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Efficacy and Safety of Rosuvastatin Therapy for Children With Familial Hypercholesterolemia

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Objectives This study was undertaken to evaluate the efficacy and safety of rosuvastatin therapy for children with familial hypercholesterolemia.

Background Familial hypercholesterolemia is a common inherited disorder causing markedly elevated low-density lipoprotein cholesterol (LDL-C) levels from birth and resulting in premature atherosclerosis. In children, statins have been shown to be effective in reducing LDL-C, restoring flow-mediated dilation, and slowing carotid intima-media thickening. However, few children in these trials achieved current LDL-C goals.

Methods This study comprised a 12-week double-blind, randomized, placebo-controlled trial, followed by a 40-week open-label, titration-to-goal extension phase in 177 pubertal children, ages 10 to 17 years, with familial hypercholesterolemia. Participants were randomly assigned to placebo or rosuvastatin 5, 10, or 20 mg once daily.

Results Compared with placebo, rosuvastatin 5, 10, and 20 mg reduced LDL-C by 38%, 45%, and 50%, respectively ($p < 0.001$ for each group vs. placebo). With a maximum allowed dose of 20 mg, 40% achieved the treatment goal of <110 mg/dl during the open-label, titration-to-goal phase. Rosuvastatin was well tolerated, with no apparent adverse impact on growth or development.

Conclusions In children with familial hypercholesterolemia, rosuvastatin 20 mg daily reduced LDL-C by 50%. Nonetheless, only 40% attained the consensus LDL-C target of <110 mg/dl, reflecting these patients' high baseline LDL-C levels (mean, 232 mg/dl). (Pediatric Lipid-Reduction Trial of Rosuvastatin [PLUTO]; NCT00355615) (J Am Coll Cardiol 2010;55:1121–6) © 2010 by the American College of Cardiology Foundation

Familial hypercholesterolemia (FH) is an autosomal dominant genetic disorder (1) characterized by markedly elevated low-density lipoprotein cholesterol (LDL-C) levels leading to premature atherosclerosis and cardiovascular events (2). Children with FH exhibit functional and morphologic atherosclerotic arterial wall changes from a young age (3–5).

Placebo-controlled trials have demonstrated the safety and efficacy of short-term treatment with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) for reducing LDL-C in pediatric populations (6). Furthermore, a 2-year trial involving children with FH showed that statin therapy slowed carotid intima media thickening (7). On the basis of these observations and the known morbidity and

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Abbreviations and Acronyms

AE = adverse event
Apo = apolipoprotein
CK = creatine kinase
CVD = cardiovascular disease
FH = familial hypercholesterolemia
HDL-C = high-density lipoprotein cholesterol
LDL-C = low-density lipoprotein cholesterol

mortality of untreated FH, current consensus-based guidelines recommend initiation of pharmacologic treatment in childhood (8), with LDL-C treatment goals of <130 mg/dl, or <110 mg/dl in patients with other risk factors (9).

Although statins are the mainstay of treatment for children with FH, even the LDL-C target of <130 mg/dl is difficult to achieve (10). Rosuvastatin effectively lowers LDL-C in adults (11), but has not been previously studied in children. This study investigated the efficacy and safety of rosuvastatin in children with FH.

Methods

Study design. The PLUTO (Pediatric Lipid-redUction Trial of rOsuvastatin [D3561C00087]) study protocol was approved by local institutional review boards, and written informed consent was obtained from participants and their parents. The study was a multicenter (Online Appendix), 2-stage trial: after a 6-week diet-only lead-in, eligible participants were randomly allocated (1:1:1:1 to placebo or rosuvastatin 5, 10, or 20 mg daily), stratified by center, for 12 weeks, followed by a 40-week open-label, dose-titration phase. After the double-blind phase, placebo recipients and subjects with LDL-C <110 mg/dl on their assigned rosuvastatin dose began the open-label phase on rosuvastatin 5 mg. All others continued their rosuvastatin dose from the double-blind phase. In the open-label phase, LDL-C values were reported to investigators as well as to participants. The rosuvastatin dose was uptitrated, at the discretion of the investigator, to a maximum dose of 20 mg to attain the LDL-C target of <110 mg/dl.

Study population. Patients were enrolled at 20 centers in Europe and North America, with the first patient enrolled in July 2006 and the trial completed in June 2008. Adolescents, age 10 to 17 years, were eligible if they had: 1) diagnosis of heterozygous FH by documentation of a genetic defect or by pre-defined clinical criteria (12); 2) Tanner stage ≥II, with female subjects being at least 1 year post-menarche; and 3) fasting LDL-C ≥190 mg/dl, or LDL-C >160 mg/dl if there was a family history of premature cardiovascular disease (CVD) or if the patient had ≥2 other risk factors for CVD.

