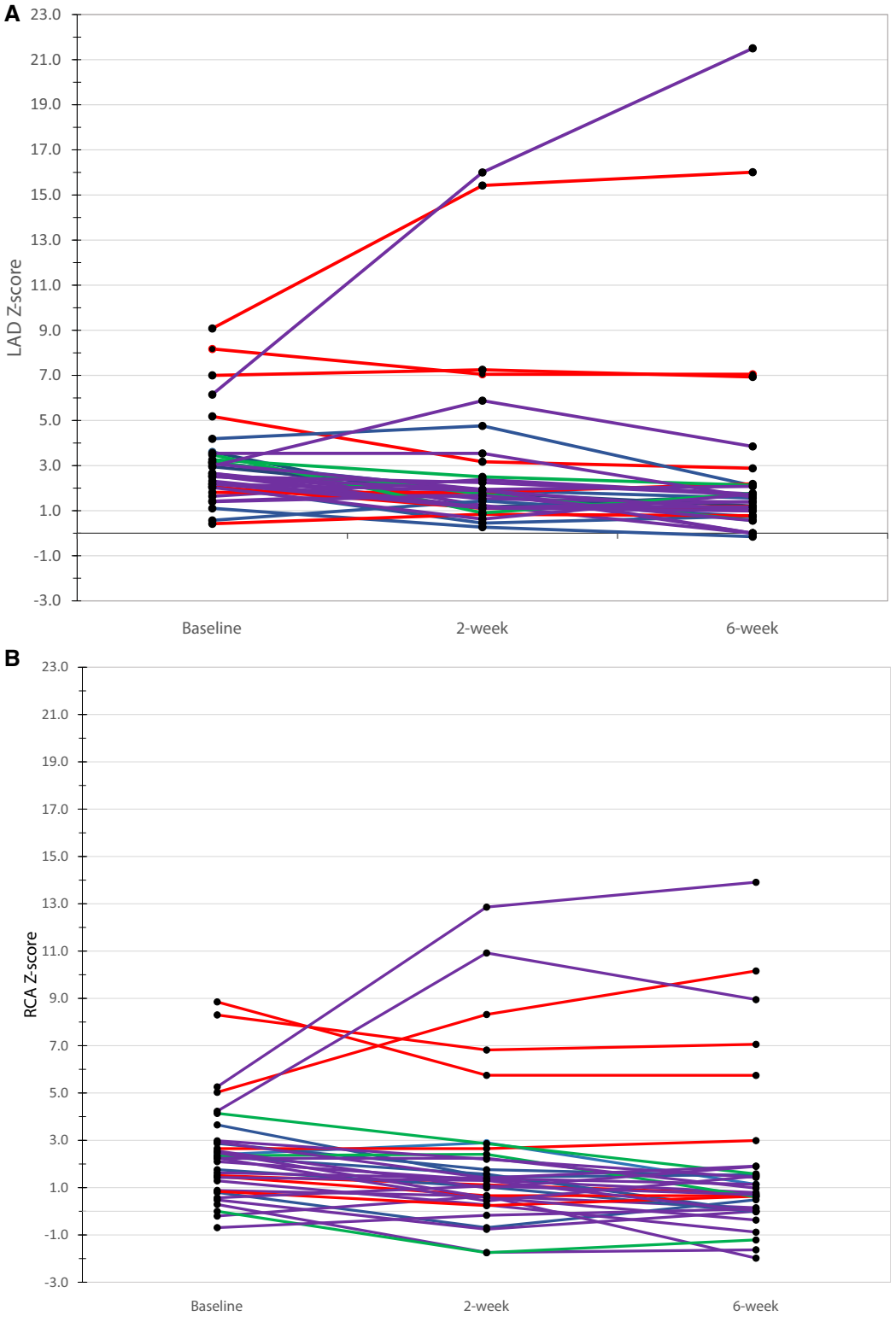
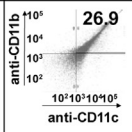
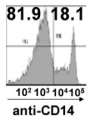
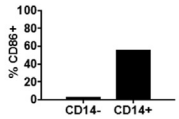
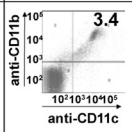
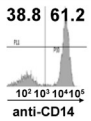
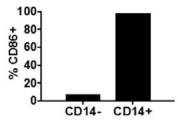
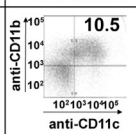
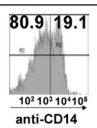
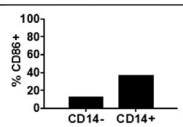
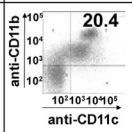
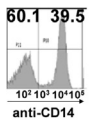
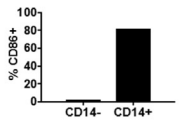


