Effect of evolocumab versus placebo added to standard lipid-lowering therapy on fasting and post fat load lipids and lipoproteins in familial dysbetalipoproteinemia

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Background: Familial Dysbetalipoproteinemia (FD) is the second most common genetic lipid disorder (prevalence ranging from 1 in 1000–2500), characterized by impaired postprandial lipoprotein clearance and associated with increased cardiovascular (CVD) risk. The majority of FD patients do not achieve non-HDL-cholesterol treatment goals, indicating the medical need for additional lipid-lowering treatment options.

Purpose: To evaluate the effect of the PCSK9 monoclonal antibody evolocumab added to standard lipid-lowering therapy on fasting and post fat load lipids and lipoproteins in FD patients.

Methods: A randomized placebo-controlled double-blind crossover trial comparing evolocumab (140 mg subcutaneous every 2 weeks) with placebo during two 12 week treatment periods. At the start and end of each treatment period FD patients received an oral fat load. The primary endpoint was the 8 hour post fat load non-HDL-cholesterol level expressed as area under the curve (AUC). Levels of other fasting and post fat load lipids and (apo)lipoproteins were assessed with ultracentrifugation, polyacrylamide gels, retinyl palmitate and SDS-PAGE.

Results: In total, 28 patients completed the study. Mean age was 62±9 years and 93% had an ε2ε2 genotype. Compared with placebo, evolocumab reduced fasting non-HDL-cholesterol with 51% (95% CI 43–57) and the 8 hours post fat load non-HDL-cholesterol AUC with 49% (95% CI 42–55). Fasting triglyceride levels were reduced with 24% (95% CI 14–37) and the 8 hours post fat load triglyceride AUC was reduced with 22% (95% CI 11–29). Except for HDL-cholesterol, all fasting and 8 hour post fat load lipids and (apo)lipoproteins were significantly reduced by evolocumab, including apolipoprotein B (8 hour post fat load AUC reduction 47% (95% CI 41–53) and remnant cholesterol (8 hour post fat load AUC reduction 49% (95% CI −38 to 59)), compared with placebo. After treatment with evolocumab, 89% of patients achieved their non-HDL-cholesterol treatment goal compared with 36% after placebo.

Conclusion: Evolocumab added to standard lipid-lowering therapy significantly reduced fasting and post fat load non-HDL-cholesterol and other atherogenic lipids and lipoproteins in FD patients. This is the largest clinical trial in FD to date and the first to investigate evolocumab in this very high-risk group. The large decrease in fasting and post fat load lipids and lipoproteins will likely lower CVD risk in these patients.

Figure 1

The effect of evolocumab and placebo on fasting and post fat load lipids

Panel A. 8h post fat load non-HDL-cholesterol

Panel B. Triglycerides

Figure 2

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