

## Cholesteryl Ester Transfer Protein Inhibition for Coronary Heart Disease Prevention: Real Hope or Despair?

The concentration of high-density lipoprotein-cholesterol (HDL-C) in the blood has been shown to be independently and inversely associated with an increased risk of coronary heart disease.<sup>1</sup> In epidemiologic studies, it has been shown that for every increase of 1 mg/dL of HDL-C, there is an associated 2%-3% decreased risk of developing coronary heart disease, independent of low-density lipoprotein (LDL)-C levels.<sup>1</sup> Although the exact mechanisms by which HDL-C provides its cardioprotective actions are not known, both experimental and human interventional and observational studies using available cholesterol-lowering therapies have suggested that higher HDL-C levels will reduce the risk of coronary heart disease.<sup>2,3</sup>

The available cholesterol-lowering drugs (niacin, fibrates, statins, and ezetimibe), although effective for reducing LDL-C and triglycerides, are not effective in causing major elevations in HDL-C.<sup>4</sup> During the last 2 decades, cholesteryl ester transfer protein (CETP) inhibition has received attention as a potential pharmacologic approach for causing major elevations of HDL-C.<sup>5</sup> A genetic deficiency of CETP activity in a long-living Japanese population without coronary heart disease was found to be associated with substantial elevations in HDL-C.<sup>6</sup>

CETP is a plasma hydrophobic glycoprotein that is secreted by the liver and is bound to HDL in the plasma. Its biologic role is to facilitate the net mass transfer of cholesteryl esters from HDL to apolipoprotein-B-containing and triglyceride-rich lipoproteins such as LDL and very low-density lipoprotein (VLDL), and reciprocal transfer of triglycerides from VLDL to LDL and HDL.<sup>7</sup> CETP inhibition due to a genetic deficiency or by pharmacologic inhibition will result in larger HDL-C particles with an elevated cholesteryl ester and decreased triglyceride content, and a non-HDL fraction with elevated triglycerides and decreased cholesteryl ester. These changes lead to an increased HDL-C due to its delayed clearance from plasma.<sup>8</sup>

In animal studies with mice, a species naturally lacking CETP, transduction with the human CETP gene resulted in dose-related reductions in HDL-C and the development of atherosclerosis.<sup>9</sup> When rabbits, a species with naturally high levels of CETP, were given a synthetic CETP inhibitor, JTT-705, the animals demonstrated a 90% increase in

HDL-C as well as a 70% reduction in experimentally induced aortic atherosclerotic lesion area.<sup>10</sup>

In humans, Boekholdt et al were the first to demonstrate a direct link between baseline CETP levels and the risk of future coronary heart disease.<sup>11</sup> Likewise, an analysis of data from the Regression Growth Evaluation Study revealed that a high CETP concentration was associated with a faster progression of coronary atherosclerosis in men who were followed with angiographic studies.<sup>12</sup>

Human interventions have been carried out with 3 different orally active synthetic selective CETP inhibitors: JTT-705 (Roche; Basel, Switzerland), torcetrapib (Pfizer; New York, NY), and anacetrapib (MK-0859, Merck & Co.; Whitehouse, NJ). The largest experience accrued to date has been with torcetrapib.

In phase I clinical trials, compared with placebo, torcetrapib has been shown to cause substantial elevations in HDL-C and modest reductions in non-HDL-C, including LDL-C.<sup>13</sup> Used in combination with atorvastatin in phase II clinical trials in dyslipidemic patients, this regimen resulted in additional increases in HDL-C and additional decreases in LDL-C beyond those seen with atorvastatin alone.<sup>14</sup>

However, the results from a series of large phase III clinical trials with torcetrapib plus atorvastatin versus atorvastatin alone demonstrated unexpected results on measured clinical endpoints with the combination regimen. The Investigation of Lipid Level Management to Understand its Impact in Atherosclerotic Events (ILLUMINATE) study evaluated 15,000 subjects with coronary heart disease or high-risk equivalents.<sup>15</sup> Excess deaths were found in the combination treatment group, as well as an increase in the incidence of heart failure, myocardial infarction, angina, and the need for revascularization procedures. Also, an increase in systolic blood pressure of 4-6 mm Hg was observed in the combination group.<sup>15</sup>

