### **Brief Report**

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# Long-term use of a combination of atorvastatin and ezetimibe in children with homozygous familial hypercholesterolemia

Devi Dayal<sup>1\*</sup>, Keerthivasan Seetharaman<sup>1</sup>, Savita Bhunwal<sup>1</sup>, Nimisha Jain<sup>2</sup>

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## \*Correspondence: Dr. Devi Dayal,

E-mail: drdevidayal@gmail.com

E-maii: drdevidayai@gmaii.com

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#### **ABSTRACT**

**Background:** Homozygous familial hypercholesterolemia (HoFH) is an underdiagnosed and undertreated genetic disorder of lipoprotein metabolism associated with mortality during young age due to accelerated atherosclerosis. There is limited data on the efficacy of lipid lowering therapies in HoFH.

**Methods:** Medical records of 3 children with HoFH who received a combination of atorvastatin and ezetimibe for a mean duration of 11.6±1.5 years were retrospectively analysed.

**Results:** There was a significant decrease in total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C) and triglyceride (TG) from the baseline levels (mean percent change in TC, LDL-C, TG and HDL-C of 58.5%, 56.2%, 67.5% and 29.7% respectively).

**Conclusions:** We conclude that long-term use of a combination of atorvastatin and ezetimibe significantly lowers the plasma LDL-C concentrations in patients with HoFH without causing any significant adverse effects. Ours is the first study from India on long-term use of lipid modifying drug therapy in children with HoFH.

Keywords: Atorvastatin, Ezetimibe, Familial hypercholesterolemia, Homozygous, Lipid lowering therapy

#### INTRODUCTION

Familial hypercholesterolemia (FH) is an autosomal dominant genetic condition characterized by high low-density lipoprotein cholesterol (LDL-C) levels that lead to development of early atherosclerotic cardiovascular disease (CVD). The diagnosis is made by applying one of the several clinical diagnostic criteria such as the Simon Broome Register Group criteria, Dutch Lipid Clinic Network criteria, Make Early Diagnosis to Prevent Early Deaths (MEDPED) criteria and Japanese criteria, all of which show similarity of the major items but differ with respect to specific values. However, confirmation of diagnosis by a genetic mutation consistent with FH is desirable. The treatment of FH often requires multiple lipid lowering agents aimed at a reduction of circulating

LDL-C by 50% or more from baseline.<sup>1,2</sup> The diagnosis and treatment of the homozygous FH (HoFH) is very difficult due to rarity of its occurrence (1:1,000,000 live births) and the requirement of additional modalities such as LDL-C apheresis.<sup>1,2</sup> There is a limited data on the long-term use of lipid lowering drugs in children with HoFH, especially from the developing countries.<sup>2,3</sup>

#### **METHODS**

Of the 10 patients diagnosed with FH at our hospital between 2004 and 2016, five had HoFH, three had familial hypertriglyceridemia while two others had heterozygous FH (HeFH). Two of the five children with HoFH were lost to follow up; the data of the remaining three were extracted from the clinic files retrospectively.

<sup>&</sup>lt;sup>1</sup>Department of Pediatrics, Postgraduate Institute of Medical Education and Research, Chandigarh, India <sup>2</sup>Department of Endocrinology, Postgraduate Institute of Medical Education and Research, Chandigarh, India

All three were diagnosed with HoFH on the basis of an untreated LDL-C >500 mg/dL alongwith either cutaneous or tendon xanthoma appearing before age 4 years or LDL-C levels consistent with HeFH in parents.<sup>1,4</sup> All 3 were treated with a combination of Atorvastatin and Ezetimibe. The drug doses were titrated to achieve and maintain at least 50% reduction in LDL-C concentrations and avoid muscle symptoms or rise in transaminases. All patients were instructed to adhere to the National Cholesterol Education Program Step I (<30% of total energy from fat, <10% from saturated fat, and <300 mg cholesterol per day) or stricter diet. At 6 monthly follow up visits, lipid profiles and liver function tests were obtained in addition to a thorough physical assessment. Mean values for the lipid parameters were calculated for analysis. Creatine kinase levels were estimated if patients developed any symptoms or signs of muscle weakness.

