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A 3-year study of atorvastatin in children and adolescents with heterozygous familial hypercholesterolemia

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BACKGROUND: The efficacy and safety of atorvastatin in children/adolescents aged 10–17 years with heterozygous familial hypercholesterolemia (HeFH) have been demonstrated in trials of up to 1 year in duration. However, the efficacy/safety of >1 year use of atorvastatin in children/adolescents with HeFH, including children from 6 years of age, has not been assessed.

OBJECTIVE: To characterize the efficacy and safety of atorvastatin over 3 years and to assess the impact on growth and development in children aged 6–15 years with HeFH.

METHODS: A total of 272 subjects aged 6–15 years with HeFH and low-density lipoprotein cholesterol (LDL-C) ≥4.0 mmol/L (154 mg/dL) were enrolled in a 3-year study (NCT00827606). Subjects were initiated on atorvastatin (5 mg or 10 mg) with doses increased to up to 80 mg based on LDL-C levels.

RESULTS: Mean percentage reductions from baseline in LDL-C at 36 months/early termination were 43.8% for subjects at Tanner stage (TS) 1 and 39.9% for TS ≥2. There was no evidence of variations in the lipid-lowering efficacy of atorvastatin between the TS groups analyzed (1 vs ≥2) or in subjects aged <10 vs ≥10 years, and the treatment had no adverse effect on growth or maturation. Atorvastatin had a favorable safety and tolerability profile, and only 6 (2.2%) subjects discontinued because of adverse events.

CONCLUSIONS: Atorvastatin over 3 years was efficacious, had no impact on growth/maturation, and was well tolerated in children and adolescents with HeFH aged 6–15 years.

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Clinical trial registration number: Clinicaltrials.gov #NCT00827606.

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Introduction

Elevated cholesterol levels in childhood are associated with an increased incidence of atherosclerosis in adulthood.[1,2] The severity of atherosclerosis can be correlated to

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the extent and duration of hypercholesterolemia.[3] Familial hypercholesterolemia (FH) is a common inherited autosomal dominant disorder of lipoprotein metabolism characterized by reduced clearance of low-density lipoprotein cholesterol (LDL-C) from the circulation leading to elevations of LDL-C.[4,5] In most cases (85%–90%), FH is caused by defects in the low-density lipoprotein-receptor (LDL-R) gene. Defects in the genes for apolipoprotein B (apoB) and proprotein convertase subtilisin/kexin type 9 account for about 5% and <5% of cases, respectively.[4] Rarely, autosomal recessive hypercholesterolemia can cause FH.[6,7] In most populations, heterozygous familial hypercholesterolemia (HeFH) affects ~1 in 200–250 individuals.[8] FH is associated with increased morbidity of coronary heart disease and with premature death[8–11], and children with FH have greater carotid intima media thickness than their unaffected siblings.[12,13]

Early intervention with cholesterol-lowering treatment, primarily statins, has been shown to prevent early coronary heart disease.[14–16] The evidence base for the efficacy and safety of statins in children is growing.[17–28] However, gaps in this evidence base remain.[29] For example, studies conducted with atorvastatin in children/adolescents with HeFH were up to 1 year in duration with the impact on growth/development evaluated at 26 weeks.[26] Furthermore, the 1-year study was conducted in children/adolescents of 10–17 years,[26] whereas statins are now considered in children with HeFH <10 years.[5] This 3-year study enrolling ~250 subjects aged 6–15 years with genetically confirmed HeFH was therefore conducted to characterize the long-term efficacy and safety of atorvastatin and to assess the impact of this medication on growth and development. Also, as part of this work, we examined the impact of atorvastatin treatment on endothelial function in the brachial arteries assessed by flow-mediated dilation (FMD).[30] This was an optional exploratory study to assess the potential for a change in the FMD to act as a surrogate biomarker for the efficacy of LDL-C lowering as previously shown in a study with simvastatin therapy in children and adolescents with FH.[31]

Methods

Standard protocol approvals, registrations, and patient consents

This open-label, multicenter, prospective study was conducted between March 30, 2009 and October 8, 2013 at 30 centers across 14 counties in compliance with the Declaration of Helsinki and International Conference on Harmonization Good Clinical Practice guidelines. In addition, all local regulatory requirements were followed. The protocol and the informed consent documents were reviewed and approved by the institutional review boards and/or independent ethics committees at each participating center. Parents or legal guardians provided informed consent. The subject could also sign a written consent form, if they were able to do so. The exact processes and procedures for attaining assent and consent varied between countries. However, all country-specific guidelines were complied with.

Study population

Girls and boys aged 6–15 years with genetically confirmed HeFH (those girls and boys who had no prior record of genetically confirmed HeFH underwent genetic testing pre-randomization to confirm whether they had HeFH). DNA was extracted from saliva or from blood, and the 18 exons and flanking regions of the LDL-R gene and exon 26 of the apoB gene were sequenced using SANGER methodology. Samples were also tested for large deletions or insertions in the LDL-R gene, using Multiplex Ligase-dependent Probe Amplification (MLPA) analysis (Details provided in Supplementary Material).

All those who did not have genetically confirmed HeFH were excluded. All patients also had to have an LDL-C of ≥4.0 mmol/L (154 mg/dL) for inclusion. Exclusion criteria included a history of active liver disease, hepatic dysfunction, or persistent elevations of serum transaminases >3× the upper limit of normal (ULN) or conditions likely to delay puberty. Pregnant or breastfeeding females, and females of childbearing potential not using adequate contraception, were excluded. Subjects with hypersensitivities to statins or receiving statin therapy within 4 weeks of randomization were excluded. However, a 4-week washout of lipid-lowering medication was permitted.

Study design

The doses of atorvastatin used in this study were based on the results of a study comparing the efficacy and safety of different starting doses of atorvastatin in adults with dyslipidemia[32] and earlier studies conducted in 6–17-year-old subjects.[21,26]

In total, 272 subjects with HeFH were stratified into 2 cohorts according to their Tanner stage (TS) (1 or ≥2) at screening. Subjects aged 6 to <10 years (mostly TS 1) initiated therapy on atorvastatin 5 mg per day (a pediatric chewable formulation), and those aged 10 to 15 years (mostly TS ≥ 2) initiated treatment with atorvastatin 10 mg per day.

Subjects had their dose titrated based on an LDL-C target of <3.35 mmol/L (<130 mg/dL). Doses were increased from 5 to 10 to 20 mg or 10 to 20 to 40 mg per day. Titrations above 40 mg per day were permitted after discussions with the study sponsor. Subjects initiating treatment on atorvastatin 10 mg per day were permitted to decrease their dose if their LDL-C decreased to <2.59 mmol/L (100 mg/dL). Subjects with LDL-C <2.59 mmol/L on the 5 mg dose were discontinued.