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Original Articles

Efficacy and safety of rosuvastatin therapy in children and adolescents with familial hypercholesterolemia: Results from the CHARON study

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KEYWORDS:
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OBJECTIVE: Heterozygous familial hypercholesterolemia (HeFH) is an autosomal dominant disorder leading to premature atherosclerosis. Guidelines recommend initiating statins early to reduce low-density lipoprotein cholesterol (LDL-C). Studies have evaluated rosuvastatin in children aged ≥10 years, but its efficacy and safety in younger children is unknown.

METHODS: Children with HeFH and fasting LDL-C >4.92 mmol/L (190 mg/dL) or >4.10 mmol/L (>158 mg/dL) with other cardiovascular risk factors received rosuvastatin 5 mg daily. Based on

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Rosuvastatin;
Safety;
Tolerability

LDL-C targets (<2.85 mmol/L [<110 mg/dL]), rosuvastatin could be uptitrated to 10 mg (aged 6–9 years) or 20 mg (aged 10–17 years). Treatment lasted 2 years. Changes in lipid values, growth, sexual maturation, and adverse events (AEs) were assessed.

RESULTS: The intention-to-treat analysis included 197 patients. At 24 months, LDL-C was reduced by 43, 45, and 35% vs baseline in patients aged 6–9, 10–13, and 14–17 years, respectively ($P < .001$ for all groups). Most AEs were mild. Intermittent myalgia was reported in 11 (6%) patients and did not lead to discontinuation of rosuvastatin treatment. Serious AEs were reported by 9 (5%) patients, all considered unrelated to treatment by the investigators. No clinically important changes in hepatic biochemistry were reported. Rosuvastatin treatment did not appear to adversely affect height, weight, or sexual maturation.

CONCLUSIONS: In HeFH patients aged 6–17 years, rosuvastatin 5–20 mg over 2 years significantly reduced LDL-C compared with baseline. Treatment was well tolerated, with no adverse effects on growth or sexual maturation.

Introduction

Familial hypercholesterolemia (FH) is an inherited disorder of lipoprotein metabolism[1] with the heterozygous (HeFH) form of the disease affecting an estimated 1 in 200 to 1 in 300 people worldwide.[2,3] It is characterized by severely elevated levels of circulating low-density lipoprotein cholesterol (LDL-C),[4] and without early diagnosis and adequate treatment, it can lead to premature atherosclerosis, morbidity, and mortality.[2,5] Studies have shown that early signs of atherosclerosis are already present in childhood,[6,7] and current guidelines state that treatment of children with FH should be considered at an early age (8–10 years) to reduce LDL-C.[2,8,9]

The 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (or statins) are effective and well-tolerated agents that significantly decrease the incidence of atherosclerotic cardiovascular disease (CVD), ischemic stroke, and peripheral vascular disease in adults.[10] Although a number of studies have demonstrated the LDL-C–lowering efficacy and safety of statin therapy in pediatric patients with FH,[11,12] a large proportion of children still do not achieve the recommended LDL-C target of ≤3.4 mmol/L (≤130 mg/dL).[8] There is therefore a need for more intensive lipid-lowering therapy.

In a previous study in children and adolescents aged 10 to 18 years with HeFH, rosuvastatin 20 mg for 52 weeks significantly reduced LDL-C levels by an average of 50% compared with baseline.[13] The use of rosuvastatin in children younger than 10 years, however, has not been examined.

The primary objective of this study was to investigate the efficacy, pharmacokinetics (PK), tolerability, and safety of rosuvastatin over 2 years in children and adolescents aged 6–17 years with HeFH.

Methods

Study design

The hyperCholesterolaemia in cHildren and Adolescents taking Rosuvastatin OpeN label (CHARON; clinicaltrials.gov identifier: NCT01078675) study was a 2-year, open-label, multicenter study assessing the efficacy and safety of rosuvastatin in children and adolescents with HeFH. The full study design has been previously published and is described briefly here.[7]

The study was approved by each participating site's institutional review board and conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonization Good Clinical Practice Guidelines, and current local regulatory requirements. Written informed consent was obtained from participants and/or their parents before participation.

Patients

Patients were enrolled at 14 centers in the Netherlands (n = 6), Canada (n = 5), Belgium (n = 1), Norway (n = 1), and the United States (n = 1).