#### **RESULTS**

The mean age at appearance of xanthomas and at diagnosis was  $2.4\pm1.2$  years (range 1-3.5 years) and  $4.6\pm3.2$  years (range 1-7 years) respectively. The mean concentrations of total cholesterol (TC), LDL-C and triglyceride (TG) were elevated at diagnosis and showed a significant fall after therapy (Table 1).

Table 1: Change in lipid parameters with combination of atorvastatin and ezetimibe.

Lipid parameter	Mean untreated level	Mean treated level	Percent change
TC (mg/dL)	734.0	304.0	-58.5
LDL-C (mg/dL)	527.6	231.0	-56.2
TG (mg/dL)	931.3	302.0	-67.5
HDL-C (mg/dL)	40.3	52.3	+29.7

The mean treated HDL-C levels also increased from the baseline (Table 1). The mean percent decrease in TC, LDL-C and TG concentrations was 58.5, 56.2 and 67.5 while mean treated HDL-C rose by 29.7% from baseline level (Table 1).

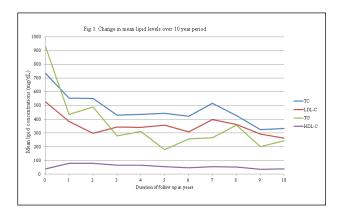


Figure 1: Change in mean lipid levels over 10-year period.

After a significant initial fall during the first year of therapy, the mean lipid parameters almost plateaued during the subsequent 9 years (Figure 1). Similarly, the mean HDL-C levels increased during first year of therapy and remained unchanged thereafter (Figure 1). None developed any muscle weakness or rise of liver enzymes during the treatment period. The mean duration of follow up was 11.6±1.5 years (range 10-13 years).

#### **DISCUSSION**

Homozygous FH is a rare genetic disorder associated with significant reduction in LDL receptor function.<sup>1</sup> The exposure to highly elevated LDL-C concentrations from birth predisposes the affected children to early atherosclerotic CVD and death during adolescence or young adulthood.<sup>1,4</sup> The treatment is difficult and the response to conventional drug therapies is modest. Multimodality therapies with various combinations of lipid lowering agents and additional LDL apheresis often fail to achieve the desired target levels of plasma lipids.<sup>4</sup>

Most guidelines identify LDL-C as the primary target for treatment.<sup>1,4</sup> Although the absolute target LDL-C levels still are under debate, a reduction by 50% or more from baseline is recommended in children with FH.4 These recommendations are mainly based on studies in children with HeFH<sup>5</sup>. Whether a similar reduction in LDL-C levels is sufficient to reduce CVD risk in children with HoFH is unknown due to scarce data.<sup>5</sup> In this context, our experience is similar to studies in patients with HeFH which showed LDL-C reductions of upto 55% with maximally tolerated doses of combinations of statins and ezetimibe.4-7 Further reductions in plasma lipid concentrations are possible with LDL apheresis which is widely practiced in developed countries but has only recently been conducted successfully in India.8 The increase in HDL-C achieved in our patients was more as compared to previous studies (29.7% versus 5-10 %).<sup>5,6</sup> It is well known that children with HoFH may still remain poorly controlled and show progression to atherosclerosis despite an aggressive therapy.9

Newer lipid modifying drugs such as microsomal triglyceride transfer protein inhibitor (lomitapide), apolipoprotein B inhibitor (mipomersen) and PCSK9 inhibitors (alirocumab, bococizumab, evolocumab) offer promise of further reductions in LDL-C levels in patients with HoFH but are very costly and not available in India at present.4 Also, due to a variety of reasons, the emphasis on screening and treatment of patients with FH seems to be neglected in India.<sup>3</sup> Understandably, there are no studies on use of lipid lowering therapies in Indian patients with HoFH.<sup>3</sup> Even in the developed countries, the data on efficacy and safety of various lipid lowering therapies is limited.<sup>4,5,7</sup> We did not observe statin induced myopathy in our patients although a recent Indian study shows that 7.5% of adult statin users developed myopathy. 10

#### **CONCLUSION**

In conclusion, our experience indicates that long-term use of a combination of atorvastatin and ezetimibe significantly lowers the plasma LDL-C concentrations in patients with HoFH and is well tolerated. There is an urgent need to conduct multi-centered studies on efficacy and safety of various lipid lowering therapies in Indian patients with HoFH.

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Institutional Ethics Committee

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