Intermediate-Term Efficacy and Tolerance of Statins in Children

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Objectives To evaluate the intermediate-term efficacy and tolerance of statins in children and adolescents with familial hypercholesterolemia.

Study design A total of 131 children or adolescents treated with statins for familial hypercholesterolemia were prospectively included. The efficacy of treatment was established by the percentage of children who achieved low density lipoprotein-cholesterol (LDL-C) levels <160 mg/dL during treatment. Treatment tolerance was evaluated by the occurrence of clinical or laboratory side effects, regularity of increases in height and weight, and pubertal development.

Results The median duration of treatment with statins was 4 years. A median decrease of 32% in LDL-C levels was observed ($P < .0001$). The therapeutic target (LDL-C <160 mg/dL) was achieved in 67% of cases. Increases in height and weight and sexual maturation were not affected by the treatment. Minor side effects were reported for 24 (18.4%) patients including 3 cases of a clinically asymptomatic increase in creatine phosphokinase (CPK) levels, 2 cases of an increase in CPK levels with muscular symptoms, 14 cases of myalgia without an increase in CPK levels, 3 cases of abdominal pain, 1 case of dysuria, and 1 case of diffuse pain. None of these side effects led to the discontinuation of statin therapy, although a change of statin was required in 7 cases. This new statin was tolerated in all cases. No patients had abnormal liver function during treatment.

Conclusions The results of this large cohort confirm the intermediate-term safety and efficacy of statin therapy in children with familial hypercholesterolemia. *(J Pediatr 2019;210:161-5)*.

Familial hypercholesterolemia is one of the most common inherited diseases. It is an autosomal dominant disease which affects 1 of 200 to 1 of 300 people in its heterozygous form.[1] It is due to mutations in the low density lipoprotein (LDL) receptor, apolipoprotein B-100 (ApoB), or proprotein convertase subtilisin/kexin type 9 gene, leading to elevated plasma levels of LDL-cholesterol (LDL-C) from early age and increased risk for cardiovascular disease in early adulthood.[2-6] This risk of premature cardiovascular events has prompted recommendations to lower LDL-C levels from childhood.[7] Treatment is usually based on statins (3-hydroxy-3-methyl-glutaryl coenzyme A reductase inhibitors), which can be initiated from the age of 8 years.[8,9] The efficacy of statins has been widely demonstrated in adults, whether for the primary or secondary prevention of cardiovascular risk.[10] However, no studies have evaluated the efficacy of statin therapy initiated during childhood on the incidence of long-term cardiovascular events. However, it is known that statins reduce carotid intima-media thickness[11] and improve arterial endothelial function[12] in children with hypercholesterolemia.

Efficacy and good tolerance of short-term statin therapy have been widely reported in children.[13] These studies had a median duration of 24 weeks and only 1 lasted up to 2 years.

The objective of our study was to evaluate the efficacy and safety of intermediate-term statin therapy in a large cohort of children and adolescents.

Methods

All children and adolescents treated with statins for familial hypercholesterolemia between August 1992 and April 2017 in the Pediatric Nutrition and Gastroenterology Department of Trousseau Hospital were prospectively included. The diagnosis of familial hypercholesterolemia was based on either a causal mutation of familial hypercholesterolemia identified in the LDL receptor, ApoB, or proprotein convertase subtilisin/kexin type 9 gene, or both a LDL-C level >190 mg/dL despite 6 months of a well-followed cholesterol-lowering diet, and a family

ApoB	Apolipoprotein B-100
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
CPK	Creatine phosphokinase
EAS	European Atherosclerosis Society
HDL-C	High density lipoprotein-cholesterol
LDL	Low density lipoprotein
LDL-C	LDL-cholesterol
N	Normal

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history suggesting familial hypercholesterolemia: hypercholesterolemia in a first-degree relative or history of early cardiovascular events (angina pectoris, myocardial infarction, percutaneous coronary intervention, coronary artery bypass, ischemic stroke, sudden cardiac death, or peripheral arterial disease) before age 55 years in men and age 60 years in women in a first or second degree relative. All children received advice from a dietician for the implementation of a cholesterol-lowering diet during the 6 months before statin therapy. According to local expert opinion, a statin was prescribed when the LDL-C level remained >160 mg/dL in the presence of another cardiovascular risk factor (obesity, diabetes, high blood pressure, lipoprotein (a) > 500 mg/L) or >190 mg/dL in the absence of a cardiovascular risk factor. Children with homozygous familial hypercholesterolemia were excluded.