Patients aged 6–17 years with HeFH and fasting LDL-C at baseline >4.92 mmol/L (>190 mg/dL) or >4.10 mmol/L (>158 mg/dL) in combination with another risk factor for coronary heart disease, that is, family history of premature CVD in first- or second-degree relatives, were included. HeFH was defined as a documented genetic defect in the LDL receptor or apolipoprotein (Apo) B or documented evidence of HeFH in a first-degree relative (LDL-C >4.9 mmol/L [>189 mg/dL] in an adult or >4.1 mmol/L [>158 mg/dL] in a child <18 years old). Children aged 6 to 9 years were all statin naïve and were advised to follow regional guidelines for a low cholesterol diet.

The main exclusion criteria were history of statin-induced myopathy; fasting triglycerides ≥2.87 mmol/L (≥254 mg/dL); fasting serum glucose >9.99 mmol/L (>180 mg/dL) or glycosylated hemoglobin >9%; uncontrolled hypothyroidism (defined as thyroid-stimulating hormone >1.5 × upper limit of normal [ULN]); current active liver disease or hepatic dysfunction (defined as alanine aminotransferase [ALT], aspartate aminotransferase [AST], or bilirubin >1.5 × ULN); serum creatine kinase (CK) ≥3 × ULN; estimated glomerular filtration rate (eGFR) <50 mL/min; ≥2 + proteinuria on urine dipstick; stage 2 hypertension (systolic and/or diastolic blood

pressure >5 mm Hg above the 99th percentile for age, gender, and height); history of solid organ transplant; clinically significant abnormalities in clinical chemistry and hematology or urinalysis; and weight <20 kg (44 lbs).

Outcome measures

The 5-mg starting dose of rosuvastatin was titrated at 3-monthly intervals to a maximum tolerated dose of 10 mg (6- to 9-year olds) or 20 mg (10- to 17-year olds) to achieve an LDL-C goal of <2.85 mmol/L (<110 mg/dL). LDL-C was estimated by the Friedewald equation.[14]

The primary efficacy outcome variable was the percentage change from baseline in fasting LDL-C after 3, 12, and 24 months of treatment with rosuvastatin 5, 10, or 20 mg.

Secondary efficacy outcomes were percentage change from baseline in high-density lipoprotein cholesterol (HDL-C), total cholesterol, triglycerides, non-HDL-C, ApoA-1 and ApoB, and ratios of atherogenic/protective lipids at 3, 12, and 24 months. Change from baseline in high-sensitivity C-reactive protein was also assessed.

The primary safety outcomes were growth (assessed by height velocity) and sexual maturation (assessed by Tanner staging) at baseline, 12, and 24 months. The incidence and severity of adverse events (AEs) and serious AEs, rate of discontinuations due to AEs, and abnormal serum laboratory values were also assessed. Laboratory assessments included AST, ALT, urine protein:creatinine ratio, and CK.

Adherence to treatment was assessed by pill count at every study visit.

Blood samples were also collected for assessment of the PK end points after a single dose of rosuvastatin. The following PK parameters were assessed: maximum plasma concentration (C_{max}), area under the plasma concentration vs time curve from time 0 to 24 hours after rosuvastatin administration ($AUC_{(0–24)}$) and time to C_{max} (t_{max}) of rosuvastatin, N-desmethyl rosuvastatin, and rosuvastatin lactone. The PK population included 12 patients aged from 6 years to below Tanner stage II who were treated and had at least 1 serial PK assessment.

Sample size calculation and statistical analyses

No formal sample size calculation was performed for this study as it was an exploratory study and all objectives in the study were exploratory in nature. The study plan was to enroll a minimum of 180 patients, equally distributed between the 3 age groups. The intention-to-treat (ITT) population was the primary analysis set for efficacy analyses. It included patients who received at least 1 dose of study medication and had a baseline and at least 1 LDL-C measure from a subsequent visit.

Efficacy variables, including percentage change from baseline in lipid parameters, were summarized mainly using descriptive statistics and presented by age group and overall. Least-squares (LS) mean percentage changes from baseline in LDL-C at 3, 12, and 24 months were compared between age groups using an analysis of covariance model with center and baseline values as covariates. In the ITT analysis set, missing data were input using last observation carried forward data. An analysis of covariance was also used to compare LDL-C reduction among age groups, using center and the baseline value as covariates.

The percentage of patients achieving an LDL-C target of <2.85 mmol/L (<110 mg/dL) during titration to goal was also summarized at baseline, 3, 12, and 24 months, as was the percentage of patients achieving an LDL-C target of <3.36 mmol/L (<130 mg/dL).

