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Comparative effects of cholesteryl ester transfer protein inhibition, statin or ezetimibe on lipid factors: The ACCENTUATE trial

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ABSTRACT

Background and aims: The optimal approaches to management of patients treated with moderate statin doses on lipid parameters are unknown. The ACCENTUATE study aimed to compare the effects of adding the cholesteryl ester transfer protein inhibitor (CETP) evacetrapib, ezetimibe or increasing statin dose in atorvastatin-treated high-vascular risk patients on lipid parameters.

Methods: 366 patients with atherosclerotic cardiovascular disease (ASCVD) and/or diabetes were treated with atorvastatin 40 mg/day for 28 days prior to randomization to atorvastatin 40 mg plus evacetrapib 130 mg, atorvastatin 80 mg, atorvastatin 40 mg plus ezetimibe 10 mg or atorvastatin 40 mg plus placebo, daily for 90 days at 64 centers in the United States. Lipid parameters, safety and tolerability were measured.

Results: Addition of evacetrapib significantly reduced LDL-C (−33%) compared with ezetimibe (−27%, p=0.045), increasing statin dose (−6%) and statin alone (0%, p<0.001). Evacetrapib also decreased apoB by 23% compared to 19% with ezetimibe (p=0.06) and 7% with increased statin dose (p<0.001), and reduced Lp(a) by 29% (p<0.001 *vs.* other groups). Evacetrapib increased HDL-C (+125%), apoA-I (+46%), apoC-III (+50%) and apoE (+28%) (p<0.001 *vs.* other groups). Non-ABCA1-mediated efflux increased by 53% (p<0.001 *vs.* other groups) with evacetrapib. ABCA1-mediated efflux also increased by 13% with evacetrapib (p<0.001 *vs.* ezetimibe, p=0.002 *vs.* increasing statin dose, and p=0.004 *vs.* statin alone). Addition of evacetrapib to atorvastatin produced an increase in hsCRP compared with ezetimibe (p=0.02).

Conclusions: While evacetrapib improved traditional atherogenic and putative protective lipid measures compared with ezetimibe and increasing statin dose in patients with ASCVD and/or diabetes, it also adversely affected novel atherogenic risk factors. These findings may contribute to the lack of clinical benefit observed in the ACCELERATE trial.

1. Introduction

While lowering levels of low-density lipoprotein cholesterol (LDL-C) with statins has consistently been demonstrated to reduce cardiovascular morbidity and mortality in large outcome trials, there remains a substantial residual risk of clinical events [1–10]. This has prompted the search to identify additional therapies that will complement the role of statins to more effectively reduce cardiovascular risk [11]. By virtue of their ability to raise levels of high-density lipoprotein cholesterol (HDL-C), pharmacological inhibitors of cholesteryl ester transfer protein (CETP) have received considerable attention as a potential cardioprotective strategy [12–16].

Potent CETP inhibitors have also been demonstrated to reduce

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levels of atherogenic lipid parameters including both LDL-C and lipoprotein (a) [Lp(a)]. As a result, these agents may also be of utility in terms of their ability to increase the proportion of statin-treated patients who are able to achieve LDL-C treatment goals. While the LDL-C lowering effects of potent CETP inhibitors have been evaluated when administered as monotherapy or in combination with commonly used statin doses, they have not been directly compared with use of alternative lipid modifying strategies in statin-treated patients who have not currently achieved their treatment goals.

Evacetrapib is a potent CETP inhibitor, which has been demonstrated to raise HDL-C and cholesterol efflux, in addition to lowering LDL-C and Lp(a) in phase 2 studies.[15] The ACCENTUATE study was performed with the objective of comparing the effect of evacetrapib on lipid parameters with other lipid modifying strategies when used in combination with statin therapy.[17] Given the recent report that evacetrapib failed to reduce cardiovascular events in a large clinical outcome trial, despite favorable effects on both LDL-C and HDL-C, there is an urgent need to further understand the impact of this pharmacological strategy on atherogenic and putative protective lipid parameters [18].

2. Materials and methods

2.1. Study population

The study was a multicenter, randomized, double-blind, parallel, placebo-controlled clinical trial designed by the academic steering committee in collaboration with the sponsor. The institutional review boards of all participating centers approved the protocol and all patients provided informed written consent. Eligible patients were at least 18 years of age, with either atherosclerotic cardiovascular disease (defined as either [1] coronary stenosis ≥50%, [2] myocardial infarction or unstable angina ≥30 days prior to screening, [3] stable angina pectoris, [4] myocardial ischemia on stress testing, [5] coronary revascularization or [6] non-coronary atherosclerotic disease [peripheral arterial disease, atherosclerotic aortic disease or carotid artery disease]) or type 1 or 2 diabetes mellitus, treated with atorvastatin 40 mg daily for at least 30 days prior to screening and compliant with study drug for the 28 day lead-in phase, had a LDL cholesterol >70 mg/dL or non-HDL cholesterol >100 mg/dL at screening and prior to randomization and a triglyceride ≤400 mg/dL. Exclusion criteria included recent stroke or acute coronary syndrome, uncontrolled hypertension (systolic blood pressure ≥180 mmHg or diastolic blood pressure ≥110 mmHg), documented hyperaldosteronism, uncontrolled diabetes (hemoglobin A1c >9.5%), malignancy or significant liver, kidney or cardiac disease.