The following clinical and epidemiologic data were collected for each patient: age, sex, weight, height, family history of first- or second-degree hypercholesterolemia, with or without cholesterol-lowering treatment, and history of early cardiovascular events in a first or second degree relative. The Waterlow score, consisting of the weight divided by the expected weight for the child's height (as a percentage), and the height divided by the expected height for the child's age (as a percentage) were used to evaluate growth.[14] Puberty was assessed by Tanner stage.

Patients were generally seen once or twice a year at follow-up. Before each consultation, a fasting lipid test was performed, including plasma total cholesterol, high density lipoprotein-cholesterol (HDL-C), and triglycerides levels (by enzymatic colorimetric method) and LDL-C level (calculated using the Friedewald equation). The liver enzymes aspartate aminotransferase (AST) and alanine aminotransferase (ALT) and the muscle enzyme creatinine phosphokinase (CPK) were assessed at the same time.

The efficacy of treatment was evaluated first, by the decrease (as a percentage) in total cholesterol and LCL-C levels following statin therapy between the start of treatment and the last follow-up consultation and second, by the percentage of children who achieved an LDL-C level <160 mg/dL. At each consultation, data on self-reported undesirable clinical effects potentially related to the treatment were collected: cramps, unexplained muscle pain, weakness or stiffness, asthenia, abdominal pain, and headache.

Biological tolerability was assessed by searching for muscle-related adverse effects, defined as a rise in CPK levels to more than 5 times above normal (5N). An elevation of ALT and/or AST levels to more than 3 times above the laboratory-defined upper limit was considered to be a sign of hepatic cytolysis.

The global tolerability of treatment was assessed by monitoring the occurrence of clinical or biological side effects, their severity, the need to change the statin, regularity of increase in height and weight, and pubertal development. When none of these side effects occurred, we considered that statin therapy was well tolerated. The study was approved by the local ethics committee.

Statistical analyses were performed using GraphPad Prism software (v 7.03, Dr. Harvey Motulsky, San Diego, California). The Wilcoxon test, with sample matching, was used to compare clinical and laboratory measures between the start of statin therapy and the end of follow-up. Significance was set at $P < .05$.

Results

A total of 131 children and adolescents were included (sex ratio = 1.05), for whom the main characteristics are presented in **Table I**. Most parents (92.3%) were known to have hypercholesterolemia and 90.1% of parents with hypercholesterolemia were treated. A family history of early cardiovascular events was frequently found (69% of cases, including 14.5% first degree relatives), most involving coronary heart disease.

The diagnosis was based on targeted (family history based) screening for 121 children. For the 10 others, the lipid blood test that led to the diagnosis of hypercholesterolemia was performed for another reason: 7 as part of a systematic health check, 1 because of the child being overweight, 1 for visual disorders, and 1 for xanthomas. Among these 10 children, 9 parents did not know their lipid profile or those of their relatives and 1 child was adopted. The discovery of hypercholesterolemia in the children allowed the diagnosis of familial hypercholesterolemia in 6 of these 9 parents. Finally, only 3 of the 131 children (2.3%) did not have a known family history of either first- or second-degree hypercholesterolemia or premature cardiovascular events. However, 2 of these 3 children had a family history of treated hypercholesterolemia in a third-degree relative.

