Familial hypercholesterolemia in childhood

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Chapter 4

Efficacy, Safety and Tolerability of Simvastatin in Children with Familial Hypercholesterolemia
Rationale, Design, and Baseline Characteristics

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Abstract

**Objective:** To describe the rationale, design, and baseline data of a study conducted to determine the efficacy, safety, and tolerability of simvastatin in children and adolescents with heterozygous familial hypercholesterolemia (FH).

**Methods:** Patients were recruited from nine lipid clinics worldwide. After a 4-week diet/placebo run-in period, patients were randomized to receive either simvastatin or placebo. Simvastatin was started at 10 mg/day and titrated at 8-week intervals to 20 and then 40 mg/day. During a second 24-week extension period, patients continued to receive simvastatin 40 mg or placebo daily according to the original allocation.

**Results:** A total of 173 patients [98 boys (age: 13.2 y), 75 girls (age: 14.5 y)] were included in the study. Baseline total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) were severely elevated in FH boys and girls compared to 69 healthy non-affected controls who were not part of the study. In FH boys and the male siblings, respectively, mean TC was 6.78 ± 1.03 vs. 3.80 ± 0.11 mmol/L (p<0.001), and mean LDL-C was 5.09 ± 0.97 vs. 2.53 ± 0.69 mmol/L (p<0.001). In FH girls and the female siblings, respectively, mean TC was 7.44 ± 1.35 vs. 4.24 ± 0.47 mmol/L (p<0.001) and mean LDL-C was 5.68 ± 1.28 mmol/L vs. 2.44 ± 0.50 mmol/L (p<0.001).

**Conclusion:** This is the first and largest randomized, controlled, long-term clinical study to test the efficacy, safety, and tolerability of a statin in boys and girls with FH. The baseline data suggest that the sample selected for this study is representative of patients with FH.
Introduction

Heterozygous familial hypercholesterolemia (FH) is an inherited autosomal dominant disorder of lipoprotein metabolism caused by a plethora of mutations in the low-density lipoprotein receptor gene. In the Netherlands, the frequency of FH is estimated at 1 in 400 persons and, hence, is the most common dominant inborn metabolic abnormality. Familial hypercholesterolemia is associated with elevated levels of low-density lipoprotein cholesterol (LDL-C) and premature atherosclerosis, and patients show symptoms of atherosclerotic cardiovascular disease at a relatively young age. In men with untreated FH, the risk of clinically overt coronary heart disease (CHD) is approximately 5% by the age of 30, 20% by the age of 40, and 50% by the age of 50 years. Without proper treatment, only about 15% of FH men reach age 65 without an ischemic coronary event and about 25% die from CHD before the age of 50.

In children, the disease is mostly asymptomatic. However, even in the general population, autopsy reports of healthy children and adolescents show atherosclerotic lesions at a young age. Morphological and functional changes of the arteries have been shown to be predictive of future cardiovascular disease and have been documented in young children. These data underscore the importance of considering an aggressive and early treatment of dyslipidemia to prevent premature atherosclerotic events.

The recommended therapy for children consists of dietary intervention; nevertheless, clinical experience shows that the long-term cholesterol-lowering efficacy of dietary intervention in children is very poor. If, after a diet, LDL-C remains higher than 4.9 mmol/L (or higher than 4.1 mmol/L in children with a family history of premature coronary artery disease), the US National Cholesterol Education Program (NCEP) recommends drug therapy for children 10 years or older. Bile acid sequestrants are considered the drugs of choice and have been used in children for more than 20 years. The sequestrants appear safe, but the lipid-lowering efficacy is modest and the long-term compliance remains poor.

The 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) are effective, safe, and well tolerated lipid-altering agents in adults. Statins have been proven to reduce the incidence of CHD, stroke, and peripheral vascular disease significantly and are widely used in adults with various dyslipidemias. While statins are not registered or recommended to treat hypercholesterolemia in children and adolescents, they are often prescribed off label. To ensure that
children are not exposed to unnecessary risks, controlled clinical trials are needed to determine the most appropriate dose for children of different ages and to assess the effects of the drugs on maturation and growth. Thus far, only a few studies with statins in children have been performed, but these studies either were not randomized or controlled, included only boys, had an inadequate sample size, or were of short duration. In contrast, the present study was designed to evaluate (a) the LDL-C-lowering efficacy of simvastatin in a large cohort of both boys and girls with FH, (b) the overall safety and tolerability of simvastatin, and (c) the influence of simvastatin on growth and pubertal development. In this paper we present the baseline characteristics of the population who participated in the simvastatin in children study from 1999 to 2001.