Figure 5. *z*-scores over the course of treatment with atorvastatin. **A,** LAD coronary artery Z-score at baseline (pre-IVIG) and at 2 and 6 weeks after treatment with atorvastatin. **B,** RCA Z-scores pre-IVIG and at 2 and 6 weeks after treatment with atorvastatin. *Blue*, 0.125 mg/kg/day; *red*, 0.25 mg/kg/day; *green*, 0.5 mg/kg/day; *purple*, 0.75 mg/kg/day.

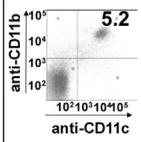
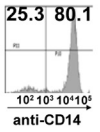
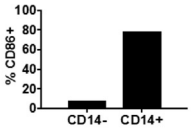
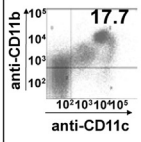
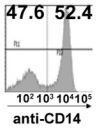
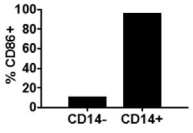
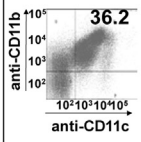
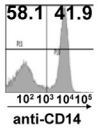
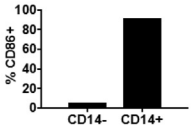
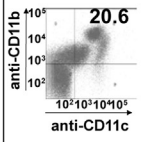
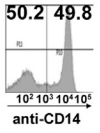
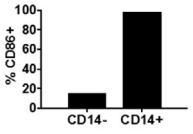
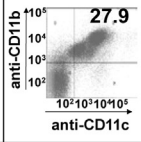
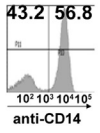
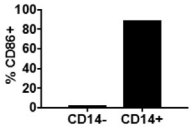
A IVIG – infliximab – atorvastatin

Subject #	Age, yrs	Sex	Ethnicity	Days from IVIG infusion	Zmax	AMCC*	% of DC in PBMC	% of CD14- and CD14+ DC	Expression of CD86 on CD14- and CD14+ DC
1	2.4	M	Hispanic	15	2.7	4,503			
2	3.0	M	Hispanic	15	3.9	2,132			
3	3.9	M	Mixed	18	4.1	5,676	Not tested	Not tested	Not Tested
4	5.0	F	Hispanic	19	3.2	3,550			
5	7.7	M	Hispanic	15	2.8	2,288			
Median (IQR)	**3.9 (3-5)**	**NA**	**NA**	**15 (15-18)**	**3.2 (2.8-3.9)**	**3550 (2288-4503)**			

*Absolute mononuclear cell count

Figure 6. Immunophenotyping of PBMCs in subjects with Kawasaki disease treated with IVIG, infliximab, and atorvastatin or with IVIG and infliximab only. Subjects 1, 2, 4, and 5 received 0.75 mg/kg/day of atorvastatin, and subject 3 received 0.5 mg/kg/day. **A** and **B,** Characterization of mDCs by flow cytometry. $CD11c^+CD11b^+$ mDCs (*dot plots*) were gated on $CD14^-$ and $CD14^+$ populations (histograms) and evaluated for CD86 expression to determine their maturation/activation stage. **C** and **D,** Characterization of T cell lineages by flow cytometry. $CD4^+$ and $CD8^+$ T cells were enumerated and evaluated for their activation/expansion by measuring DR and IL-7R expression. Tregs were enumerated by gating on $CD4^+CD25^{high}$ cells (*dot plots*) and evaluated for IL-7R and CD45RA expression that define iTregs. nTregs, Tregs that mature in the thymus, are $IL\text{-}7R^-$ and $CD45RA^-$. DR expression on iTregs and nTregs defines their activation stage. *(Continues)*