Familial hypercholesterolemia was confirmed by genetic testing for 117 of the 126 children tested. All children had a heterozygous LDL receptor mutation, and 1 child had both a heterozygous mutation of the LDL receptor and ApoB. The same mutation was sought in 64 parents with

Table I. Characteristics of the 131 children studied

Sex, n (%)	Male: 67 (51.1)/Female: 64 (48.9)
First-degree history:	
Parental history of hypercholesterolemia	121 (92.3)
Undetermined	10 (7.6)
Lipid-lowering therapy in a first-degree relative	109 (83.2)
Early cardiovascular disease in a first or second-degree relative, n = 126 (%)	87 (69.0)
Diagnosis with targeted screening, n (%)	121 (92.3)
Age at diagnosis, mean (minimum-maximum)	6.8 y (12 mo-14.4 y)
Genetic testing of children (n = 126):	
LDLR mutation	117
ApoB mutation	1*
PCSK9 mutation	0
No mutation found	9
Genetic testing of parents (n = 64):	
Same mutation in one of the parents	63
No mutation in parents	1

LDLR, LDL receptor; *PCSK9*, proprotein convertase subtilisin/kexin type 9.
*One child had both LDLR and ApoB mutations.

Table II. Lipid balance before the initiation of statin treatment and at the end of follow-up

Lipids (mg/dL)	Before statin therapy	With statin, at the end of follow-up	Percentage difference	*P*
TC (n = 126)	283 (190-472)	214 (124-376)	−24.4%	<.0001
LDL-C (n = 126)	209 (117-413)	142 (45-295)	−32.0%	<.0001
HDL-C (n = 122)	58 (26-119)	54.5 (27-101)	−6.0%	.0025
TG (n = 122)	61 (23-165)	60 (25-229)	−1.6%	.8

TC, total cholesterol; *TG*, triglycerides.
Results are expressed as the median (minimum-maximum).

hypercholesterolemia and found for 63. For 1 child, neither the mother nor father had the mutation. Among the 9 children in whom no mutation was found, 8 had 1 parent with hypercholesterolemia (7 of whom were undergoing cholesterol-lowering therapy).

Fifty-three children (40.5%) were receiving another cholesterol-lowering treatment before the statin treatment: 36 received cholestyramine, 6 fibrate, 10 cholestyramine and then fibrate, and 1 ezetimibe.

The median age at the beginning of statin therapy was 10.0 years (5.2-17.7 years of age), and 25.7% of children started treatment before the age of 8 years, in all cases because of early cardiovascular events in the family. Pravastatin was first prescribed for 101 patients (77%, median age: 9.9 years [5.2-17.7]), rosuvastatin for 22 (16.8%, median age: 9.9 years [5.9-14.2]), and atorvastatin for 8 (6.1%, median age: 12.0 years [9.6-17.2]). The statin was always started at the smallest dose. Dosages were increased to the maximum allowable dose (pravastatin: 20 mg before age 13 years, 40 mg before age 18 years; rosuvastatin 10 mg before age 9 years, 20 mg before age 18 years; atorvastatin 40 mg whatever the age); if efficacy was not within the defined criteria at the maximum allowed dose, the class of statin was changed.

The median duration of statin treatment was 48 months (2.3 months-13.3 years). Ninety-four children (71.8%) were followed-up for more than 2 years. The median age at the end of follow-up was 14.3 years (6.5-22.5 years of age). At the end of the study, 26 children were still followed- up. Seventy-two children were lost to follow-up after an average of 35 months, and 33 children kept being followed up in an adult department after reaching 18 years of age. The average number of visits during follow-up was 10.4 (ie, every 8 months in average).

Children were seen for the first time, on average, 6 months after the initiation of statin treatment. At this first consultation, a median 24% decrease in LDL-C levels was observed ($P < .0001$). At the end of follow-up, a median 32.0% decrease in LDL-C levels was observed ($P < .0001$). Eighty-seven (67.4%) of the 126 patients for whom the LDL-C levels were known at the end of follow-up achieved the therapeutic goal of an LDL-C level <160 mg/dL. The lipid profiles before statin initiation and at the end of follow-up are reported in Table II. Among the 53 children who received another cholesterol-lowering treatment before the statin, 8 had an LDL-C level <160 mg/dL, all with cholestyramine, which was replaced by a statin because cholestyramine was refused due to poor palatability. For the remaining 45 children, cholesterol-lowering treatment was replaced by a statin because LDL-C level remained >160 mg/dL.