**Study design**

This was an international, multi-center (n=9), double blind, randomized, parallel study of 173 patients with FH. Eligible patients were children, 10 to 17 years of age with LDL-C levels between 4.1 and 10.3 mmol/L and one parent with a confirmed diagnosis of FH. Heterozygous FH of the parent was confirmed clinically by tendon xanthomas and/or a mutation in the LDL receptor gene. Excluded were children with homozygous familial hypercholesterolemia, secondary hyperlipidemia, children treated with lipid-lowering agents within 8 weeks of randomization, and children with delayed puberty (Table 1). The independent Ethics Committees or Institutional Review Boards of the participating centers approved the protocol, and written informed consent was obtained from children and parents.

Patients had their lipid-lowering medications discontinued prior to randomization (6 weeks for statins, 8 weeks for fibrates, and 1 year for probucol). After a 4-week diet/placebo run-in period (-4 to week -1), children who still had increased levels of LDL-C were randomized to active treatment or matching placebo. Randomization was stratified by gender to simvastatin or placebo in a ratio of 3:2. Randomization was done by computer-generated sequence, concealed in sequentially numbered and sealed envelopes and kept at the hospital pharmacy of the 9 centers. Within the active treatment group, simvastatin was started at 10 mg/day and increased at 8-weeks intervals (week 8 and 16) to 20 and then 40 mg/day. Patients who were randomized to placebo received placebo tablets that matched simvastatin.
throughout the first 24 weeks (period 1). During the next 24-week extension period (weeks 25 to 48; period 2), patients in the active treatment arm received 40 mg/day of simvastatin, whereas those in the placebo group continued with placebo (figure 1).

Table 1. Inclusion and exclusion criteria

Inclusion criteria
- Males and females 10 to 17 years of age
- Postmenarchal females (defined as at least 1 year after first menstrual period and having had at least 3 menstrual periods)
- Height and weight between the 10th and 95th percentile for age with a minimum body weight of 32 kg
- LDL-C between 4.1 mmol/L and 10.3 mmol/L and 1 parent with confirmed diagnosis of FH, or had died of CHD
- TG ≤ 5.4 mmol/L
- Highly unlikely to conceive as assessed by the investigator
- Negative pregnancy test

Exclusion criteria
- Reduction of LDL-C below 4.1 mmol/L after dietary treatment
- Homozygous FH; type I, III, V dyslipidemias; or TG ≥ 5.4 mmol/L
- Diabetes, hypothyroidism, nephrotic syndrome, anorexia nervosa or any other cause of secondary hyperlipidemia
- Chronic treatment with lipid-lowering agents including bile acid sequestrants, HMG-CoA reductase inhibitors and nicotinic acid taken within 6 weeks, fibrates taken within 8 weeks, and probucol taken within 1 year of randomization.
- Delayed puberty
- Renal insufficiency as measured by serum creatine > 179 mmol/L
- Elevations of liver transaminases ≥ 20% above the ULN or CK > 50% above the ULN during screening/diet and placebo phase, or active liver disease
- Alcohol or drug abuse
- Patients on systemic immunosuppressive drugs
- Partial ileal bypass
- Hypersensitivity to HMG-CoA-reductase inhibitors
- Any other condition or therapy, which in the opinion of the investigator, might pose a risk to the patient or confound the results of the study
- Poor mental function or any other reason to expect patient difficulty in complying with the requirements of the study
- Treatment with any other investigational drug within 30 days prior to visit 1
- Previous pregnancy

LDL-C=low-density lipoprotein cholesterol, FH=familial hypercholesterolemia, CHD=cardiac heart disease, TG=triglycerides, ULN=upper limit of normal, CK=creatine kinase.
Lipid data of non-affected children were reported in this manuscript for comparison with the FH children in the study. These children are siblings of FH children from the Dutch lipid clinic (Academic Medical Center, Amsterdam) and were not part of the study.

**Figure 1. Study flow-chart**

![Study flow-chart diagram]

**Treatment phase**

Simvastatin or matching placebo was taken daily after the evening meal. Compliance was assessed by tablet count at every visit. During the 48 weeks of treatment, visits took place every 4 weeks. Every visit included dietary monitoring; measurement of vital signs, serum chemistries, and lipids/lipoproteins; and monitoring of adverse experiences. In addition, length of menstruation was monitored throughout the study period by recording the first day of the menstrual flow. An EKG and full physical examination (blood pressure, heart rate, pubertal development, weight and length) were performed at study entry (week 1) and at weeks 24 and 48. Tanner staging was used for pubertal development\(^3\)\(^{-33}\).