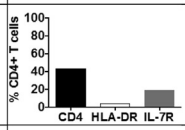
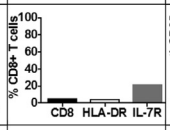
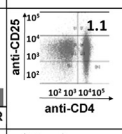
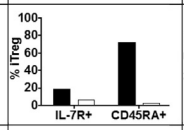
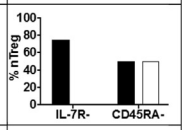
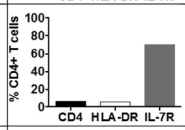
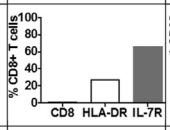
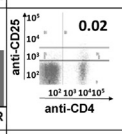
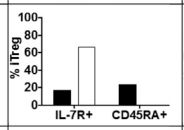
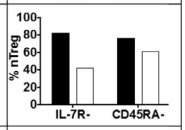
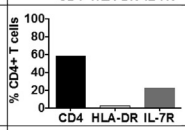
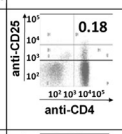
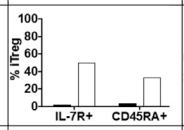
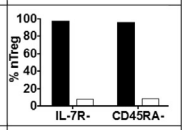
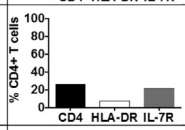
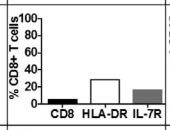
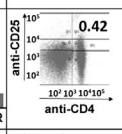
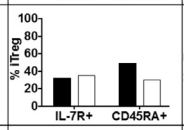
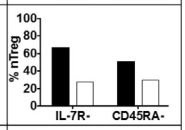
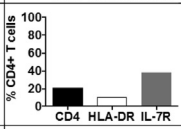
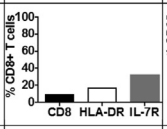
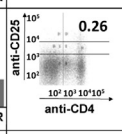
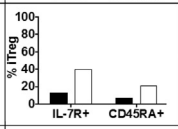
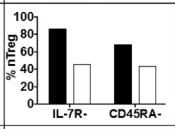
B IVIG – infliximab

Subject #	Age, yrs	Sex	Ethnicity	Days from IVIG infusion	Zmax	AMMC*	% of DC in PBMC	% of CD14- and CD14+ DC	Expression of CD86 on CD14- and CD14+ DC
6	2.3	M	White	19	3.1	2,210			
7	3.4	M	Mixed	30	0.8	3,150			
8	4.2	F	White	15	0.6	3,424			
9	6.1	F	White	15	2.9	7,857			
10	8.1	M	White	16	2.0	903			
Median (IQR)	**4.2 (3.4-6.1)**	**NA**	**NA**	**16 (15-19)**	**2.0 (0.8-2.9)**	**3150 (2210-3424)**			

* Absolute mononuclear cell count

Figure 6. Continues

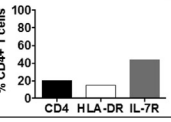
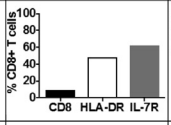
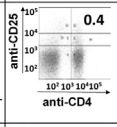
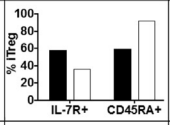
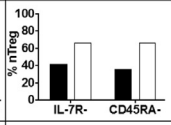
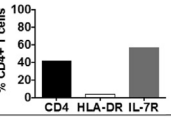
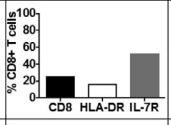
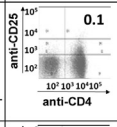
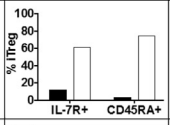
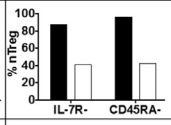
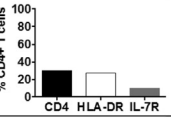
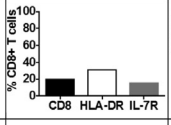
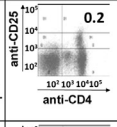
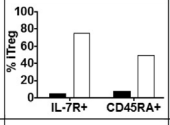
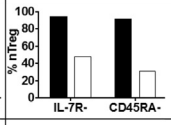
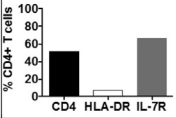
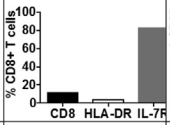
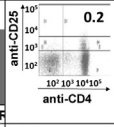
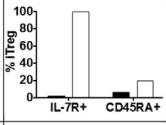
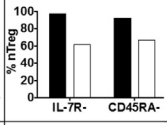
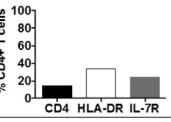
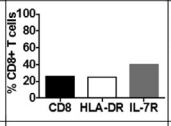
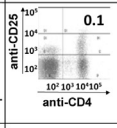
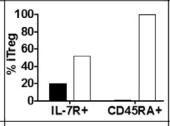
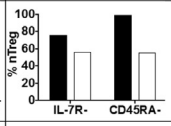
C IVIG – infliximab – atorvastatin