The safety analysis population included all patients who received at least 1 dose of rosuvastatin and had follow-up data. Descriptive statistics were used to summarize the safety parameters. For growth, data were presented by z-scoring, in addition to means and standard deviations (SDs) for observed data. The z-score used represented normalized data relative to the mean for children of the same age and sex according to National Health and Nutrition Examination Survey growth data collected by the Centers for Disease Control and Prevention. The shift in Tanner stage from baseline at 12 and 24 months for individual patients was summarized to assess the normal progression of sexual maturation over the 2 years of treatment.

Results

Of the 250 patients with HeFH screened, 198 met the eligibility criteria and were included in the 2-year open-label efficacy and safety phase of the study. One patient received a single dose of study drug but was not included in the ITT and safety analyses populations due to a lack of follow-up data. The allocation and disposition of study subjects are summarized in Figure 1.

Baseline characteristics of the patients in each age group and overall are presented in Table 1. The mean age of the participants at baseline was 11.6 (SD, 3.3) years, 44% were boys, mean LDL-C level was 6.1 (SD, 1.3) mmol/L (236 [SD, 49.0] mg/dL) and 77% had a family history of premature CVD in first- or second-degree relatives.

Efficacy outcomes

In the ITT population at 3 months, the LS mean percentage reductions in LDL-C were 41, 41, and 35%, in patients aged 6 to 9, 10 to 13, and 14 to 17 years, respectively (Fig. 2; $P < .001$ for all 3 age groups vs baseline). This effect was sustained over the 2 years of treatment; the LS mean percentage reductions in LDL-C at 24 months were 43, 45, and 35%, respectively.

At 24 months, there was also a significant reduction in total cholesterol ($P < .001$), non-HDL-C ($P < .001$), and ApoB ($P < .001$) and a significant increase in HDL-C level ($P \leq .001$) compared with baseline across all age groups and overall (Table 2). The median percentage reduction in triglycerides from baseline was significant for the 6-to

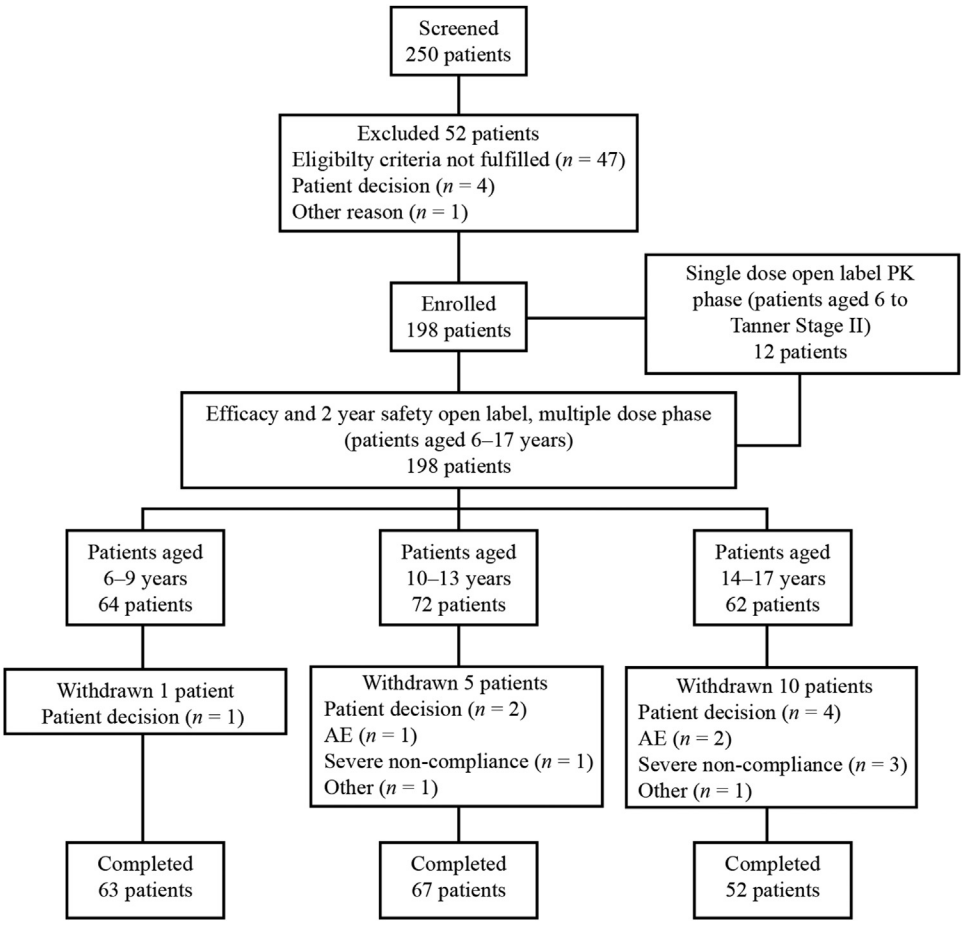

Figure 1 Study flow chart. AE, adverse event; PK, pharmacokinetic.