**Laboratory methods**

Efficacy measurements were performed at every visit (total cholesterol [TC], triglycerides [TG], LDL-C, and high-density lipoprotein cholesterol [HDL-C]) or every other visit (apolipoproteins [Apo] B and A-I).

Safety measurements including hematology and urinalysis were performed at the placebo/diet run-in period (week -4), at entry (week 1) and at 24 weeks and 48 weeks. However, hepatic transaminases (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]), and creatine kinase (CK) were measured during
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every visit. Thyroid function (T4 and TSH) was measured once at baseline. Adrenal hormones (cortisol and dehydroepiandrosterone sulfate [DHEAS]), pituitary hormones (lutropin [LH] and follicle-stimulating hormone [FSH]) and gonadal hormones (estradiol for girls and testosterone for boys) were measured at weeks 1 (pre-drug), 8, 16, 24, and 48. In girls, beta human chorionic gonadotropin (b-hCG) was measured in serum and urine during every visit. High-sensitivity C-reactive protein (hs-CRP) was measured at weeks 1, 24, and 28.

Samples for serum chemistry, hematology, urinalysis, hormones, and lipids/lipoproteins were analyzed by Medical Research Laboratories (Highland Heights, Kentucky, USA) or Clinical Research Laboratories (Zaventem, Belgium). Throughout the study, the laboratories participated in, and remained certified by the National Heart Lung and Blood Institute, Centers for Disease Control Part III Program. Samples for lipoproteins were collected in ethylenediaminetetraacetate (1 mg/ml) and centrifuged within 30 minutes; the plasma was separated, kept at 4°C, and shipped overnight to the central laboratory. Total C and TG were analyzed by enzymatic methods on a Hitachi 747 analyzer as previously described. HDL-C was isolated with heparin-2M manganese chloride. High-sensitivity assays for CRP were done according to the manufacturer's instructions (Behring Diagnostics, Behring Nephelometer 100 instruction manual). LDL-C was determined by ultracentrifugation at baseline and week 8, 16, 24 and 48. The Friedewald formula was used for other timepoints. Serum concentrations of FSH, LH, estradiol and DHEAS were assayed with a competitive binding assay (I125-radiolabeled hormone) and an antihormone antibody. Serum cortisol was measured by a fluorescence polarization immunoassay, and total serum testosterone was measured in a solid-phase radio immunoassay using a competitive binding assay.

**Statistical analysis**

For the primary hypothesis (efficacy), a sample size of 160 patients (n=96 simvastatin versus n=64 placebo) provided 90% power to detect a difference between treatments in LDL-C percent change from baseline of 7.9% (α = 0.05, two tailed). This calculation was based on an estimated pool between-subjects SD of the LDL-C percent change from baseline of 14.9%.

Two-sample t-tests were used to assess the differences between children with FH versus their non-affected sibling cohorts for the lipid and apolipoprotein parameters. All tests of significance were performed at α = 0.05, two-tailed.
Chapter 4

Results

Demographics
Baseline demographic data for study participants are shown in table 2. Ninety-eight boys and 75 girls with an average age of 13.2 (SD 2.3) and 14.5 (SD 1.6) years, respectively, participated in the study. BMI, fasting plasma glucose levels, and blood pressure were similar in boys and girls. Alcohol usage was higher among girls (30.7%) than boys (19.4%). One percent of the boys and 5.4% of the girls used 5 to 10 units weekly.

Forty male and 29 female non-affected siblings of study participants were evaluated for lipid/lipoprotein levels. The mean ages of these children were 12.7 (SD 2.3) years for boys and 13.4 (SD 1.7) years for girls.

Table 2. Demographic and baseline characteristics of children with FH (n=173)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Boys (n=98)</th>
<th>Girls (n=75)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>13.2 ± 2.3</td>
<td>14.5 ± 1.6</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>21.2 ± 4.1</td>
<td>22.0 ± 3.8</td>
</tr>
<tr>
<td>Alcohol use in U/week (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>none</td>
<td>79 (80.6)</td>
<td>52 (69.3)</td>
</tr>
<tr>
<td>1-4</td>
<td>18 (18.4)</td>
<td>19 (25.3)</td>
</tr>
<tr>
<td>5-7</td>
<td>1 (1.0)</td>
<td>2 (2.7)</td>
</tr>
<tr>
<td>8-10</td>
<td>0</td>
<td>2 (2.7)</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>119 ± 16</td>
<td>117 ± 14</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>65 ± 7</td>
<td>68 ± 10</td>
</tr>
<tr>
<td>Fasting serum glucose (mmol/L)</td>
<td>4.9 ± 0.5</td>
<td>4.8 ± 0.4</td>
</tr>
</tbody>
</table>