Subject #	Age, yrs	Sex	Ethnicity	Days from IVIG infusion	Zmax	AMCC*	Expression of HLA-DR and IL-7R on CD4+ T cells	Expression of HLA-DR and IL-7R on CD8+ T cells	% of Treg in PBMC	Expression of HLA-DR on iTreg ■ Gated on CD4+ CD25^{high} □ HLA-DR expression	Expression of HLA-DR on nTreg ■ Gated on CD4+ CD25^{high} □ HLA-DR expression
1	2.4	M	Hispanic	15	2.7	4,503					
2	3.0	M	Hispanic	15	3.9	2,132					
3	3.9	M	Mixed	18	4.1	5,676		Not detectable			
4	5.0	F	Hispanic	19	3.2	3,550					
5	7.7	M	Hispanic	15	2.8	2,288					
Median (IQR)	**3.9 (3-5)**	**NA**	**NA**	**15 (15-18)**	**3.2 (2.8-3.9)**	**3550 (2288-4503)**					

*Absolute mononuclear cell count

Figure 6. Continues

D IVIG – infliximab

Subject #	Age, yrs	Sex	Ethnicity	Days from IVIG infusion	Zmax	AMMC*	Expression of HLA-DR and IL-7R on CD4+ T cells	Expression of HLA-DR and IL-7R on CD8+ T cells	% of Treg in PBMC	Expression of HLA-DR on iTreg ■ Gated on CD4+ CD25^{high} □ HLA-DR expression	Expression of HLA-DR on nTreg ■ Gated on CD4+ CD25^{high} □ HLA-DR expression
6	2.3	M	White	19	3.1	2,210					
7	3.4	M	Mixed	30	0.8	3,150					
8	4.2	F	White	15	0.6	3,424					
9	6.1	F	White	15	2.9	7,857					
10	8.1	M	White	16	2.0	903					
Median (IQR)	**4.2 (3.4-6.1)**	**NA**	**NA**	**16 (15-19)**	**2.0 (0.8-2.9)**	**3150 (2210-3424)**					