A statin switch was necessary for 57 patients during the follow-up: in 52 cases because LDL-C levels remained >160 mg/dL and in 5 cases because of side effects related to treatment. Seven children required a second switch: in 2 cases because of insufficient efficacy of treatment, with an LDL-C level >160 mg/dL, in 2 cases because of side effects, in 1 case to facilitate treatment (giving a single tablet instead of 2), in 1 case in which the statin was changed by the family, and finally for 1 child because of the significant consumption of grapefruit juice while taking atorvastatin (grapefruit juice inhibits CYP 3A4, which is involved in the catabolism of atorvastatin). Three children had ezetimibe in addition to the third statin because of persistent hypercholesterolemia (LDL-C levels still >160 mg/dL).

Statin therapy was well tolerated by 107 (81.6%) of the patients. Side effects occurred in 19 patients. No side effects resulted in permanent discontinuation of statin therapy. The statin had to be stopped in 7 cases because of side effects, but the switch with another class of statin was well tolerated each time, without the recurrence of side effects. For the 12 remaining children, the same statin therapy was continued because their symptoms disappeared. Tolerance of the treatment is reported in Table III.

Five children required a change of statin because of clinical symptoms and/or abnormal CPK concentrations. Two others had to temporarily interrupt their treatment but were then able to resume without new side effects.

Table III. Tolerance of statin therapy in 131 children

Tolerance of the statin therapies	n (%)
No side effects	107 (81.6)
Muscular side effect:	19 (14.5)
Asymptomatic increase of CPK >5 N	3
Increase of CPK level with muscular symptoms	2
Muscular symptoms without an increase in CPK	14
Hepatic side effect:	0
Increase of AST or ALT >3 N	0
Other reported side effects:	5
Dysuria	1
Diffuse pain	1
Abdominal pain	3
Statin switch because of side effect	7 (5.3)
Statural growth and weight gain (n = 124):	
Weight/ideal weight for height before treatment	103.9 %
Weight/ideal weight for height at the end of follow-up	104.2 %
Height/height expected for age before treatment	101.4 %
Height/height expected for age at the end of follow-up	101.6 %

Two children taking rosuvastatin had muscle pain resulting in daily discomfort and elevated CPK levels. For the first, the symptoms occurred after 4 years of treatment with rosuvastatin (5 mg). The CPK level was 4N and spontaneously normalized when rosuvastatin was discontinued and switched to pravastatin, which was well tolerated. For the second, pain appeared 1 year after the start of treatment with rosuvastatin (5 mg) and the CPK level was moderately high at 6N. The switch to pravastatin was well tolerated.

Three children had to temporarily discontinue statin therapy because of an isolated increase of CPK levels to >5N, but without any clinical symptoms; the elevation of CPK levels was found each time during systematic blood tests. No significant physical activity in the previous days was reported. The first child was treated with rosuvastatin (10 mg) for 6 years, and the CPK level reached 24N. CPK spontaneously normalized within a few days after discontinuing rosuvastatin. Given the magnitude of the elevation of the CPK level, the child was switched to pravastatin, which was well tolerated with a follow-up of 18 months. The second child was treated with rosuvastatin for 22 months and had an increase in the CPK level to 6N on a systematic blood test but spontaneously normalized. The continuation of rosuvastatin at a one-half dose (5 mg) 2 weeks later was well tolerated. The third child showed an increase of CPK levels up to 16N after being treated with pravastatin for 3 years (the dose was increased from 20 to 30 mg per day 6 months previously). Fifteen days later, the level of CPK returned to normal and treatment with pravastatin was then continued at the same dose of 30 mg per day. CPK levels remained normal with a follow-up of 5 years.

Myalgia or cramps without an increase in CPK levels were reported for 14 children. For 2, the statin was changed and resulted in the resolution of symptoms. The symptoms of the other 12 resolved spontaneously without a change of statin.

Ten children showed a transient elevation of CPK levels (but <5N). Intense physical activity before the blood test was found in all cases.

There were no cases of increased ALT and/or AST levels >3N. Abdominal pain or intercurrent nausea was reported for 3 children, but the role of the statin was questionable in all cases. Transaminase levels were normal and statin therapy could be continued for each case without the recurrence of symptoms.