Outcome measures. The primary outcome measure was the percentage change from baseline in LDL-C during the double-blind period for each treatment group compared with placebo. Secondary measures were the changes in other lipoproteins and attainment of LDL-C goal. LDL-C was estimated by the Friedewald equation (13). Compliance was assessed by pill count. Safety assessments included incidence

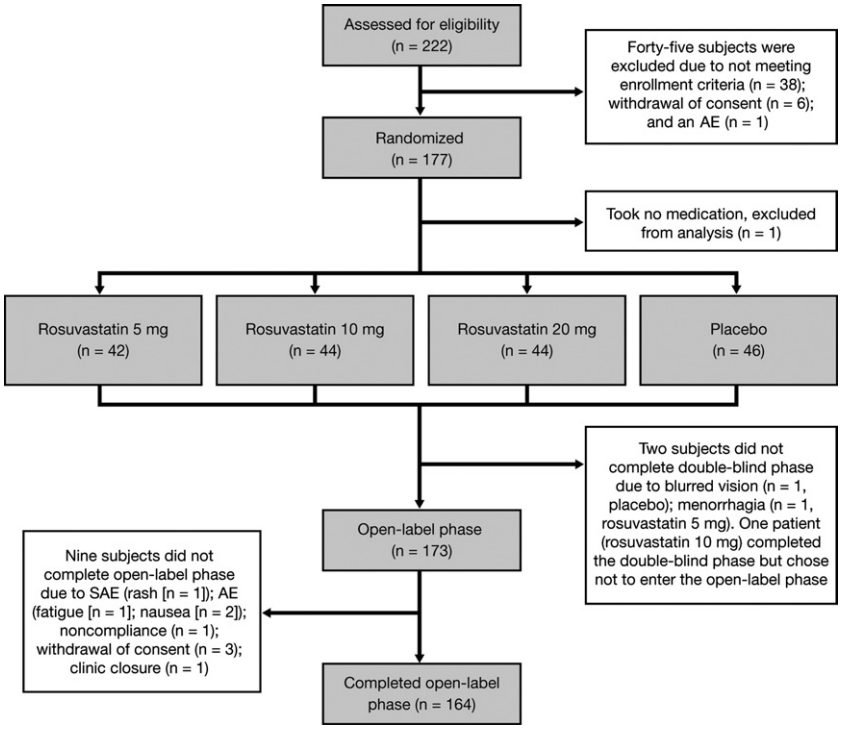

Figure 1 Allocation and Disposition of Study Subjects

The flow chart details the allocation and disposition of subjects in the PLUTO study. AE = adverse event; SAE = serious adverse event.

Table 1 Baseline Characteristics and Compliance With Study Treatment During the Double-Blind Phase (All Randomized Patients, n = 177)

	Treatment Assignment During Double-Blind Phase			
		Rosuvastatin		
	Placebo (n = 46)	5 mg (n = 42)	10 mg (n = 44)	20 mg (n = 45)
Male	24 (52)	26 (62)	25 (57)	22 (49)
Age, yrs				
Male	13.9 ± 1.5	13.9 ± 1.9	14.0 ± 1.5	13.6 ± 1.8
Female	14.8 ± 1.7	14.4 ± 2.0	15.2 ± 1.2	14.8 ± 1.6
Caucasian	41 (89)	39 (93)	42 (96)	43 (96)
Tanner stage				
II	8 (17)	6 (14)	7 (16)	9 (20)
III	8 (17)	14 (33)	4 (9)	5 (11)
IV	20 (44)	11 (26)	20 (46)	20 (44)
V	10 (22)	11 (26)	13 (30)	11 (24)
Height, cm	163.3 ± 8.6	165.2 ± 11.5	167.0 ± 10.3	163.3 ± 10.9
Weight, kg	58.0 ± 13.4	56.6 ± 13.0	60.8 ± 13.7	59.0 ± 12.6
BMI kg/m^2, *z*-score	0.4 ± 0.9	0.1 ± 1.2	0.3 ± 1.1	0.5 ± 0.8
Waist circumference, cm	76.2 ± 10.6	74.7 ± 11.2	76.3 ± 11.1	75.8 ± 10.8
Blood pressure, mm Hg				
Systolic	110 ± 11	109 ± 11	112 ± 11	112 ± 14
Diastolic	66 ± 9	63 ± 8	66 ± 6	67 ± 8
Overall compliance ≥80%	37 (80)	37 (88)	40 (91)	40 (89)

Values are n (%) or mean ± SD. *A z-score of 0 indicates the population mean for age and sex.
BMI = body mass index.

and severity of adverse events (AEs), laboratory values (full blood count and cell indices, albumin, total protein, liver enzymes, bilirubin, creatine kinase [CK], blood urea nitrogen, serum creatinine, calcium, fasting glucose, phosphorus, potassium sodium, thyroid-stimulating hormone, glycosylated hemoglobin, and urinalyses including creatinine and protein), and growth and development. For height, weight, and body mass index, *z*-scores were calculated (14); a *z*-score of 0 indicates the population mean for age and sex. Pubertal development was assessed by Tanner stage.

