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Design and baseline data of a pediatric study with rosuvastatin in familial hypercholesterolemia

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BACKGROUND: Statin therapy is recommended for children with familial hypercholesterolemia (FH), but most children do not reach treatment targets.

OBJECTIVE: Here we present the design and results at baseline of the ongoing CHARON study, to evaluate the safety and efficacy of rosuvastatin.

METHODS: This study comprises an international 2-year open label, titration-to-goal study in 198 children with heterozygous FH aged 6 to 18 years, with rosuvastatin in a maximum dose of 10 mg (<10 years of age) or 20 mg (older children). In addition, 64 unaffected siblings were enrolled as controls. The primary efficacy outcome is the change from baseline in low-density lipoprotein cholesterol, and the secondary outcome is the change in carotid intima-media thickness (c-IMT) in patients with FH compared with their siblings. The primary safety outcomes are growth and sexual maturation; secondary outcomes are the change in other lipoprotein levels and the incidence of adverse events, discontinuation rates, and abnormal laboratory values.

RESULTS: At baseline, mean age of patients with FH was 12.1 ± 3.3 years, 44% were boys, and mean low-density lipoprotein cholesterol levels were 6.1 ± 1.3 mmol/L (235.9 ± 48.7 mg/dL). Mean c-IMT was 0.399 mm (95% CI, 0.392–0.406 mm) in children with FH versus 0.377 (95% CI, 0.366–0.388 mm) in unaffected siblings ($P = .001$).

CONCLUSIONS: At baseline, as expected according to on previous observations, children with FH proved to have a greater c-IMT than their healthy siblings. These differences had already occurred at a

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very young age, which emphasizes the importance of considering early statin initiation in this high-risk population.

Familial hypercholesterolemia (FH) is an autosomal dominant genetic disorder of lipoprotein metabolism, characterized by severely elevated levels of low-density lipoprotein cholesterol (LDL-C) that lead to premature atherosclerosis and cardiovascular disease (CVD).[1] In a meta-analysis of 14 randomized trials in 90,056 patients, statins have been shown to be safe and well-tolerated agents that reduce CVD morbidity and mortality in a wide range of patients,[2] and all guidelines recommend statins as the first-line therapy for cardiovascular risk reduction in patients with FH.[3,4] Because children with FH already exhibit functional and structural arterial wall changes from a young age,[5–7] current pediatric guidelines recommend initiation of statin therapy to achieve a LDL-C reduction of 50% or with LDL-C treatment goals of <3.4 mmol/L (130 mg/dL), or even the optimal LDL-C goal of <2.85 mmol/L (110 mg/dL) in children with FH.[8] Although, formally, there is no strong evidence base for guideline targets in children with FH, one might hypothesize that the contention that "lower is better" can be translated from adults to the pediatric population. The highest doses of statins tested in several pediatric trials resulted in LDL-C reductions of 24% for pravastatin,[6] 27% for lovastatin,[9] 40% for atorvastatin,[10] and 41% for high-dose simvastatin[11]; however, use of these statins generally does not result in attainment of these LDL-C targets. For example, in atorvastatin-treated children the highest dose tested (20 mg) resulted in only 44% of patients attaining an LDL-C target of 3.4 mmol/L (130 mg/dL), and few (<10%) achieved the optimal LDL-C goal of <2.85 mmol/L (110 mg/dL).[10] However, a recent 1-year study with rosuvastatin in children with FH aged 10 to 17 years showed a 50% reduction in LDL-C with the highest dose of 20 mg, and 40% of subjects reached the more stringent LDL-C goal of <2.85 mmol/L (110 mg/dL).[12]

Because of the greater LDL-C reduction with rosuvastatin than with other statins,[13] a trial with rosuvastatin in pediatric patients with FH in a wide age range to assess the long-term efficacy, safety, and tolerability is warranted. The CHARON (hyperCholesterolaemia in cHildren and Adolescents taking Rosuvastatin OpeN label) study will assess the 2-year efficacy, safety, tolerability, and adherence of rosuvastatin in children with FH aged 6 to younger than 18 years. The study design allows for measurement of LDL-C reduction and LDL-C goal attainment, as well as assessments of arterial wall changes by carotid intima-media thickness (c-IMT). In addition, the design provides for including a control group of unaffected siblings, allowing for comparison of the mean c-IMT between pediatric patients with FH before and after 2 years of treatment and unaffected, untreated pediatric controls. This will give insight into the extent of IMT progression of patients with FH at baseline and into possible regression from baseline due to treatment.

Furthermore, in a small cohort of the youngest patients (aged 6 years to less than Tanner Stage II), serial pharmacokinetic (PK) samples will be obtained to characterize the PK of rosuvastatin in these younger children and to compare PK profiles in children and adolescents or adults from previous studies. These PK data are crucial to determine the maximum rosuvastatin titration dose for long-term treatment of this particular age group in the present study.

Here we present the design of this study and the results at baseline.

Methods

Study design

The study flow chart is shown in Figure 1. Patients were enrolled at 14 centers in 5 countries (Belgium, Canada, The Netherlands, Norway, and the United States). During the screening visit (week –4 or week –1), medical history, physical examination, electrocardiogram, and laboratory testing (lipid profile, full blood count and cell indices, albumin, total protein, aspartate aminotransferase [AST], alanine aminotransferase [ALT], bilirubin, creatine kinase [CK], blood urea nitrogen, serum creatinine, calcium, phosphate, uric acid, chloride, carbon dioxide, lactic dehydrogenase, high-sensitivity C-reactive protein, fasting glucose, phosphorus, potassium sodium, thyroid-stimulating hormone [TSH], glycosylated hemoglobin, and urinalyses that include creatinine and protein) were performed. For patients previously treated with statins (ages 10 to younger than 18 years), a drug washout period was instituted, and a second screening visit (week –1) was scheduled to allow LDL-C results to meet the inclusion criterion.

All patients were started on 5 mg of rosuvastatin once daily and underwent up-titration to achieve an LDL-C target of <2.85 mmol/L (110 mg/dL) in 3-month intervals from visit 3. Up-titration will be from 5 to 10 mg for patients aged from 6 to younger than 10 years of age and from 5 to 10 mg or from 10 mg to a maximum of 20 mg for patients aged 10 to younger than 18 years.

Sexual maturation was assessed by using the Tanner Staging for pubertal development, and c-IMT was measured by B-mode ultrasound scanning at baseline (visit 0), and these measurements will be repeated at 12 months and at 24 months. In addition, assessment of c-IMT in healthy siblings in whom FH is excluded was performed at baseline and will be done at 12 months and at 24 months. Siblings will not take part in any other assessments.