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Defining the Safety of Anacetrapib, a CETP Inhibitor, in Patients at High Risk for Coronary Heart Disease: the DEFINE study

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Introduction

In 2004, the Third Report of the National Cholesterol Education Panel Adult Treatment Panel (ATP) III Guidelines were updated based on recent trials available at that time to expand the scope and intensity of low-density lipoprotein cholesterol (LDL-C) lowering therapy [1]. That report also recommended consideration of combination therapy for high-risk patients with high triglycerides and low high-density lipoprotein cholesterol (HDL-C).

One pharmacologic approach to such a regimen is the use of cholesterol ester transfer protein (CETP) inhibitors, which raise HDL-C and may decrease LDL-C. The Investigation of Lipid Level Management to Understand its Impact in Atherosclerotic Events (ILLUMINATE) trial attempted to test the hypothesis that CETP inhibition with torcetrapib would decrease clinical cardiovascular events, but despite substantial increases in HDL-C, the trial was terminated early due to excess adverse events, including increased mortality in the group that received torcetrapib plus atorvastatin compared to the group that received atorvastatin alone [2]. Hypotheses for the increased mortality, both due to cardiovascular and noncardiovascular causes, included an off-target effect of the drug unrelated to CETP inhibition, or an adverse effect of CETP inhibition itself, including possibly the generation of dysfunctional or even proatherogenic HDL-C. The ILLUMINATE trial did find a known off-target effect of torcetrapib (an increase in blood pressure) but could not definitively rule in or out either of the two potential explanations. Other effects of torcetrapib included increased sodium and bicarbonate levels, decreased potassium levels, and apparent increases in aldosterone levels. Other CETP inhibitors, including anacetrapib [3], have not shown increases in blood pressure and appear to be better candidates for further study.

Aims

The Determining the Efficacy and Tolerability of CETP Inhibition with Anacetrapib (DEFINE) study was a 76-week, randomized, double-blind, placebo-controlled trial designed to evaluate the side effects and overall safety profile, and the effects on lipids of anacetrapib in patients with coronary heart disease (CHD) or its risk factors.

Methods

Eligible patients were 18 to 80 years of age and had prior known CHD or 10-year Framingham Risk Score > 20% as defined by ATP III [4]. Lipid eligibility included LDL-C level 50 to 100 mg/dL (1.3–2.6 mmol/L) while taking a statin with or without other lipid-

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modifying agents; HDL-C level < 60 mg/dL (1.6 mmol/L); and triglyceride level 400 mg/dL (4.5 mmol/L). Exclusions were severe chronic heart failure (New York Heart Association III or IV), uncontrolled hypertension (sitting diastolic blood pressure 100 [90 if diabetic] mm Hg or systolic blood pressure 160 [150 if diabetic] mm Hg), or uncontrolled cardiac arrhythmias; recent (within 3 months) myocardial infarction (MI), coronary revascularization, unstable angina or stroke; creatine phosphokinase (CPK) > 2 times upper limit of normal (ULN); alanine aminotransferase (ALT) and aspartate aminotransferase (AST) > 2 times ULN; newly diagnosed (within 3 months) or poorly controlled (HbA1C 8.5%) diabetes mellitus; hyper- or hypothyroidism; homozygous familial hypercholesterolemia or hyperlipidemia types I or V; active or chronic hepatobiliary or hepatic disease or severe renal impairment (estimated glomerular filtration rate < 30 mL/min per 1.73m²); or treatment with warfarin, corticosteroids or potent CYP3A4 inhibitors or inducers.

Patients entered a 2-week, single-blind, placebo run-in phase and if more than 75% adherent, they were eligible for randomization in a 1:1 ratio to anacetrapib 100 mg or matching placebo daily. Patients returned every 6 to 8 weeks for an assessment of adverse events, blood pressure measurement, and blood samples. After the 76-week treatment phase, patients were followed for a 12-week safety assessment phase with a visit or phone follow-up at week 88.