* Absolute mononuclear cell count

Figure 6. Continues

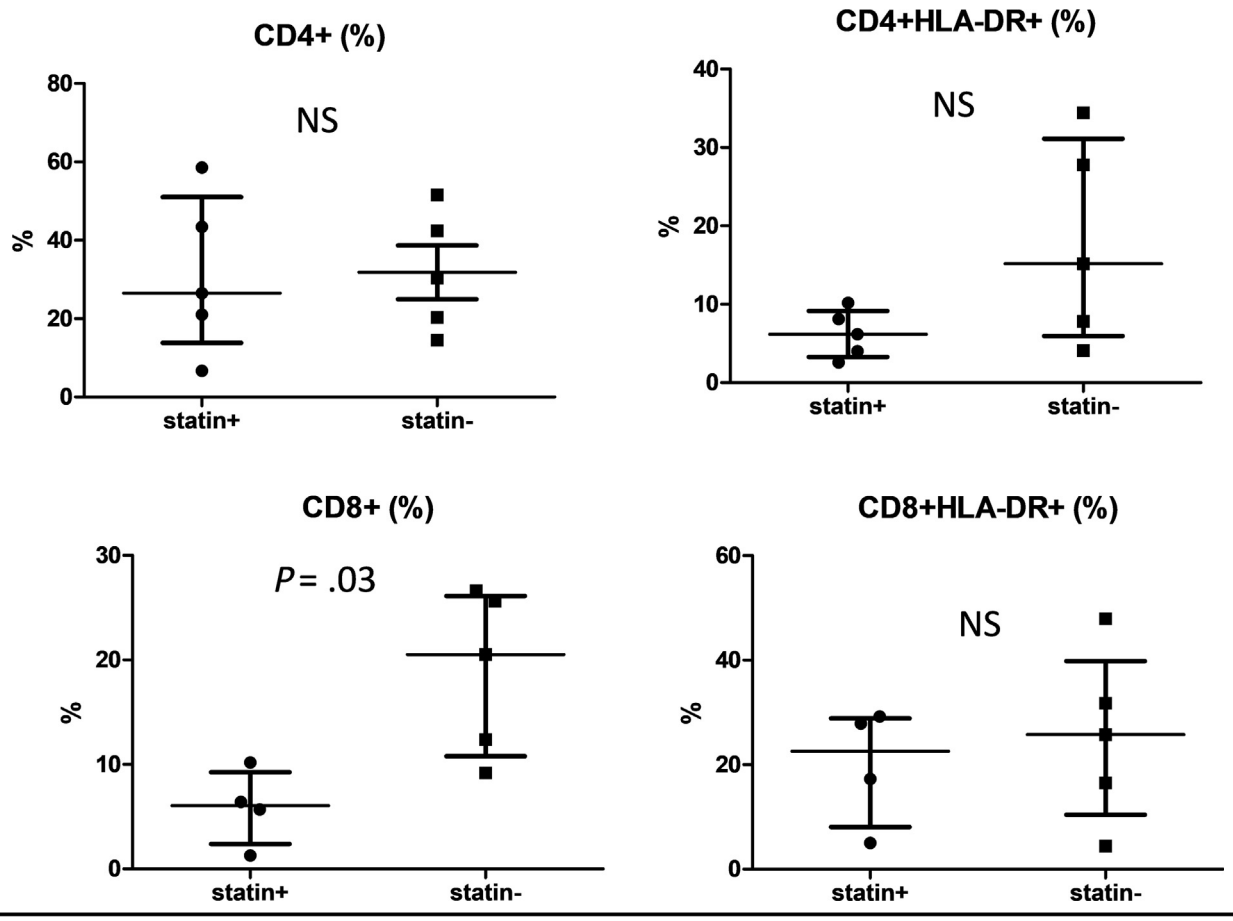


Figure 7. Percentages of circulating $CD4^+$ and $CD8^+$ T cells, including activated ($HLA\text{-}DR^+$) T cells, in patients with Kawasaki disease treated with atorvastatin (statin +) and without atorvastatin (statin –).

Table I. Demographic and clinical laboratory characteristics of atorvastatin-treated subjects with Kawasaki disease and controls evaluated for protein carbonyl levels

Characteristics	Atorvastatin-treated (N = 9)	Controls* (N = 18)	*P* value
Statin concentration, mg/kg, n			
0.125	1	NA	NA
0.25	1	NA	NA
0.75	7	NA	NA
Age, y, median (IQR)	2.9 (2.8-5.1)	3.5 (2.5-5.4)	.8
Male sex, n (%)	8 (89)	13 (72)	.6
Days of illness at sample collection, median (IQR)			
Pre-IVIG	5 (4-6)	5 (4-6)	.7
2 wk	20 (20-22)	20 (17-23)	.6
WBC count, $\times 10^9$/L, median (IQR)	11.7 (10.7-13.2)	10.4 (7.8-14.5)	.4
CRP, mg/dL, median (IQR)	8.1 (6.0-10.1)	5.5 (4.1-17.7)	1.0
ESR, mm/hr, median (IQR)	60 (33-80)	42 (27-60)	.6
ALT, IU/L, median (IQR)	63 (35-107)	87 (46-108)	.4
Zmax, median (IQR)	3.2 (2.8-3.7)	2.0 (1.3-2.8)	.1

ESR, erythrocyte sedimentation rate; *NA*, not applicable; *WBC*, white blood cell.
*Controls are subjects with Kawasaki disease treated only with IVIG and infliximab.

Table III. Change in laboratory parameters in the study population by dose level between baseline and weeks 2 and 6 of the study