Sample size calculation and statistical analyses. The sample size was set to achieve at least 150 evaluable patients at the end of the double-blind period. Assuming that the percentage change from baseline for LDL-C has a standard deviation of 15% and using a 2-sided alpha of 0.05, a sample size of 37 patients per group would have allowed 90% power to detect a true treatment effect size of 12%. The primary efficacy analysis was based on the intention-to-treat population, defined as patients who had taken at least 1 dose of study medication. For the primary efficacy end point, analysis of covariance, with treatment group as an independent variable and baseline LDL-C as the covariate, was used to compare each active-dose group with placebo. For analyses of secondary end points, no adjustment was made for multiple comparisons. A p value <0.05 was considered statistically significant.

Results

Of 222 participants screened, 177 were randomized (Fig. 1). One patient did not take any study medication after randomization, resulting in 176 patients being included in the analyses. The mean (SD) age of the participants was 14.5 (1.8) years (range 10 to 17 years); 97 (55%) were male. At baseline, demographic and clinical characteristics were similar in the 4 treatment groups (Table 1). Of 174 patients completing the double-blind phase, 173 continued to the open-label phase, and 164 (95%) completed the trial.

Baseline LDL-C and other lipoprotein levels were comparable among treatment arms. Reductions from baseline in LDL-C during the double-blind phase were 1%, 38%, 45%, and 50% for placebo, rosuvastatin 5, 10, and 20 mg, respectively ($p < 0.001$ for all doses vs. placebo) (Table 2). Significant reductions, relative to placebo, were also found for total cholesterol and apolipoprotein (Apo) B, but not for triglycerides (Table 2). High-density lipoprotein-cholesterol (HDL-C) and ApoA-I were not significantly different from placebo.

During the double-blind phase, the LDL-C target of <110 mg/dl was achieved in no patient treated with placebo versus 12%, 41%, and 41% of patients treated with rosuvastatin 5, 10, and 20 mg, respectively. In the open-label phase, this goal was attained in 40% of participants. The secondary goal of <130 mg/dl was reached in 68% of subjects during the open-label phase. At the end of the open-label phase, 26 participants were receiving rosuvastatin 5 mg, 25 were receiving rosuvastatin 10 mg, and 122 were receiving rosuvastatin 20 mg.

Approximately 90% of subjects in the double-blind phase and 60% of subjects in the open-label phase maintained ≥80% compliance to study medication. During the double-blind phase, compliance was 88.7 ± 12.4% on rosuvastatin

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Table 2 Lipid Values and Percent Change From Baseline During Double-Blind, Randomized, Placebo-Controlled Phase (Intention-to-Treat Population, n = 176)

		Rosuvastatin		
	Placebo (n = 46)	5 mg (n = 42)	10 mg (n = 44)	20 mg (n = 44)
Lipids, mg/dl				
TC				
Baseline	293 (50)	300 (60)	297 (49)	302 (50)
Week 12	293 (54)	207 (37)	195 (44)	183 (36)
% change	0	−30	−34	−39
p value		<0.001	<0.001	<0.001
LDL-C				
Baseline	229 (43)	238 (55)	229 (45)	237 (48)
Week 12	227 (49)	143 (31)	128 (40)	117 (33)
% change	−1	−38	−45	−50
p value		<0.001	<0.001	<0.001
HDL-C				
Baseline	45 (11)	46 (12)	49 (10)	47 (13)
Week 12	48 (10)	48 (12)	54 (11)	50 (13)
% change	7	4	10	9
p value		0.4	0.2	0.5
TG*				
Baseline	82 (57–124)	80 (55–100)	81 (53–105)	81 (59–107)
Week 12	78 (60–107)	61 (48–83)	61 (49–77)	64 (46–92)
% change	−7	−13	−15	−16
p value		0.8	0.1	0.1
Apolipoproteins, g/l				
ApoB				
Baseline	1.4 (0.3)	1.5 (0.4)	1.4 (0.2)	1.5 (0.3)
Week 12	1.4 (0.3)	1.0 (0.2)	0.9 (0.3)	0.9 (0.2)
% change	−2	−32	−38	−41
p value		<0.001	<0.001	<0.001
ApoA-I				
Baseline	1.3 (0.2)	1.3 (0.2)	1.4 (0.3)	1.3 (0.3)
Week 12	1.3 (0.2)	1.3 (0.2)	1.5 (0.2)	1.4 (0.2)
% change	4	2	4	4
p value		0.7	0.3	0.6