Study endpoints included LDL-C levels and safety and side-effect assessment (Table 1). The study sample size was overpowered for a typical lipid-lowering study to allow for a comprehensive safety profile characterization of the drug. Safety analyses were pre-planned for 24- and 54-week end-of-treatment phase, and during post-treatment follow-up time points. A Bayesian analysis was planned to interpret cardiovascular events, using prior data on torcetrapib and assumptions [4]. The Bayesian approach was used to compute confidence intervals to test the probability that a deleterious safety signal of the magnitude observed with torcetrapib (25% increase in cardiovascular events) could be dismissed. The pre-specified cardiovascular safety endpoints were cardiovascular death, nonfatal MI, stroke, and hospitalization for unstable angina. Unstable angina was defined as new or accelerating symptoms of cardiac ischemia accompanied by ischemic ST-T wave changes not qualifying as MI, or in the absence of electrocardiogram changes, either thrombus on cardiac catheterization or 6-week history of worsening angina with chest pain at rest and emergency revascularization. These cardiovascular disease (CVD) outcomes and total mortality were adjudicated by a masked, external committee. Other cardiovascular endpoints were hospitalization for severe heart failure and revascularization for nonacute ischemic events.

Patients were instructed to follow the ATP Therapeutic Lifestyle Changes Diet or a comparable lipid-lowering diet, and remained on lipid-modifying therapies for the duration of the study. If the LDL-C was < 25 mg/dL (0.6 mmol/L), study drug was discontinued. If LDL-C was confirmed by re-measurement as > 15% above the baseline value or > 15% above ATP III goal, and compliance was verified, investigators were instructed to adjust LDL-lowering therapy. The investigators and sponsor (Merck & Co., Whitehouse Station, NJ) were unaware of the lipid measurements from randomization forward.

Results

Between April, 2008 and January, 2009, 2757 patients were screened at 153 centers in 20 countries. Of these, 1697 entered placebo run-in and 1623 were randomized. At baseline, the mean age of patients was 63 years, 54.7% of patients had prior CHD, mean HDL-C was 41 mg/dL, mean LDL-C was 81 mg/dL, and 99.3% were taking statins.

Study drug was discontinued for LDL-C < 25 mg/dL in 142 patients (17.6%) receiving active drug and 1 in the placebo group (1%). Other reasons for discontinuation were balanced between the groups, with 14.6% and 17.4% assigned to active versus placebo, respectively. Of these, 46 in both groups were because of adverse experiences. Patients took active medication for a mean of 424 days in the active and 483 days in the placebo groups, and follow-up assessments were completed in 99.1% and 99.4% of the patients, respectively.

By 24 weeks, there was a 39.8% greater reduction in LDL-C with anacetrapib beyond that seen with placebo ($P < 0.001$), and a 138.1% increase in HDL-C ($P < 0.001$). Apolipoprotein (Apo) B levels decreased by 21.0%, and Apo A-I levels increased by 44.7% more in the anacetrapib group than in the placebo group. Other changes beyond that due to placebo in the anacetrapib group were a 31.7% reduction in non-HDL-C, a 36.4% reduction in lipoprotein(a), and a 6.8% reduction in triglyceride level. There were no significant decreases in high-sensitivity C-reactive protein (hs-CRP). All the changes in lipid levels were sustained throughout the 76-week treatment period.

There were no significant differences between the groups in adverse events thought to be drug-related, in clinical adverse events leading to discontinuation of study drug, in drug-related adverse events leading to discontinuation of study drug, in serious adverse events, or in drug-related serious adverse events. For safety variables of interest, there were no significant differences in blood pressure elevations between the groups, in electrolytes, in CPK elevations, or in muscle symptoms. Significantly more patients in the placebo group experienced confirmed elevation in ALT or AST (0.1% vs 1.0%; $P = 0.02$).