	Overall		Dose 1 (0.125 mg/kg) (N = 6)		Dose 2 (0.25 mg/kg) (N = 7)		Dose 3 (0.5 mg/kg) (N = 3)		Dose 4 (0.75 mg/kg) (N = 18)	
Parameters	Δ2 wk minus baseline	Δ6 wk minus baseline	Δ2 wk minus baseline	Δ6 wk minus baseline	Δ2 wk minus baseline	Δ6 wk minus baseline	Δ2 wk minus baseline	Δ6 wk minus baseline	Δ2 wk minus baseline	Δ6 wk minus baseline
WBC count, × 10^9/L	−6.3 (−8.4 to −2.4)	−6.2 (−9.4 to −3.9)	−7.5 (−7.7 to −3.3)	−6.1 (−8.3 to −3.4)	−6.4 (−12.3 to −4.3)	−7 (−13 to −5.1)	−4.4 (−6.3 to −1.8)	−4 (−5 to −2.5)	−5.3 (−8.9 to −1.5)	−6.2 (−9.4 to −4.8)
Polys, %	−30 (−37 to −17)	−22.4 (−32.3 to −14.2)	−30 (−35.5 to −1.1)	−18.3 (−33.3 to −11.1)	−30 (−38 to −25)	−25 (−29.5 to −22.5)	−35 (−36 to −13.5)	−7 (−20 to 0)	−28 (−35.7 to −17.6)	−22.4 (−30.7 to −14.2)
Bands, %	−4 (−12 to −1)	−4 (−11 to 0)	−4 (−15 to −2.5)	−5 (−16 to −2.5)	−1 (−8 to 1)	−1 (−8 to −1)	−12 (−16.5 to −8)	−12 (−17.5 to −8)	−3 (−11 to −0.5)	−1 (−10.5 to 0.25)
Lymphs, %	29.3 (22-35)	27.5 (22-38.3)	26 (21-32)	35 (26.1-39)	29.4 (26-37.5)	36 (25.6-38.5)	34 (24.5-36)	38 (19.5-38.5)	29.1 (22.2-35)	25.2 (21.1-29.4)
ZHgb*	0.7 (−0.7 to 1.8)	1.4 (0.7-3)	0.7 (0.7-1.3)	1.8 (1.4-2.9)	1.8 (0.6-2.1)	1.4 (0.3-2.5)	0.2 (−0.1 to 1.1)	1.5 (1-2.1)	0.1 (−1.2 to 1)	1.3 (0.7 to 3.2)
Platelets, × 10^9/L	16.5 (−74 to 175)	−34 (−122 to 37.8)	−7 (−157 to 28)	−71.5 (−144.3 to 8.8)	−24 (−78.5 to 125)	−40 (−102 to 43.5)	52 (20-175.5)	17 (5.5-69)	20 (−57 to 200)	−23 (−127 to 36.5)
CRP, mg/dL	−13.4 (−21 to −5.8)	−15.1 (−21 to −4.5)	−12 (−19.9 to −3.6)	−7.4 (−19.7 to −4.5)	−18.2 (−21.6 to −8.3)	−15.1 (−18.7 to −10.6)	−17.2 (−17.2 to −17.2)	−17.2 (−17.2 to −17.2)	−10.2 (−15.5 to −5.8)	−13.9 (−23.5 to −4.4)
ESR, mm/h	−12 (−35 to 2)	−46 (−67 to −34)	−12 (−15 to 30)	−51 (−54 to −38)	−13 (−19 to −5)	−46 (−99 to −38)	−36 (−71 to 30)	−80 (−99 to −56)	−7 (−42 to 4)	−46 (−60 to −29)
GGT, IU/L	−43 (−90 to −3)	−43 (−104 to −9)	−115 (−132 to −72.5)	−133 (−163 to −88)	−55 (−75 to −6.5)	−62 (−84 to −11)	−43 (−67 to −21)	−68 (−94 to −39)	−13 (−77 to −1)	−19 (−85 to −7)
ALT, IU/L	−23 (−75 to −3)	−23 (−90 to 2)	−34 (−42 to 0)	−42 (−52 to 6)	−15 (−53 to −2)	−22 (−61 to 3)	−16 (−66 to −8)	−26 (−76 to −12)	−27 (−85 to −6)	−18 (−98 to −8)
AST, IU/L†	9 (−11 to 17)	2 (−20 to 11)	18 (−2 to 33)	−9 (−18 to 2)	−7 (−32 to 12.5)	−5 (−52 to 11)	1 (−3 to 5)	1 (−6 to 8)	12 (3 to 17)	3 (−7 to 6)
CK, IU/L†	18 (6-29)	57 (34-83)	23 (9-35)	44 (28-59)	11 (6-18)	75 (50-75)	24 (2-28)	63 (56 to 81)	19 (8-27)	55 (26-92)
hsCRP, mg/L†	−62.9 (−105.9 to −31.1)	−63.4 (−120.6 to −31.9)	−78.4 (−83.1 to −64)	−78.5 (−83.5 to −64.2)	−30.7 (−62.8 to −8.2)	−32.3 (−63.7 to −8.3)	−53.4 (−68.8 to −43.4)	−56 (−70.9 to −44.2)	−66.3 (−130.9 to −35.1)	−67.5 (−142.7 to −32)
Cholesterol, mmol/L†	15 (−5 to 37)	−7 (−25 to 3)	28 (10-57)	1 (−14 to 22)	22 (−27 to 33)	−32 (−42 to −13)	−1 (−10 to 18)	−7 (−8 to 5)	15 (−8 to 35)	−7 (−22 to 2.3)
LDL, mmol/L	−7 (−24 to 13)	−24 (−38 to −12)	−11 (−30 to 27)	−14 (−37 to −1)	7 (−48 to 14)	−34 (−63 to −19)	−11 (−16 to −9)	−13 (−26 to −8)	−1 (−24 to 15)	−24 (−33 to −12)
HDL, mmol/L	29 (21-36)	35 (26-40)	33 (26-36)	40 (34-43)	26 (23-30)	29 (26-37)	32 (22-35)	34 (30-36)	28 (21-41)	36 (26-41)
Triglycerides, mmol/L	−58 (−97 to −30)	−87 (−122 to −55)	−53 (−174 to −45)	−91 (−208 to −81)	−91 (−104 to −20)	−90 (−98 to −48)	−61 (−89 to −8)	−90 (−98 to −48)	−53 (−83 to −35)	−67 (−127 to −62)