9-year age group and in the overall population at 3 months ($P = .006$ and $P = .001$, respectively) and 12 months ($P = .029$ and $P = .004$, respectively), but the changes were no longer significant at 24 months. There was a significant increase vs baseline in ApoA-1 in the 10- to 13- ($P = .007$) and 14- to 17-year ($P = .033$) age groups and in the overall population ($P < .001$) at 3 months vs baseline, but this difference was not significant at 12 or 24 months, except in the overall population at 24 months ($P = .030$; Table 2). No consistent changes were observed in high-sensitivity C-reactive protein.

After 24 months of treatment, the percentage of patients achieving an LDL-C of <2.85 mmol/L (<110 mg/dL) was 38% in the 6- to 9-year age group, 46% in the 10- to 13-year age group and 28% in the 14- to 17-year age group (Table 3). In addition, 64, 68, and 39%, respectively, achieved an LDL-C of <3.36 mmol/L (<130 mg/dL).

Assessment by dose showed that at final rosuvastatin doses of 5, 10, and 20 mg, 48, 46, and 32% of patients achieved the LDL-C goal of <2.85 mmol/L (<110 mg/dL) and 62, 67, and 53% achieved an LDL-C goal of <3.36 mmol/L (<130 mg/dL), respectively, at 24 months. The mean (SD) dose of rosuvastatin in each of the age groups was 9.7 (2.8) mg, 13.9 (4.2) mg, and 14.0 (3.9) mg, in the 6- to 9-, 10- to 13-, and 14- to 17-year age groups, respectively.

Treatment adherence for the total population was high at 90% during the 2-year study period. The adherence rate was highest in the youngest group: 93, 89, and 87% in the 6- to 9-, 10- to 13-, and 14- to 17-year age groups, respectively.

Safety outcomes

The incidence of treatment-emergent AEs was 88, 86, and 89% in the 6- to 9-, 10- to 13-, and 14- to 17-year age groups, respectively (Table 4). The most commonly reported AEs were nasopharyngitis, headache, influenza, and vomiting (all ≥10% of total patients; Table 4). Myalgia was reported in 0, 7, and 10% of patients aged 6 to 9, 10 to 13, and 14 to 17 years, respectively, but did not lead to discontinuation of treatment.

Overall, 29 patients (15%) had AEs considered at least possibly related to study medication, including gastrointestinal disorders (8%), myalgia (2%), increased blood CK (1%), and skin disorders (1%). All other drug-related AEs were isolated reports. Three patients experienced treatment-related AEs (nausea, migraine, and paresthesia) that lead to discontinuation of treatment.

Most AEs were considered mild by investigators. Nine (5%) patients had serious AEs. All were considered

Table 1 Baseline characteristics (safety population)

Characteristic	Age group			
	6–9 y (n = 64)	10–13 y (n = 72)	14–17 y (n = 61)	Total (n = 197)
Age (y)	—	—	—	11.6 ± 3.3
Boys, n (%)	29 (45)	30 (42)	28 (46)	87 (44)
Caucasian, n (%)	58 (91)	65 (90)	54 (89)	177 (90)*
Height (cm)	133 ± 9	152 ± 10	169 ± 9	151 ± 17
Weight (kg)	30 ± 7	46 ± 15	63 ± 13	46 ± 18
BMI (kg/m^2)	17 ± 2	20 ± 5	22 ± 4	19 ± 4
Sitting blood pressure (mm Hg)				
Systolic	103 ± 9	107 ± 9	112 ± 12	107 ± 11
Diastolic	61 ± 8	63 ± 8	68 ± 7	64 ± 8
Family history of premature CVD, n (%)	44 (69)	62 (86)	46 (75)	152 (77)
First-degree relative with HeFH, n (%)†	54 (84)	69 (96)	59 (97)	182 (92)
Lipids and lipoproteins				
TC, mmol/L (mg/dL)	7.8 ± 1.5 (301 ± 57)	7.9 ± 1.3 (304 ± 49)	8.0 ± 1.3 (308 ± 50)	7.9 ± 1.3 (305 ± 52)
LDL-C, mmol/L (mg/dL)	6.1 ± 1.4 (234 ± 52)	6.1 ± 1.3 (234 ± 49)	6.2 ± 1.2 (240 ± 46)	6.1 ± 1.3 (236 ± 49)
HDL-C, mmol/L (mg/dL)	1.4 ± 0.3 (52 ± 13)	1.3 ± 0.3 (52 ± 13)	1.2 ± 0.3 (46 ± 12)	1.3 ± 0.3 (50 ± 13)
TG, mmol/L (mg/dL) median, range	0.7; 0.3–2.1 (61; 27–188)	0.9; 0.3–2.8 (79; 28–243)	1.1; 0.4–4.0 (96; 39–350)	0.9; 0.3–4.0 (80; 27–350)
Non–HDL-C, mmol/L (mg/dL)	6.4 ± 1.4 (249 ± 54)	6.5 ± 1.3 (252 ± 50)	6.8 ± 1.3 (262 ± 48)	6.6 ± 1.3 (254 ± 51)
ApoA-1 (g/L)	1.4 ± 0.2	1.4 ± 0.2	1.3 ± 0.2	1.4 ± 0.2
ApoB (g/L)	1.5 ± 0.3	1.5 ± 0.3	1.6 ± 0.3	1.5 ± 0.3

