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Effects of anacetrapib on plasma lipids in specific patient subgroups in the DEFINE (Determining the Efficacy and Tolerability of CETP INhibition with AnacEtrapib) trial

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BACKGROUND: In the Determining the Efficacy and Tolerability of cholesteryl ester transfer protein (CETP) INhibition with AnacEtrapib (DEFINE) trial, anacetrapib added to statin produced robust low-density lipoprotein cholesterol (LDL-C)-lowering and high-density lipoprotein cholesterol (HDL-C)-raising vs placebo in patients with coronary heart disease (CHD). Predictors of the degree of LDL-C and HDL-C responses to anacetrapib, however, are poorly understood.

OBJECTIVE: Lipid effects of anacetrapib in patient subgroups within the DEFINE trial (clinicaltrials.gov: NCT00685776) are reported.

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[1] See Appendix for the complete list of DEFINE study investigators.

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METHODS: The percent of placebo-corrected changes from baseline for LDL-C (estimated by Friedewald calculation [Fc-LDL-C]) and HDL-C after 24 weeks of anacetrapib 100 mg/day were compared among patients by age, gender, race, diabetes status, type of concomitant statin with or without other lipid therapies, and baseline HDL-C, Fc-LDL-C, and triglyceride (TG) levels.

RESULTS: Percent decreases in Fc-LDL-C and increases in HDL-C with anacetrapib were similar (magnitude of difference generally <1/5 of the overall treatment effect) across subgroups by age, gender, diabetes status, lipid-modifying regimen, and baseline Fc-LDL-C, HDL-C, or TG. On the other hand, anacetrapib effects on Fc-LDL-C (−24% vs −41%) and HDL-C (+75% vs +139%) appeared to be less in black vs white patients, respectively.

CONCLUSION: Effects of anacetrapib on Fc-LDL-C and HDL-C were generally comparable across subgroups, including being relatively independent of baseline Fc-LDL-C, HDL-C, or TG levels. The clinical impact of the lipid-modifying effects of anacetrapib is being evaluated in the cardiovascular disease outcomes trial, Randomized EValuation of the Effects of Anacetrapib though Lipid-modification (REVEAL).

Introduction

Elevated plasma levels of low-density lipoprotein cholesterol (LDL-C) and reduced high-density lipoprotein cholesterol (HDL-C) are major cardiovascular disease (CVD) risk factors.[1–3] Low HDL-C levels partly account for the residual risk of CVD despite statin monotherapy.[4] Thus, improving lipid parameters beyond the LDL-C–lowering achieved with the use of statins may further reduce CVD risk in dyslipidemic patients.[5,6] A novel mechanism for raising HDL-C, and also lowering LDL-C, is the inhibition of cholesteryl ester transfer protein (CETP).

Anacetrapib is an orally active, potent, selective inhibitor of CETP currently in late-stage clinical development.[7,8] Studies to date demonstrate that anacetrapib produces robust lipid-modifying efficacy, without associated adverse effects on blood pressure, aldosterone levels, or serum electrolytes,[7,8] as was observed with the CETP inhibitor, torcetrapib.[9] In the randomized, double-blind, placebo-controlled trial, Determining the Efficacy and Tolerability of CETP INhibition with AnacEtrapib (DEFINE), the effects of anacetrapib on lipids and safety parameters were studied in 1623 patients with coronary heart disease (CHD) or CHD risk equivalents on background statin therapy.[10] After 24 weeks of treatment, anacetrapib increased HDL-C by 138% and reduced LDL-C (estimated by Friedewald calculation [Fc-LDL-C]) by 40%, relative to placebo.[10] A subsequent assay comparison study demonstrated that the Friedewald formula[11] underestimates LDL-C levels after treatment with anacetrapib relative to the reference beta-quantification method.[12] Thus, the actual reduction in LDL-C with anacetrapib may be closer to 25% to 35%, although the exact magnitude is unknown.

The present analysis examines the consistency of the effects of anacetrapib on these key lipid endpoints across various subgroups of DEFINE patients.

Methods

Study design

This analysis included data from a worldwide, multicenter (153 centers), randomized, double-blind, placebo-controlled trial to assess the efficacy and safety profile of anacetrapib in patients with CHD or CHD risk equivalents (anacetrapib DEFINE protocol 019, Clinicaltrials.gov: NCT00685776).[10] Details about the study design and patient selection criteria were published previously.[10,13] Briefly, 1623 eligible patients who were taking a statin and who had Fc-LDL-C <100 mg/dL were assigned in a 1:1 ratio to receive anacetrapib 100 mg daily or matching placebo. The study was conducted in accordance with the principles of Good Clinical Practice and was approved by the appropriate institutional review boards and regulatory agencies. Informed consent was obtained from all patients. The primary endpoints included the percent change in Fc-LDL-C[11] from baseline at 24 weeks (primary) as well as safety and tolerability. The percent change in HDL-C from baseline was a secondary endpoint. The present analyses focus on the effects of anacetrapib on these 2 key lipid endpoints across various prespecified patient subgroups at week 24.

Assessments

Mean percent placebo-corrected Fc-LDL-C decreases and HDL-C increases from baseline after 24 weeks of anacetrapib 100 mg/day were compared among prespecified patient subgroups according to baseline age (<65, ≥65); gender; race (white, black, or other); diabetes status; type of concomitant statin (atorvastatin, simvastatin, rosuvastatin, or other); use of concomitant ezetimibe, niacin, or fibrate; and baseline HDL-C, Fc-LDL-C, and triglyceride (TG) levels above or below the median (calculated from all randomized patients with a baseline measurement, irrespective of