hs, high sensitivity.

Data are median (IQR). For the following laboratory values, the number of subjects differed from 34: bands (N = 24), platelets (N = 32), CRP (N = 19), ESR (N = 32), ALT (N = 32), AST (N = 24), CK (N = 27), hsCRP (N = 30), cholesterol (N = 28).

*zHgb, SD units from the mean for age-adjusted hemoglobin values.[35]

†Because these laboratory values were measured once subjects had enrolled in the atorvastatin trial, the baseline values are post-IVIG.

Table V. AEs by body system

AEs, n (%)	All dose levels (N = 87)	Dose 1 (0.125 mg/kg/d) (N = 11)	Dose 2 (0.25 mg/kg/d) (N = 14)	Dose 3 (0.5 mg/kg/d) (N = 6)	Dose 4 (0.75 mg/kg/d) (N = 56)
Cardiac	2 (2.3)	-	-	-	Worsening coronary artery aneurysm
Dermatologic	12 (13.8)	Hives/viral exanthema	-	-	Rash, hair loss, insect bites
Gastrointestinal	5 (5.8)	Constipation	Diarrhea	Emesis	Emesis, elevated AST and/or ALT
Hematologic	15 (17.2)	Bruising/epistaxis	Bruising/epistaxis	-	Bruising/epistaxis
Immunologic	19 (21.8)	Fever	Fever	Fever	Fever
Metabolic	3 (3.5)	-	Decreased cholesterol	-	Decreased cholesterol
Musculoskeletal	12 (13.4)	Myalgia with transient thigh or foot pain	Myalgia with bilateral leg pain	-	Arthritis, arthralgia
Neurologic	7 (8.1)	-	Headache	Headache	Irritability, headache
Ophthalmic	1 (1.2)	-	-	-	Viral conjunctivitis
Oropharyngeal	2 (2.3)	-	-	-	Otitis media, otalgia
Respiratory	8 (9.2)	Viral illness	Viral illness	Congestion	Viral illness
Urologic	1 (1.2)	-	-	-	Urinary tract infection

N represents the number of AEs for the dose level.