Apo, apolipoprotein; BMI, body mass index; CVD, cardiovascular disease; HeFH, heterozygous familial hypercholesterolemia; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride.

Data are expressed as mean ± standard deviation, unless otherwise noted.

*The remainder were African, n = 2; Chinese or East Asian, n = 4; Indian (subcontinent), n = 4; other Asian, n = 6; Hispanic, n = 1; and other race, n = 3.

†Defined as LDL-C >4.91 mmol/L (>190 mg/dL).

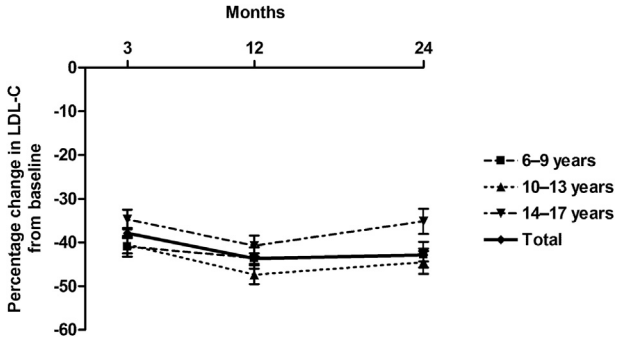

Figure 2 Percent change from baseline in low-density lipoprotein cholesterol (LDL-C) at 3, 12, and 24 months. $P < .001$ for all values vs baseline.

unrelated to treatment by the investigators. There were no cases of myopathy or rhabdomyolysis and no deaths during the study.

There were no clinically important changes in hematology, clinical chemistry or hepatic, skeletal muscle, and renal biochemistries. Three patients had CK levels >5 × ULN, one of which had a CK level >10 × ULN; none of these patients had any associated muscle symptoms. One patient had an increase in creatinine ≥50% of baseline; this patient had a normal eGFR, and no patients had abnormalities in eGFR.

Seven patients had ≥50% increases from baseline in urine protein:creatinine ratio during treatment. In 4 of these patients, the urine protein:creatinine ratio levels had returned to normal by the last study visit and may have been related to exercise. In 3 patients, however, urine

Table 2 Percent change from baseline in lipid parameters at 2-year follow-up

Lipid parameter	6–9 y (n = 64)	10–13 y (n = 72)	14–17 y (n = 61)	Total (n = 197)
LDL-C				
Month 3	−41 (−37, −45)	−41 (−37, −44)	−35 (−31, −39)	−38 (−36, −40)
Month 12	−44 (−39, −48)	−47 (−44, −51)	−41 (−37, −45)	−44 (−42, −46)
Month 24	−43 (−38, −48)	−45 (−40, −49)	−35 (−30, −40)	−43 (−40, −45)
P value	<.001	<.001	<.001	<.001
TC				
Month 3	−32 (−35, −29)	−32 (−34, −29)	−28 (−31, −24)	−30 (−31, −28)
Month 12	−34 (−37, −30)	−37 (−40, −34)	−32 (−35, −29)	−34 (−36, −32)
Month 24	−32 (−36, −28)	−34 (−37, −30)	−26 (−30, −22)	−32 (−34, −30)
P value	<.001	<.001	<.001	<.001
HDL-C				
Month 3	4 (−1, 9)	5 (0, 9)	7 (2, 12)	6 (3, 8)
Month 12	6 (2, 11)	2 (−2, 6)	8 (3, 12)	6 (4, 9)
Month 24	13 (8, 18)	8 (3, 13)	9 (4, 15)	12 (9, 15)
P value	<.001	.001	.001	<.001
TG*				
Month 3	−10	−17	−12	−13
Month 12	−16	−11	−20	−14
Month 24	−8	−3	−7	−5
P value	.179	.231	.178	.963
Non–HDL-C				
Month 3	−39 (−43, −36)	−39 (−42, −35)	−34 (−37, −30)	−36 (−38, −34)
Month 12	−42 (−46, −38)	−45 (−49, −42)	−39 (−43, −35)	−42 (−44, −40)
Month 24	−41 (−46, −36)	−42 (−46, −37)	−33 (−37, −28)	−40 (−43, −38)
P value	<.001	<.001	<.001	<.001
ApoB				
Month 3	−32 (−35, −29)	−31 (−34, −28)	−26 (−29, −23)	−29 (−31, −28)
Month 12	−36 (−39, −32)	−38 (−41, −35)	−33 (−36, −29)	−36 (−37, −34)
Month 24	−36 (−40, −32)	−36 (−40, −32)	−28 (−32, −24)	−36 (−38, −34)
P value	<.001	<.001	<.001	<.001
ApoA-1				
Month 3	3 (−1, 7)	5 (1, 8)	4 (0, 8)	5 (3, 7)
Month 12	2 (−2, 5)	−1 (−4, 2)	2 (−1, 6)	1 (−1, 3)
Month 24	2 (−2, 6)	2 (−2, 5)	3 (0, 7)	2 (0, 4)
P value	.268	.317	.082	.030