Data are expressed as mean (SD); changes are least squares mean % change from baseline. *For triglycerides (TG), data are expressed as median (interquartile range); changes are median % change from baseline assessed by the Kruskal-Wallis Test. Differences from placebo were assessed by analysis of covariance with treatment group and baseline level as covariates.

ApoA = apolipoprotein A; ApoB = apolipoprotein B; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; TC = total cholesterol.

5 mg, 91.8 ± 10.1% on rosuvastatin 10 mg, 90.9 ± 11.4% on rosuvastatin 20 mg, and 88.4 ± 18.5% on placebo.

During the double-blind phase, the overall frequencies of AEs were 54%, 50%, 64%, and 55%, with the most common AEs being headache (n = 9, n = 6, n = 7, n = 9), nasopharyngitis (n = 5, n = 3, n = 7, n = 7), influenza (n = 4, n = 2, n = 2, n = 0), myalgia (n = 0, n = 1, n = 1, n = 2), and nausea (n = 2, n = 2, n = 0, n = 2) in the placebo and rosuvastatin 5, 10, and 20 mg groups, respectively. One serious AE of blurred vision occurred in the placebo group during the double-blind phase, and 1 patient receiving rosuvastatin 20 mg had a vesicular rash during the open-label phase that progressed to cellulitis.

There were no hepatic, skeletal muscle, or renal AEs that led to permanent treatment discontinuation. Changes in aspartate aminotransferase, alanine aminotransferase, and CK values during the double-blind phase were similar among groups (Table 3). Transaminase elevation ≥3 times the upper limit of normal was observed in 3 patients (1 receiving rosuvastatin 10 mg, 2 receiving rosuvastatin 20 mg) during the double-blind phase. In the open-label phase, 1 patient experienced transaminase elevation ≥3 times the upper limit of normal. For all patients, transaminases normalized while continuing treatment or remained normal after resumption of rosuvastatin therapy.

Creatine kinase elevation >10 times the upper limit of normal was observed in 4 patients during the double-blind phase (2 each on rosuvastatin 10 and 20 mg) and 4 during the open-label phase. Myalgia was reported by 4 patients (3%) taking rosuvastatin during the double-blind phase and 5 (3%) during the open-label phase. Myopathy attributed to physical activity was reported in 2 patients (1 each on rosuvastatin 10 and 20 mg). For all patients, symptoms and/or CK elevation normalized while continuing treatment

Table 3 Baseline Values and Change at End of Double-Blind Phase for Transaminases, CK, GFR, and Urine P:C (Safety Analysis Population, n = 176)

		Rosuvastatin		
	Placebo (n = 46)	5 mg (n = 42)	10 mg (n = 44)	20 mg (n = 44)
Median (Q1, Q3)				
AST, U/l				
Baseline	19.5 (17, 23)	21 (19, 25.5)	21 (18, 25)	21 (18, 23)
Change at week 12	0 (−2, 3)	1 (−2, 5)	1 (−1, 4)	1 (−2, 5)
ALT, U/l				
Baseline	14 (12, 17)	15 (12, 18)	14 (11, 18)	13 (12, 17)
Change at week 12	0.5 (−1, 3)	2 (−1, 5)	4 (−1, 8)	3 (0, 7)
CK, μg/l				
Baseline	106 (72, 138)	103 (75, 142)	120 (78, 148)	106 (73, 170)
Change at week 12	1.5 (−25, 52)	1.5 (−37, 22)	6 (−16, 38)	7 (−22, 26)
Mean (SD)				
GFR, ml/min/1.73 m^2				
Baseline	147 (27)	149 (29)	144 (25)	139 (24)
Change at week 12	−3.9 (12)	0.0 (17)	1.6 (17)	0.0 (14)
Urine P:C, mg/mg				
Baseline	0.07 (0.05)	0.06 (0.04)	0.06 (0.04)	0.07 (0.04)
Change at week 12	−0.01 (0.03)	0.01 (0.03)	0.00 (0.04)	0.00 (0.03)

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CK = creatine kinase; GFR = glomerular filtration rate; P:C = protein/creatinine ratio; Q1 = first quartile; Q3 = third quartile.

or remained normal after resumption of rosuvastatin therapy. No clinically meaningful renal abnormalities were observed.