All values are given as mean (SD), except for alcohol (number and percentages), FH= familial hypercholesterolemia, BMI=Body Mass Index

Lipids and apolipoproteins
Baseline lipid and apolipoprotein levels for FH and non-affected sibling cohorts are shown in table 3. For both boys and girls, the levels of TC, LDL-C, TG and Apo B were significantly higher in FH children and adolescents than in the sibling group (p<0.001). Plasma levels of HDL-C and Apo A-I were lower in the FH cohort than in the siblings and these differences were significant (p<0.05 to p<0.001) in all cases except for Apo A-I in girls (p=0.200). Very low-density lipoprotein cholesterol (VLDL-C) and hs-CRP data were not available for the non-affected siblings.
Table 3. Baseline lipids, apolipoproteins, and CRP of children with FH (n=173) and non-affected siblings

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Boys</th>
<th></th>
<th></th>
<th>Girls</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FH (n=98)</td>
<td>Siblings (n=40)</td>
<td>p-value</td>
<td>FH (n=75)</td>
<td>Siblings (n=29)</td>
<td>p-value</td>
</tr>
<tr>
<td>TC (mmol/L)</td>
<td>6.78 ± 1.03</td>
<td>3.80 ± 0.11</td>
<td>&lt;0.001</td>
<td>7.44 ± 1.35</td>
<td>4.24 ± 0.47</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL-C (mmol/L)</td>
<td>1.20 ± 0.28</td>
<td>1.45 ± 0.39</td>
<td>&lt;0.001</td>
<td>1.25 ± 0.24</td>
<td>1.40 ± 0.34</td>
<td>0.016</td>
</tr>
<tr>
<td>VLDL-C (mmol/L)</td>
<td>0.52 ± 0.32</td>
<td>n.a.</td>
<td>0.56 ± 0.29</td>
<td>n.a.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL-C (mmol/L)</td>
<td>5.09 ± 0.97</td>
<td>2.53 ± 0.69</td>
<td>&lt;0.001</td>
<td>5.68 ± 1.28</td>
<td>2.44 ± 0.50</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TG (mmol/L)</td>
<td>0.87 [0.44-3.68]</td>
<td>0.23 [0.02-0.73]</td>
<td>&lt;0.001</td>
<td>0.93 [0.55-3.15]</td>
<td>0.33 [0.13-0.84]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Apo A-I (mg/dL)</td>
<td>124.3 ± 21.4</td>
<td>138.2 ± 27.7</td>
<td>0.003</td>
<td>130.9 ± 22.4</td>
<td>136.4 ± 18.3</td>
<td>0.200</td>
</tr>
<tr>
<td>Apo B (mg/dL)</td>
<td>175.0 ± 31.1</td>
<td>77.9 ± 18.5</td>
<td>&lt;0.001</td>
<td>192.0 ± 38.8</td>
<td>87.6 ± 24.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>hs-CRP (mg/L)</td>
<td>0.2 [0.0-25.5]</td>
<td>n.a.</td>
<td></td>
<td>0.4 [0.0-6.4]</td>
<td>n.a.</td>
<td></td>
</tr>
</tbody>
</table>

All values are given as means (SD) except for triglycerides and hs-CRP (median and range). FH = familial hypercholesterolemia, TC = total cholesterol, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, TG = triglycerides, Apo A-I = apolipoprotein A-I, Apo B = apolipoprotein B, hs-CRP = high-sensitivity C-reactive protein; n.a = not available.

Pubertal development

The different Tanner stages were well distributed among the 98 boys: stage 2: 23.5%, stage 3: 22.4%, stage 4: 29.6%, stage 5: 24.5% (table 4). Mean testicular volume in boys was 15.2 cc (SD 9.3). Children with Tanner stage 1 were not included in this trial. All but one of the girls were in Tanner stage 4 (53.3%) or 5 (45.3%).