Apo, apolipoprotein; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride. Changes are least square mean (lower, upper 95% confidence interval) percentage change from baseline.

*For TG, changes are median percentage change from baseline. *P* values are for the least squares mean percentage change from baseline to Month 24.

Table 3 Patients reaching low-density lipoprotein cholesterol target of <2.85 mmol/L (<110 mg/dL) and <3.36 mmol/L (<130 mg/dL; intention-to-treat population)

Time point	6–9 y (n = 64)	10–13 y (n = 72)	14–17 y (n = 61)	Total (n = 197)
Achievement of <2.85 mmol/L (<110 mg/dL), n (%)				
Month 3	16 (25)	14 (20)	4 (7)	34 (17)
Month 12	19 (30)	31 (44)	16 (26)	66 (34)
Month 24	24 (38)	33 (46)	17 (28)	74 (38)
Achievement of <3.36 mmol/L (<130 mg/dL), n (%)				
Month 3	36 (56)	27 (38)	17 (28)	80 (41)
Month 12	41 (64)	50 (70)	28 (46)	119 (61)
Month 24	41 (64)	49 (68)	24 (39)	114 (58)

Data are expressed as n (%).

protein:creatinine ratio levels remained abnormal at the last study visit. One of these patients had an earlier episode of cystitis, which may have affected urine protein levels. The second patient was diagnosed with postural proteinuria, and in the last patient, the urine protein:creatinine ratio levels returned to normal after the study completed. All patients had a normal eGFR. No clinically significant abnormal findings were identified in the electrocardiogram or vital signs evaluations.

Rosuvastatin treatment did not appear to impact height, weight, or sexual maturation. During the 2-year study period, the mean z-score height and weight of the total population increased by 17 and 18%, respectively. The mean (SD) z-score body mass index was 0.14 (1.02) at baseline and 0.13 (1.02) at 24 months. All measurements were within normal reference ranges throughout the study. In general, the patients who were not already assessed as fully mature at baseline progressed in their sexual maturation during the study. Approximately, 82% of patients in Tanner stages II to IV progressed by at least one Tanner stage over the 2 years (Table 5).

Pharmacokinetics

Single-dose PK (10 mg) was assessed in 12 patients (5 boys and 7 girls; all Caucasian) aged 6 to less than Tanner stage II. The C_{max}, T_{max}, and $AUC_{(0–24)}$ for rosuvastatin, lactone, and N-desmethyl are summarized in Table 6.

Table 4 Treatment-emergent adverse events (AEs)