Nissen et al reported on the results of an independent parallel study called the Investigation of Lipid Management Using Coronary Ultrasound to Assess Reduction of Atherosclerosis by CETP Inhibition and HDL Elevation (ILLUSTRATE),<sup>16</sup> which showed no difference using combination torcetrapib-atorvastatin therapy versus atorvastatin alone on atherosclerosis plaque burden, using intravascular ultrasound to image plaque. The adverse

outcomes found in the ILLUMINATE trial cannot be attributed to the worsening of atherosclerotic plaque burden. However, the ILLUSTRATE study did not provide any data about stability of thrombogenic potential of the plaques.<sup>16</sup>

Finally, the results of 2 double-blind, randomized trials in patients with heterozygous familial hypercholesterolemia (RADIANCE 1) and mixed dyslipidemia (RADIANCE 2) using torcetrapib and atorvastatin in combination showed no change in the progression of carotid intima-media thickness compared with the results with atorvastatin alone.<sup>17,18</sup> In RADIANCE 1, the average increase in systolic blood pressure was 2.8 mm Hg; in RADIANCE 2, the average increase was 8.4 mm Hg.

The findings in the torcetrapib-atorvastatin clinical program have thrown an unfavorable light on the clinical development program of CETP inhibition. With torcetrapib, was it the molecule or the mechanism?<sup>19</sup> In other words, was the increase in the number of deaths in the ILLUMINATE study related directly to an unforeseen blood-pressure-raising side effect and completely unrelated to torcetrapib's mechanism for raising HDL? Torcetrapib may raise blood pressure by causing an unexpected increase in aldosterone levels. Are the hopes of those who once believed in the clinical promise of CETP inhibition as a meaningful mechanism to raise HDL shattered? Perhaps the larger cholesterol-laden HDL produced in the setting of pharmacologic CETP inhibition in vivo becomes dysfunctional and is not capable of unloading cholesterol from the vessel walls, or has proinflammatory properties, as has been recently suggested by others.<sup>20,21</sup>

The findings of ILLUMINATE, ILLUSTRATE, and RADIANCE have clearly been disappointing regarding the potential benefit of torcetrapib in preventing coronary heart disease. However, the other orally active CETP inhibitor, anacetrapib, does not adversely affect blood pressure. Recently it was shown that anacetrapib caused a powerful HDL-C-lowering effect and a modest LDL-C effect in a placebo-controlled study of dyslipidemic patients,<sup>22</sup> and in a parallel study reported in the same article, no change in blood pressure was observed in normotensive individuals using ambulatory blood pressure monitoring. JTT-705, the first CETP inhibitor, also causes elevations in HDL-C and reductions in LDL-C, and to date, there have been no reports of the drug's effect on blood pressure.<sup>22</sup>

The concept of pharmacologic inhibition of CETP for coronary heart disease prevention still remains a workable clinical goal. Forty-five years ago, clinical development programs with the first 2 beta-adrenergic blockers (dichloroisoproterenol and pronethalol) were discontinued due to efficacy and toxicity issues. However, the promise of this new class of drug would have died if investigations with other lead compounds were not carried out. Indeed, the third compound, propranolol, was found to be both safe and effective, and it was the courage of the industrial sponsor and its lead investigator, Dr. James Black (who ultimately

won the Nobel Prize in Medicine), that ushered in the current era of beta-blocker therapy.<sup>23</sup> Indeed, with the beta-blockers it was a problem with early compounds in the class, not the concept. Of note, the fourth beta-blocker tested, practolol, the first beta<sub>1</sub>-selective agent, also had a serious toxicity. Fortunately it was tested after propranolol.

In a similar vein, although the promise of pharmacologic CETP inhibition to prevent coronary heart disease is now unclear, safer compounds in the class, used judiciously, could still be shown to provide a clinical benefit from the marked elevations they cause in HDL-C.

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