Table 4. Baseline Tanner stages and testicular volume of children with FH (n=173)

<table>
<thead>
<tr>
<th>Tanner stage (%)</th>
<th>Boys (n=98)</th>
<th>Girls (n=75)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>23 (23.5)</td>
<td>1 (1.3)</td>
</tr>
<tr>
<td>3</td>
<td>22 (22.4)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>4</td>
<td>29 (29.6)</td>
<td>40 (53.3)</td>
</tr>
<tr>
<td>5</td>
<td>24 (24.5)</td>
<td>34 (45.3)</td>
</tr>
<tr>
<td>Testicular volume (cc)</td>
<td>15.2 (9.3)</td>
<td>N.A</td>
</tr>
</tbody>
</table>

All values are given as numbers and percentages, except for testicular volume (mean and SD). FH = familial hypercholesterolemia; N.A = not applicable.
Discussion

Patients with FH suffer from a severe cardiovascular disease that becomes evident at a relatively young age, sometimes even before age 30. As a consequence, the process of atherosclerosis starts early in childhood. Statins have proved to be effective, safe and well tolerated in adult patients, but only incomplete data are available for children or adolescents. Hence, a large, randomized, placebo-controlled study is necessary to support the use of statins in this group of high-risk patients. The Simvastatin in Children Study was designed and conducted to investigate the lipid-altering efficacy and the influence on growth and pubertal development of simvastatin in children and adolescents.

Only a few studies with statins have been conducted in children and adolescents. Stein (1989) was the first to show a reduction in LDL-C of more than 40% in children treated with lovastatin or simvastatin, but this was not a placebo-controlled study and it involved only a small group of boys. In 1992, a long-term trial with simvastatin showed a 37% LDL-C reduction and excellent tolerance. However, the study was again limited in size (n=32) and uncontrolled. Three other statin studies in children and adolescents have been reported: two placebo-controlled and one uncontrolled. In the first placebo-controlled study, 72 FH children (66% girls), age 10-16 years, were randomized to placebo or pravastatin 5, 10, or 20 mg. After 12 weeks, LDL-C levels decreased by 3% in the placebo group but were reduced by 23%, 24%, and 33% in the groups receiving pravastatin 5, 10, and 20 mg, respectively. Safety issues did not arise. Lambert and colleagues reported an uncontrolled study in which boys were randomized to either lovastatin 10, 20, 30, or 40 mg/day for 12 weeks. LDL-C levels were reduced by 21 to 36% and lovastatin was well tolerated with no serious clinical adverse events reported. Although these studies confirm the efficacy of statins in children, they were mostly short term, had a limited sample size, and did not include information about growth and development. Stein and colleagues reported the results of the second controlled that recruited 132 boys, between 10 and 17 years of age, randomized to either lovastatin or placebo. Children in the lovastatin group started with 10 mg/day and the dosage was doubled every 8 weeks to a maximum of 40 mg/day. The mean LDL-C levels decreased significantly relative to placebo in all active treatment groups. Data on growth and hormonal status indicated no significant differences between lovastatin and placebo, but the study was not well powered to rigorously evaluate the safety parameters.
The current Simvastatin in Children Study is the largest placebo-controlled trial of a lipid-lowering drug in children and adolescents with heterozygous FH. Both boys and girls were included, and extensive safety parameters on growth and pubertal development were monitored. Mean body mass index in both boys and girls was within the normal range. Only 2 children used more than 8 units of alcohol a week, but they were older than 16 years and their alcohol consumption was not considered to be excessive. Systolic and diastolic blood pressures were within the normal range. Children with diabetes were not included in this study. The mean fasting glucose level was within normal range for boys and girls.

As expected, TC as well as LDL-C and Apo B were well above the 95th percentile for age and gender and significantly higher than in controls. The HDL-C and Apo A-I were below the 95th percentile and were lower than in controls. Similar differences have been reported previously. Unpublished data of 742 Dutch FH children with a mean age of 11 years also showed similar elevated mean levels of TC (7.26 ± SEM 0.06) and LDL-C (6.62 ± SEM 0.06). TC, LDL-C, and Apo A-I were higher in the FH girls than in FH boys. This may be explained by the age differences between boys and girls.

**Conclusion**

Our data indicate that the Simvastatin in Children Study randomized a group of boys and girls who are representative of patients with FH of a similar age group. Lipid levels were above the 95th percentile for age and gender. The study outcomes will provide important data on lipid-altering efficacy, safety, and tolerability to support the use of simvastatin in this group of patients at relatively high CHD risk. In addition to the effects on the lipid, lipoprotein, and apolipoprotein profile, important data will be available regarding the effects of simvastatin on markers of muscle effects and on growth and pubertal development.

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