Journal of Clinical Lipidology (2016) 10, 265–272

Journal of Clinical Lipidology

Original Articles

Long-term pharmacotherapy for elevated low density lipoprotein levels in children: A retrospective analysis

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KEYWORDS:
Pediatric;
Low-density lipoprotein;
Lipid;
Statin;
Ezetimibe

BACKGROUND: There is limited research detailing low-density lipoprotein cholesterol (LDL-C) trends over the long term in children on various lipid-lowering medications.

OBJECTIVES: This study sought to assess factors associated with stability of LDL-C levels in children on long-term pharmacotherapy and their ability to reach the LDL-C goal of ≤130 mg/dL while on pharmacotherapy.

METHODS: Medical records of children seen in a university pediatric cholesterol clinic between 1998 and 2012 treated with a statin, ezetimibe, or both were reviewed. Aggregate data were obtained to determine the number of children able to reach an LDL-C level of ≤130 mg/dL while on pharmacotherapy. Kaplan–Meier curve and proportional hazard regression analysis were used to examine the propensity for LDL-C levels to stabilize over time while on pharmacotherapy as well as factors affecting this propensity.

RESULTS: Overall, 76 patients who contributed 864 total visits were included. Of the 76 patients, 56 developed a stable LDL-C with median time to stability of 28 months on pharmacotherapy. Younger age at first visit and higher medication potencies/doses were associated with an increased propensity to stabilize. Only 36 patients were able to reach an LDL-C of ≤130 mg/dL, with only 11 of 38 patients with probable familial hypercholesterolemia reaching this goal.

CONCLUSIONS: Most children reached LDL-C stability on pharmacotherapy after a median 28-month interval. However, most children had difficulty in reaching the LDL-C goal of ≤130 mg/dL even with aggressive medication titration. This was specifically true for those with probable familial hypercholesterolemia.

Introduction

Dyslipidemia, especially elevated low-density lipoprotein cholesterol (LDL-C), is well known to be a major cardiovascular risk factor in the adult population.[1] Although the risk of premature cardiovascular events in children who have high LDL-C is still not well understood, studies such

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Submitted July 28, 2015. Accepted for publication November 21, 2015.

1933-2874/
http://dx.doi.org/10.1016/j.jacl.2015.11.012

as the Bogalusa heart study and the Pathological Determinants of Atherosclerosis in Youth study have clearly established a link between development of atherosclerosis and levels of circulating LDL-C in children.[2,3] As a result, the National Cholesterol Education Partnership developed guidelines for screening and treating dyslipidemias in children in 1992.[4] One of the cornerstones of these guidelines was the use of pharmacologic treatment for children with severe elevations in LDL-C levels. At that time, medication choices were fairly limited, and the guidelines advocated the use of bile acid binding resins as the first line therapy. Given the side effect profile of these medications, compliance suffered and they eventually fell out of favor.[5]

The emergence of 3-hydroxy-3-methylglutaryl-CoA reductase inhibitors, better known as statins, for treatment of elevated LDL-C in the adult population created a brand new potential for treating children given their favorable side-effect profile and proven efficacy for lowering LDL-C in adults. Nearly all the statins have subsequently undergone randomized controlled trials and have shown reasonably good efficacy with favorable side effect profiles in children.[6–15] In 2008, with the modification of the screening guidelines for dyslipidemias in children by the National Cholesterol Education Partnership, treatment guidelines were also modified to denote statins as the first line choice for pharmacologic treatment in children.[16] Additionally, ezetimibe, which acts to decrease absorption of dietary cholesterol at the small intestine brush border, has also been shown to be efficacious in children, both as an adjunct to statin therapy and/or as monotherapy.[17] Although the guidelines for screening children have substantially changed since this time, the treatment guidelines for hyperlipidemia in children have not. Current guidelines suggest starting with a low-dose statin for children who are eligible for treatment and titrating the dose after 3 months if the LDL-C is still greater than 130 mg/dL.[18] This is based on dose-response relationships observed in a few of the randomized clinical trials.[6,10,13] A second titration of the same statin can be done after another 3 months if the goal LDL-C is not met or a second agent could be added. Once the goal level of 130 mg/dL is reached, guidelines recommend checking a fasting lipid profile in 8 weeks and then 3 months to confirm maintenance of the goal level. If maintenance persists, then fasting lipid panels should be checked every 3–4 months in the first year of maintenance followed by every 6 months during the second year and beyond.

Although pharmacologic treatment of elevated LDL-C in children has clearly evolved and become more commonplace, longer term data on maintenance therapy have not been as well described in the literature. Furthermore, there are few studies in children looking at escalation of maintenance pharmacotherapy and effect on LDL-C levels. The authors undertook this retrospective study to look at the long-term use of pharmacologic therapy in children for treatment of elevated LDL-C. We specifically sought to determine how quickly LDL-C levels in children typically stabilize when placed on pharmacotherapy, the effect of pharmacotherapy titration on LDL-C stabilization and ability of children to reach the LDL-C goal of 130 mg/dL while on long-term pharmacotherapy.

Methods

This study was approved by the West Virginia University Institutional Review Board. A retrospective chart review was conducted using data gathered from clinic visits to the pediatric cholesterol clinic based in rural Appalachia at West Virginia University. This clinic sees patients from Pennsylvania, West Virginia, Maryland, and Ohio. This clinic began seeing patients in 1998 and data were available from this time period; the study period spanned from 1998 to the end of 2012. Data from patients were eligible for inclusion if, at any point in time, they were placed on pharmacotherapy to specifically lower LDL-C levels. Patients had to have at least two follow-up visits after addition of pharmacotherapy in addition to their baseline visit for inclusion. Patients with baseline missing data were excluded from the analysis. Other than the referral baseline LDL-C- levels, all subsequent LDL-C levels were obtained at the West Virginia University laboratory in the fasting state.

A total of 76 patients were included in this study who contributed a total of 864 visits. Follow-up intervals were variable and at the discretion of the individual provider. On average, patients were typically seen every 3–4 months. Achievement and maintenance via titration of medications were based around a goal of LDL-C $\leq$130 mg/dL. To account for varying doses and potencies of different statin medications, all statins used in the study (pravastatin, simvastatin, atorvastatin, rosuvastatin) were converted to an equivalent simvastatin dose based on the percentage of LDL-C reduction that has been typically observed for each statin/dose combination.[19]

Baseline demographic and clinical variables are summarized using the mean, standard deviation, min, max, and median. Body mass index percentiles were calculated using the sex and age Centers for Disease Control and Prevention growth charts for the United States, body mass index-for-age growth charts.[20] Comparisons between groups were made using the nonparametric Mann–Whitney–Wilcoxon test. Stabilization is defined as 2 sequential visits where there is $<$20% change from the previous LDL-C value after medication was begun. Time to stabilization is defined as the time between the initiation of medication specifically used to lower LDL-C and when the stabilization event occurs.

We used the Kaplan–Meier (KM) curve, with Greenwood's standard error, to describe the experience of LDL-C stabilization over the observation period. Confidence intervals were constructed using the log-log transform. For comparing KM curves, we used the log-rank test (Mantel–Haenszel) to assess differences in the time to LDL-C stabilization. The median event time, the time to