AE	6–9 y (n = 64)	10–13 y (n = 72)	14–17 y (n = 61)	Total (n = 197)
Any AE	56 (88)	62 (86)	54 (89)	172 (87)
Nasopharyngitis	30 (47)	34 (47)	23 (38)	87 (44)
Headache	14 (22)	24 (33)	8 (13)	46 (23)
Influenza	7 (11)	10 (14)	3 (5)	20 (10)
Vomiting	8 (13)	8 (11)	3 (5)	19 (10)
Gastroenteritis, viral	12 (19)	4 (6)	2 (3)	18 (9)
Nausea	7 (11)	3 (4)	8 (13)	18 (9)
Abdominal pain, upper	4 (6)	8 (11)	3 (5)	15 (8)
Influenza-like illness	9 (14)	4 (6)	2 (3)	15 (8)
Abdominal pain	4 (6)	8 (11)	1 (2)	13 (7)
Oropharyngeal pain	2 (3)	8 (11)	3 (5)	13 (7)
Arthralgia	2 (3)	7 (10)	3 (5)	12 (6)
Gastroenteritis	8 (13)	3 (4)	1 (2)	12 (6)
Cough	5 (8)	3 (4)	3 (5)	11 (6)
Myalgia	0	5 (7)	6 (10)	11 (6)
Pyrexia	6 (9)	4 (6)	0	10 (5)
AE leading to death	0	0	0	0
AE leading to discontinuation	0	1 (1)	2 (3)	3 (2)
Serious AE	2 (3)	4 (6)	3 (5)	9 (5)
Treatment-related AEs	5 (8)	12 (17)	12 (20)	29 (15)
Treatment-related AE leading to death	0	0	0	0
Treatment-related AE leading to discontinuation	0	1 (1)	2 (3)	3 (2)
Treatment-related serious AE	0	0	0	0

Data are expressed as n (%), unless otherwise noted.

Table 5 Change in Tanner stage from baseline to 12 and 24 months

		Tanner stage at baseline (n = 197)					
	n	I (n = 81)	II (n = 32)	III (n = 18)	IV (n = 44)	V (n = 21)	Not recorded (n = 1)
12 mo, n (%)							
I	61	61 (31)	0	0	0	0	0
II	31	17 (9)	14 (7)	0	0	0	0
III	21	1 (1)	15 (8)	5 (3)	0	0	0
IV	32	1 (1)	1 (1)	10 (5)	20 (10)	0	0
V	42	0	0	1 (1)	20 (10)	21 (11)	0
Not recorded	10	1 (1)	2 (1)	2 (1)	4 (2)	0	1 (1)
24 mo, n (%)							
I	43	43 (22)	0	0	0	0	0
II	33	27 (14)	6 (3)	0	0	0	0
III	23	8 (4)	14 (7)	1 (1)	0	0	0
IV	32	2 (1)	9 (5)	12 (6)	9 (5)	0	0
V	64	1 (1)	3 (2)	5 (3)	34 (17)	21 (11)	0
Not recorded	2	0	0	0	1 (1)	0	1 (1)

Note: percentage was based on the total number of treated patients.

Discussion

In FH, atherosclerotic changes begin early in childhood; therefore, both US and European guidelines advocate early treatment of hypercholesterolemia to prevent the development of premature cardiovascular events.[2,8,9]

Data on the efficacy and safety of statins in children aged <10 years with FH are currently limited,[6] and the rationale for this study therefore was to evaluate the efficacy, safety, and tolerability of rosuvastatin in young children and adolescents aged 6 to 17 years with HeFH over 2 years.

During the study, rosuvastatin significantly lowered LDL-C levels compared with baseline in this pediatric HeFH population; moreover, these reductions were sustained over the 2-year treatment period. Other lipids and lipoproteins, including total cholesterol, non-HDL-C, and ApoB were also significantly reduced and HDL-C was significantly increased after 24 months of rosuvastatin therapy compared with baseline. Current guidelines recommend an LDL-C target of <3.5 mmol/L (<135 mg/dL) in children.[2] In this study, a large proportion (58%) of children overall achieved the slightly more restrictive LDL-C goal of <3.36 mmol/L (<130 mg/dL). In addition, 38% of this difficult-to-treat population reached an LDL-C goal <2.85 mmol/L (<110 mg/dL).

Despite having almost identical baseline LDL-C levels and the protocol permitting uptitration of the rosuvastatin dose according to age, there tended to be a greater reduction in LDL-C levels from baseline in the 6- to 9- and 10- to 13-year age groups, compared with the 14- to 17-year age group. A possible explanation may be because of differences in the distribution and expression of transporters involved in the uptake of rosuvastatin between younger, smaller children, and older, larger children. Rosuvastatin is a substrate for certain transporter proteins, including organic anion-transporting polypeptide 1B1 and breast cancer resistance protein. Interactions or differences in the expression of these transporters may explain the variability between the groups.[15] In addition, some of the older children may have required higher doses but were not titrated up as dosing was capped at 20 mg for those aged 10 to 17 years. The mean (SD) dose was 9.7 (2.8) mg in the youngest group, 13.9 (4.2) mg in the 10- to 13-year age group and 14.0 (3.9) mg in the eldest group. It is also worth noting that compliance in the younger age