A case of dysuria in an adolescent girl treated with pravastatin for 3 years was reported. It resolved after discontinuation of pravastatin and replacement by atorvastatin. A change in treatment was also required for 1 child treated with rosuvastatin because of diffuse pain. However, the cause was uncertain, as there was a particular psychological context. The child did not come back to consultation after switching to pravastatin.

There was no difference in the anthropometric measures and Waterlow score before statin treatment and at the end of follow-up. No children had abnormalities of pubertal development during follow-up.

Discussion

Our study confirms the long-term efficacy and safety of statins in a large cohort of children and adolescents with hypercholesterolemia followed for more than 4 years. There were no serious side effects requiring definitive discontinuation of statin therapy, despite muscle symptoms observed in 12.2% of patients. This confirms the lack of muscular adverse effects in children muscular on statins already reported in other studies.[15-17] In the long-term study of Braamskamp et al, only 9.3% of patients experienced muscle symptoms.[15] Indeed, the frequency of muscle symptoms in children is identical to that observed in adults, as shown by an observational study of 7924 patients with hypercholesterolemia aged 18-75 years treated with high-dose statins, in which 10.5% of patients reported muscle symptoms.[18] This prevalence of muscle side effects is, however, higher than that reported in controlled studies in adults who experience myalgia in only 1.5%-5% of cases.[19] This suggests that most of the clinical symptoms judged to be adverse effects of treatment are probably not related to statin use. The European Atherosclerosis Society (EAS) recommends measuring CPK levels before the initiation of statin therapy and thereafter only if there are muscle symptoms during treatment.[20] However, a consensus of French experts on the pediatric use of statins recommends clinical and biological monitoring (transaminases and CPK) 1-3 months after the start of statin treatment and then at least once every year.[21] Our results support the European and American recommendation of assessing muscle enzymes in statin-treated children only if there are muscle symptoms.

There were no cases of statin-related liver damage in our study. This confirms the very good hepatic tolerance of statins already described in many randomized studies in children.[13,22,23] However, recommendations for the monitoring of liver enzymes in children with statin therapy are stricter than those for muscle enzymes. The EAS recommends systematically measuring ALT and AST levels before the initiation of statin therapy, every 3 months if there is a history of liver disease or, more frequently, if levels rise 3-fold greater than the upper limit of normal and of course if there are clinical symptoms of hepatotoxicity.[20] In France, the recommendations are to measure ALT and AST levels 1-3 months after beginning statin treatment and then at least once a year in the absence of clinical symptoms.[21] We believe that although hepatic complications related to statins are exceptional, their potential seriousness warrants systematic monitoring of transaminases.

Our results confirm that statins significantly decrease plasma LDL-C levels in children. The decrease in LDL-C levels between the initiation of statin treatment and the end of follow-up (−32.0%) was similar to that obtained in randomized controlled studies (−20% to 40%).[8,13] Although some studies have reported a significant increase in HDL-C levels with statins,[23] we did not find any significant increase in HDL-C, but a small significant decrease in HDL-C levels.

In our study, the therapeutic goal for LDL-C reduction was achieved in 67.4% of cases. We applied the objective proposed by French experts, who recommend achieving an LDL-C level <160 mg/dL in patients up to 20 years of age.[21] However, the EAS recommends achieving an LDL-C level <135 mg/dL,[24] close to US guidelines that set a target LDL-C level of <130 mg/dL or <110 mg/dL in the presence of a family history of early cardiovascular events.[25] This is an area for future research as the benefit of different levels of reduction in LDL-C during childhood in preventing cardiovascular events in adulthood is still uncertain.[8]

Our study had several limitations. It was a relatively small and a single center study. Because clinical side effects were self-reported by the children, we cannot exclude they could have been either over- or under-estimated. Although the growth of our patients was normal, the absence of a control group did not allow us to confirm that the treatment did not have any impact on growth. The average follow-up of our study was longer than that of most studies published until now.[12,13,18,23] However, undesirable effects that may occur after several decades of treatment cannot be ruled out. Further studies are necessary to assess the putative side effects that could appear after several decades of treatment. ■

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