During the 76-week study-treatment phase, the composite CVD outcome occurred in 16 patients randomized to anacetrapib (2.0%) compared to 21 randomized to placebo (2.6%; $P = 0.40$). The Bayesian analysis indicated that the event distribution provided 94% predicted probability that anacetrapib would not be associated with the 25% increase in CVD events that was seen with torcetrapib. In a post hoc analysis of death from any cause, MI, stroke, unstable angina, or revascularization, an event occurred in 27 patients in the anacetrapib group (3.3%) compared to 43 in the placebo group (5.3%; $P = 0.048$). In the post-treatment phase, there was 1 death in the anacetrapib group and 4 deaths in the placebo group, with 12 deaths occurring in each group through week 88.

Comments

This study was a moderate-sized safety study that showed anacetrapib, when used with statins, had substantial effects on plasma lipid levels. LDL-C was substantially lowered, HDL-C raised, and even lipoprotein(a), which is affected by few therapies, decreased with anacetrapib. Patients were more often discontinued in the anacetrapib group for LDL-C < 25 mg/dL, with no significant differences between study groups in other reasons for discontinuation. In fact, the safety profile was acceptable, and the increased CVD events seen in the ILLUMINATE trial [2] are unlikely to occur with anacetrapib, making it a promising compound with which to pursue larger trials to test directly the hypothesis that CETP inhibition is cardioprotective. This hypothesis has been bolstered by other recent data on the epidemiologic associations of CETP genotypes with inhibition of CETP activity with HDL-C levels and with CHD risk [5] and, more importantly, results from in vitro studies showing no evidence for an adverse effect of anacetrapib on HDL-mediated cholesterol efflux or anti-inflammatory responses [6].

Although promising, the results of the DEFINE study are limited. DEFINE was too small to definitively test the overall safety or efficacy of anacetrapib. The study was also over 80% white, with particularly small numbers of Asians. Thus, the safety and efficacy of the drug

in other groups has not been established even to the somewhat limited extent shown to date in whites. Third, anacetrapib decreases LDL-C levels significantly, and the long-term safety of such low levels of LDL-C as can be achieved with this agent is not established. The safety of anacetrapib is also not established over periods longer than a few months.

In conclusion, anacetrapib demonstrates the greatest HDL-C-raising and LDL-C-lowering potential of CETP inhibitors, and phase I and II trials with anacetrapib have revealed that it is well tolerated and does not seem to possess the pressor effects associated with torcetrapib [7]. The profile of this agent offers the reassurance needed for the conduct of large clinical outcomes trials in patients with CHD who are at high risk of recurrence in order to test the CETP-CHD hypothesis.

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Table 1

Endpoints of the DEFINE trial [4]

Endpoint	Assessment	Measurement
Primary efficacy	LDL-C	LDL-C: % change 24 weeks-baseline (calculated, or direct if triglycerides > 400 mg/dL)
Primary safety and tolerability	Tier 1 adverse experiences of special interest, subject to statistical testing	Key variables throughout the 76-week treatment period: Hepatic: ALT or AST elevations Muscle-related: CPK elevations ± muscle symptoms Aldosterone-related electrolytes: elevations in sodium, chloride, or bicarbonate, or reductions in potassium Specific adverse events of interest: myalgia, rhabdomyolysis, prespecified cardiovascular, death (all-cause)
	Tier 2 adverse experiences	Predefined limits of change in laboratory, vital signs, and ECG parameters not specified as tier 1
Secondary efficacy	Lipid/lipoproteins	LDL-C: % change 76 weeks-baseline 24- and 76-week levels of HDL-C and non-HDL-C, apoB and apoA-I, apoC-III, lipoprotein(a), apoA-II, apoE Ratios: TC/HDL-C, LDL-C/HDL-C, apoB/apoA-I, LDL-C/apoB
	Other	hs-CRP

ALT—alanine aminotransferase; apo—apolipoprotein; AST—aspartate aminotransferase; CPK—creatine phosphokinase; ECG—electrocardiogram; HDL-C—high-density lipoprotein cholesterol; hs-CRP—high-sensitivity C-reactive protein; LDL-C—low-density lipoprotein cholesterol; TC—total cholesterol.