Height, weight, and sexual development progressed normally (data not shown).

Discussion

This study is the first to our knowledge to evaluate the efficacy and safety of rosuvastatin in a pediatric population. Rosuvastatin 5, 10, and 20 mg once daily lowered LDL-C by 38%, 45%, and 50%, respectively, and 40% of participants reached an LDL-C goal of <110 mg/dl. No untoward safety effects were observed during this 1-year trial.

The LDL-C reductions observed with these rosuvastatin doses in this study are consistent with those seen in adults (11,15), and at the 20-mg dose, are the largest reported in FH children to date with any statin. Pediatric studies with other statins reported LDL-C reductions ranging from 24% for pravastatin 40 mg to as high as 40% for atorvastatin 10 to 20 mg (7,10). For this trial, the maximum statin dose evaluated was the second-highest dose approved for adults, consistent with other statin trials in children with FH (4,7,10,16).

In addition to LDL-C–lowering efficacy, this study also assessed the ability of rosuvastatin to reach the recently proposed LDL-C treatment goal of 110 mg/dl recommended for adolescents with FH and other risk factors such as a family history of premature CVD (9), which was applicable to 89% of our participants. Despite the increased LDL-C–lowering achieved with rosuvastatin 20 mg, 60% of patients still did not achieve this goal, reflecting the difficulty in meeting this target in many FH patients. The reason not all patients who did not achieve the treatment goal were receiving maximum rosuvastatin therapy is unknown, because the titration to the maximal allowed dose was at the discretion of the investigator and the rationale not to do so was not required or documented. A less stringent treatment goal of <130 mg/dl was achieved in 68% of the participants. In adults with FH, 22% and 37% achieved this goal with rosuvastatin 20 and 40 mg, respectively (15).

A consistent increase in HDL-C is well documented in adults on rosuvastatin treatment (11), and prior placebo-controlled trials in children with other statins have shown increases in HDL-C (7,10,17). In contrast, the effect of rosuvastatin on HDL-C and ApoA-I in this study was modest and not significant when compared with placebo, possibly due to a 7% increase in HDL-C in the placebo arm. While methodologic drift, specifically calibration, could account for this increase, there should still have been compensatory larger changes in the rosuvastatin-treated groups. A second methodological explanation could be higher visit-to-visit variability seen in all groups during the trial, obscuring treatment group differences.

The tested rosuvastatin doses were well tolerated, as indicated by compliance and assessment of AEs, physical findings, and laboratory measurements. Muscle-related symptoms and CK elevations appeared to be associated with physical activity, because in all cases in which information on exercise was available, the findings were preceded by strenuous or unusual physical activity. These observations are consistent with data in adults (18,19). Overall, the safety profile of rosuvastatin in this study was similar to that of placebo and of other statins investigated in children (6). Nevertheless, the study was of limited size and duration, and

future studies should focus on long-term safety and the existence of more rare or subtle AEs.

The decrease in compliance from 90% in the placebo-controlled period to 60% in the open-label phase did not seem to be related to the occurrence of AEs, and underscores the challenges of long-term medication compliance, particularly by adolescents.

The rationale behind early and aggressive initiation of LDL-C–lowering treatment in FH patients is to retard progression of atherosclerosis, thereby decreasing cardiovascular events in later life. A placebo-controlled trial to definitively prove that statin therapy in children with FH reduces cardiovascular events would be unethical, given their known risk of early CVD if left untreated (20). Therefore, guidelines are based on expert opinion, pediatric trials using surrogate markers for atherosclerosis, and cardiovascular end point trials involving high-risk adults. In children, trials have shown that pravastatin attenuates atherosclerotic progression and moderately reduces LDL-C in children with FH (3,4,7). Although it is likely that greater LDL-C lowering in children would lead to greater reductions in atherosclerotic events, just as in adults (21), neither early treatment nor LDL-C goal attainment per se has been shown to reduce atherosclerotic progression using surrogate markers, let alone subsequent CVD events in pediatric populations.

This trial, along with other studies in nearly 1,000 pediatric patients, confirms that LDL-C lowering with statins is well tolerated in adolescents with FH and, despite significant LDL-C reductions, highlights the difficulty in achieving optimal goals in these patients.

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Key Words: pediatrics ■ hypercholesterolemia ■ drugs ■ genetics ■ prevention.

APPENDIX

For a list of the investigators and institutions that participated in this study, please see the online version of this article.