Table VI. Atorvastatin and ortho-hydroxyatorvastatin PK parameters by dose level

Dose, mg/kg	C_{max}, ng/mL	C24, ng/mL	Trough 2 wk, ng/mL	Trough 6 wk, ng/mL	T_{max}, h	Half life, h	$AUC_{0-\infty}$, ng*h/mL	CL/F, L/h/kg	Vd/F, L/kg
Atorvastatin									
0.125 (n = 6)	5.80 (2.32-8.53)	BQL (BQL -0.38)	BQL (BQL -0.91)	BQL (BQL -0.26)	1.5 (1-2)	5.5 (4.4-7.9)	41.9 (31.5-42.9)	29.8 (16.6-39.8)	222 (190-287)
0.25 (n = 5)	9.49 (4.02-22.5)	BQL (BQL -1.54)	BQL (BQL -1.11)	BQL (BQL -2.19)	1 (1-6)	6.0 (5.6-6.2)	122.8 (38.4-171.7)	20.2 (14.6-60.00)	163 (130-519)
0.5 (n = 3)	21.70, 82.6	BQL, 1.33	4.30 (BQL -12.8)	BQL, 6.0	1, 2	5.3 (4.2-6.3)	330.9 (188.1-473.6)	18.7 (10.6-26.80)	153 (65-242)
0.75 (n = 6)	41.4 (29.3-469)	BQL (BQL -2.89)	BQL (BQL -10.7)	BQL (BQL -5.56)	1 (1-2)	4.3 (3.1-5.1)	356.5 (210.6-2890.9)	21.7 (14.7-34.20)	158 (65-212)
Ortho-hydroxyatorvastatin metabolite									
0.125 (n = 6)	1.87 (0.92-3.42)	BQL (BQL -0.67)	BQL (BQL -1.97)	BQL (BQL -0.87)	6 (2-6)	6.2 (4.1-9.1)	40.2 (18.1-42.7)	N/A	N/A
0.25 (n = 5)	4.91 (3.86-5.35)	BQL (BQL -1.07)	BQL (BQL-1.55)	BQL (BQL -2.59)	2 (1-6)	5.6 (2.7-8.5)	64.6 (45.6-81.0)	N/A	N/A
0.5 (n = 3)	11.10, 18.10	BQL, 2.13	7.01 (BQL-17.7)	BQL, 12.4	1, 2	6.8 (6.3-7.3)	178.6 (145.5-211.8)	N/A	N/A
0.75 (n = 6)	24.6 (9.27-49.9)	BQL (BQL -5.64)	BQL (BQL-9.57)	BQL (BQL -13.1)	2 (1-6)	5.3 (4.3-6.9)	238.4 (154.9-1062.1)	N/A	N/A

BQL, below quantitative level (<0.25 or <2.5 ng/mL).
Values are reported as median (range). If only 2 values are available, both are reported.

Table VII. Comparison of z max and change in *z*-score for the study population over time by dose level

Parameter	Overall		Dose 1 (0.125 mg/kg) (N = 6)		Dose 2 (0.25 mg/kg) (N = 7)		Dose 3 (0.5 mg/kg) (N = 3)		Dose 4 (0.75 mg/kg) (N = 18)	
Zmax*	2.9 (2.5-3.6)		3 (2.9-3.5)		5.2 (2.5-8.6)		3.5 (3.3-3.8)		2.6 (2.5-3.1)	
	2-wk *z*-score minus baseline	6-wk *z*-score minus baseline	2-wk *z*-score minus baseline	6-wk *z*-score minus baseline	2-wk *z*-score minus baseline	6-wk *z*-score minus baseline	2-wk *z*-score minus baseline	6-wk *z*-score minus baseline	2-wk *z*-score minus baseline	6-wk *z*-score minus baseline
LAD†	−0.9	−1.2	−1	−1.5	0	−0.1	−1.4	−1.7	−0.8	−1.2
	(−1.4 to 0.3)	(−1.5 to −0.2)	(−1.5 to 0.2)	(−1.8 to −1.3)	(−1 to 0.3)	(−1 to 0.4)	(−2 to −1.1)	(−2.2 to −1.4)	(−1.2 to 0.2)	(−1.2 to −0.6)
RCA†	−0.7	−1.1	−0.9	−1.4	−0.6	−0.8	−0.6	−2.2	−0.5	−0.9
	(−1.5 to 0)	(−1.8 to −0.4)	(−1.4 to −0.7)	(−1.8 to −1.3)	(−1.2 to −0.2)	(−1.0 to 0.1)	(−0.9 to −0.3)	(−2.4 to −1.9)	(−1.4 to 0.4)	(−1.6 to −0.3)

Data are median (IQR).
*Zmax is the largest *z*-score of either the LAD or RCA over the 6-week course of therapy.
†*z*-scores were calculated as described previously.[35]

Table VIII. Evolution of *z*-scores for subjects with Zmax ≥5 over the course of atorvastatin therapy

Age, y	Days of illness at study enrollment	Dose of atorvastatin, mg/kg	Baseline LAD *z*-score	Baseline RCA *z*-score	2-wk LAD *z*-score	2-wk RCA *z*-score	6-wk LAD *z*-score	6-wk RCA *z*-score
2.75	15	0.25	5.18	1.51	3.17	1.12	2.88	0.73
16.50	21	0.25	7.00	8.30	7.25	6.82	6.93	7.06
4.73	15	0.25	8.17	8.85	7.05	5.75	7.05	5.75
5.44	10	0.25	9.08	5.03	15.42	8.32	16.01	10.16
2.94	5	0.75	2.98	4.23	5.88	10.92	3.85	8.95
2.80	7	0.75	6.15	5.26	16.00	12.86	21.50	13.91

*Z*max is the largest *z*-score of either the LAD or RCA over the 6-week course of therapy.