Table 6 Single-dose pharmacokinetics

Drug/metabolite	C_{max} (GCV%), ng/mL	T_{max} (range), h	$AUC_{(0-24)}$ (GCV%), ng·h/mL
Rosuvastatin	5.7 (71.3)	2.0 (0.5–6.5)	42.7 (74.5)
N-desmethyl	0.8 (98.4)	3.4 (1.0–5.5)	4.5 (106.7)
Lactone	1.3 (107.7)	4.0 (0.5–23.8)	16.2 (86.6)

AUC, area under the curve; C_{max}, maximum concentration; GCV, geometric coefficient of variation; t_{max}, time to maximum concentration.
n = 12 patients, aged 6 years to less than Tanner stage II.

groups was higher (93% in 6- to 9-year age group and 89% in 10- to 13-year age group) compared with the older age group (87%) possibly as a result of older patients being less dependent on parents/caregivers, which may also have contributed to the slight difference in LDL-C reduction observed between the age groups. The difference in compliance may also be because of the slightly higher rate of treatment-related AEs seen in the eldest age group compared with the younger age groups (8%, 17%, and 20% for the 6- to 9-, 10- to 13-, and 14- to 17-year age groups, respectively). A further possible explanation for the difference in efficacy may be because of differences in diet in the oldest age group. Although diet was not assessed as part of the study, all patients were advised to continue following regional guidelines for a low-cholesterol diet. It may be possible that some of the older children, who were less compliant with treatment, were also less compliant in following diet recommendations. Finally, it should be noted that changes in serum lipids and lipoproteins are known to occur during adolescence and sexual maturity, and this may also have impacted on the results of this study.[16,17]

A key objective of this study was to assess the safety of rosuvastatin in young children and adolescents aged 6- to 17-year-old over 2 years. The study found that rosuvastatin treatment had no impact on growth or sexual maturation (Tanner scoring). Evaluation of z-scores (for height, weight, and body mass index) and Tanner staging indicated that growth and sexual maturation remained within normal ranges for age and sex over the course of the 2-year study.

Based on the evaluations of treatment-emergent AEs, laboratory variables, vital signs, and physical findings, rosuvastatin 5, 10, and 20 mg was generally well tolerated in this pediatric population, with no significant differences in the youngest (6- to 9-year old) patients compared with the older (10- to 17-year old) patients. Myalgia occurred at a higher incidence in the older age groups (7% in the 10- to 13-year olds and 10% in the 14- to 17-year olds) compared with the youngest age group (6- to 9-year olds; 0%). Although it is unclear why myalgia was reported more frequently in older children than in younger children, one possible explanation may be that the older children were more athletic and were participating in more physical activities. Another possible explanation is that younger children and their parents may not recognize the symptoms of myalgia and therefore do not report it, unlike older children who may be more aware of the condition perhaps via the media through researching their condition. A final explanation may be that myalgia is an age-related AE; however, only further studies in children and adolescents will determine if this is the case.

Single-dose PK analysis, performed in 12 patients from the youngest age group, found that exposure to metabolites, N-desmethyl, and lactone, was lower than that to parent rosuvastatin, which is consistent with rosuvastatin being the main circulating moiety responsible for activity. PK data collected from all patients in this study have been used in a population PK analysis in combination with pediatric data from other rosuvastatin studies and will be reported elsewhere.

To our knowledge, this is the longest study to date to evaluate the efficacy and safety of rosuvastatin in children and adolescents aged 6 to 17 years with HeFH. Concern may still remain, however, about the safety of statins in children, particularly young children. This study has now finished, and rosuvastatin is now approved in the EU for this HeFH age group and pharmacovigilance will continue. Future studies, should consider monitoring the safety of statins over an even longer period of time to fully establish the safety of statins in this population. The LDL-C reduction observed was consistent with reductions seen in adults and a previous study in children aged 10 to 17 years with HeFH receiving rosuvastatin 20 mg.[13,18] It was also similar to LDL-C reductions reported in randomized controlled studies of simvastatin and atorvastatin in HeFH[17,18] but greater than those reported with pravastatin.[6] Other studies have also shown that statins are well tolerated in children with HeFH with safety profiles similar to those observed in adults. In agreement with the current 2-year study, there is no evidence that LDL-C lowering affects sexual development or growth.[13,19–21]

In conclusion, in patients with HeFH aged 6 to 17 years, rosuvastatin 5 to 20 mg significantly reduced LDL-C compared with baseline, which was sustained over 2 years. The treatment was generally well tolerated, with growth and sexual maturation remaining within normal ranges and no new safety signals in this pediatric population.

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