Potentially eligible patients entered a 28 day lead-in period in which they were treated with atorvastatin 40 mg daily. Patients with persistent LDL cholesterol >70 mg/dL or non-HDL cholesterol >100 mg/dL after this period and met all inclusion and none of the exclusion criteria were subsequently randomized in a 2:1:2:1 ratio to treatment with (i) atorvastatin 40 mg plus evacetrapib 130 mg daily, (ii) atorvastatin 80 mg daily, (iii) atorvastatin 40 mg plus ezetimibe 10 mg daily or (iv) atorvastatin 40 mg daily for 90 days. Randomization was performed at the site level by an Interactive Web Response System (IWRS).

2.2. Clinical visits and laboratory tests

Patients were examined at scheduled visits at days 30 and 90 during the treatment phase. Those patients who demonstrated study drug compliance during this period (defined as taking 80–120% study drug dosage) subsequently entered an open label extension phase, receiving treatment with atorvastatin 40 mg plus evacetrapib 130 mg daily for a planned 9 months with visits at the end of months 3, 6 and 9. A planned final study visit was to be performed 30 days following cessation of study drug. Lipoprotein levels and safety laboratory measurements were obtained at all visits. Blood pressure was measured at each visit by three replicate measurements. A central laboratory performed all biochemical determinations (Covance). Standard lipid profiles (LDL-C, HDL-C, triglycerides) were determined by enzymatic assay. LDL-C was also determined by beta quantification (ultracentrifugation followed by enzymatic determination). Serum apolipoprotein (A-I, A-II, B, C-III and E) levels were measured with standardized commercial immunoturbidimetric assays. High-sensitivity C-reactive protein (CRP) was determined by immunonephelometry. Cellular cholesterol efflux capacity of apoB depleted serum samples was determined by incubation with J774 macrophages. (Vascular Strategies). All cardiovascular events were reported by the investigators.

2.3. Statistical analyses

Efficacy analyses were performed using patients who completed the double-blind phase prior to study termination. An analysis of covariance (ANCOVA) model, with terms for treatment and baseline values, was used to perform between treatment comparisons for change from baseline to 90 day lipid values. Mixed-Effect Model Repeated Measure (MMRM) with terms for treatment, visit, baseline values as fixed effects and patient as a random effect were used to conduct analysis of repeated lipid measures across visits. Pearson coefficients were to asses correlations between lipid parameters. Statistical significance was established at 2-tailed $p<0.05$ level. Safety events between treatment groups were compared using Pearson Chi-square test, analysis of variance for blood pressure and Wilcoxon Signed-Rank Test for C-reactive protein with all treated patients in the analyses.

3. Results

The study was terminated on 12 October, 2015 following premature cessation of the large cardiovascular outcomes trial (ACCELERATE) evaluating the impact of evacetrapib due to clinical futility. At this point in time, 366 patients were randomized, 71% of patients had completed the double-blind treatment period and mean time of treatment was 75 days (Fig. 1).

3.1. Patient characteristics

The clinical characteristics of patients randomized to study drug are presented in Table 1. Patients were predominantly male and Caucasian, with a mean age of 63.4 years and high prevalence of obesity, diabetes and prior coronary revascularization. Baseline lipid and inflammatory parameters are summarized in Table 2. In the setting of treatment with atorvastatin 40 mg daily, patients demonstrated a median LDL-C 83.0 mg/dL and HDL-C 46.0 mg/dL. Levels of triglycerides (130 mg/dL), Lp(a) (43.1 nmol/L) and CRP (1.5 mg/L) were within normal limits.

3.2. Change in lipid and inflammatory parameters

Fig. 2 illustrates the percentage change in LDL-C (the primary endpoint) and HDL-C in the treatment groups. Addition of evacetrapib produced a significant reduction in LDL-C (−33.4%), compared to ezetimibe (−27.3%, $p=0.045$ for difference between treatments), atorvastatin 80 mg (−6.2%, $p<0.001$) and atorvastatin 40 mg (0.0%, $p < 0.001$). Addition of evacetrapib also produced a greater increase in HDL-C (+125.4%) compared to that observed in