Raising High-Density Lipoprotein in Humans Through Inhibition of Cholesteryl Ester Transfer Protein: An Initial Multidose Study of Torcetrapib


Objective—The ability of the potent cholesteryl ester transfer protein (CETP) inhibitor torcetrapib (CP-529,414) to raise high-density lipoprotein cholesterol (HDL-C) levels in healthy young subjects was tested in this initial phase 1 multidose study.

Methods and Results—Five groups of 8 subjects each were randomized to placebo (n=10) or torcetrapib (n=6) at 10, 30, 60, and 120 mg daily and 120 mg twice daily for 14 days. Torcetrapib was well tolerated, with all treated subjects completing the study. The correlation of plasma drug levels with inhibition (EC50=43 nM) was as expected based on in vitro potency (IC50=50 nM), and increases in CETP mass were consistent with the proposed mechanism of inhibition. CETP inhibition increased with escalating dose, leading to elevations of HDL-C of 16% to 91%. Total plasma cholesterol did not change significantly because of a reduction in nonHDL-C, including a 21% to 42% lowering of low-density lipoprotein cholesterol at the higher doses. Apolipoprotein A-I and E were elevated 27% and 66%, respectively, and apoB was reduced 26% with 120 mg twice daily. Cholesteryl ester content decreased and triglyceride increased in the nonHDL plasma fraction, with contrasting changes occurring in HDL.

Conclusions—These effects of CETP inhibition resemble those observed in partial CETP deficiency. This work serves as a prelude to further studies in subjects with low HDL, or combinations of dyslipidemia, in assessing the role of CETP in atherosclerosis. (Arterioscler Thromb Vasc Biol. 2004;24:490-497.)

Key Words: CETP ■ HDL ■ torcetrapib ■ CP-529,414 ■ atherosclerosis

I

In the decades since the Honolulu1 and Framingham2 studies, the inverse correlation between high-density lipoprotein (HDL) levels and premature coronary heart disease (CHD) has been strengthened. A 1% decrease in HDL cholesterol (HDL-C) has been associated with a 1% to 2% increase in risk for CHD,3 and lipid intervention trials have demonstrated that increases in HDL-C4 and its main apoprotein, A-I,5 contribute to reduced risk for CHD, even in the absence of any change in low-density lipoprotein cholesterol (LDL-C).6 However, current therapies for raising HDL are limited. The fibrates and statins produce only modest elevations in HDL, and the use of niacin, although somewhat more effective, has been hampered by side effects.7 In a recent study, the combination of lovastatin and extended-release niacin (Advicor) was able to increase HDL levels by 20% to 32%,8 but withdrawal rates for incidents of flushing and other adverse events were relatively high.

The marked increase in HDL associated with human deficiency of cholesteryl ester transfer protein (CETP)9 has suggested CETP inhibition as a means of elevating HDL. Expression of CETP in transgenic mice under different metabolic settings has produced mixed results regarding its atherogenicity, whereas inhibition of endogenous CETP in rabbits has more consistently been antiatherogenic.10 With regard to human CETP mutations and the associated reduction in CETP levels, recent analysis of prospective data from the Honolulu Heart Study10 is consistent with the results of a previous study of Japanese subjects11 in concluding that CETP deficiency is protective when associated with HDL-C levels ≥60 mg/dL.

The results for a phase 2 study testing the synthetic CETP inhibitor JTT-705 in subjects with mild hyperlipidemia have been reported.12 At 900 mg daily, JTT-705 led to a 37% decrease in CETP activity, a 34% increase in HDL-C, and a 7% decrease in LDL-C. We have developed a new series of potent synthetic CETP inhibitors. In this report, we describe
the results of a phase 1 multidose study for torcetrapib (CP-529,414). Assay of CETP activity during the first day of dosing demonstrated that up to 100% inhibition of CETP was obtained, and increases in HDL-C between 16% and 91% were achieved by the end of the study. At high doses, LDL-C was reduced up to 42%.

Methods

Materials

H- and 14C-cholesteryl oleate (CO) were purchased from New England Nuclear. Iodine (I) 125 was obtained from Amersham. Reagents for enzymatic determination of cholesterol and triglyceride (TG) were obtained from Roche Diagnostics, and from Wako Chemicals for phospholipid (PL). Non-labeled lipids and other routine reagents were purchased from Sigma. Native tris/glycine 4% (TG) were obtained from Roche Diagnostics, and from Wako.

Subjects and Study Design

Healthy males and females between the ages of 18 and 55 were recruited at a single study site, Pharos GMBH, Ulm, Germany. The center’s Ethics Committee approved the protocol and all subjects provided written informed consent. Subjects included were judged to be in good health by a detailed medical history, a full physical examination, and clinical laboratory testing. Fasting lipids, expressed as triglyceride, total cholesterol, and HDL-C, were measured on a Hitachi 747 analyzer. Nonfrozen EDTA-plasma samples were shipped on dry ice to Northwest Bioanalytical Laboratories in Highland Heights, Kentucky for plasma lipid analysis (including TG, HDL-C, LDL-C, TGs, and apolipoproteins A-I, B, and E). Medical Research Laboratories is a participant in the Centers for Disease Control–National Heart, Lung, and Blood Institute’s Lipid Standardization Program. Nonfrozen EDTA-plasma samples were shipped on ice to Pfizer in Groton, Connecticut for CETP activity/mass and FPLC lipid analysis.

Preparation of H- and 14C-Labeled Lipoproteins

Labeled lipoproteins were prepared similarly to the method described previously. Briefly, phosphatidylcholine liposomes containing H- or 14C-labeled-CO were added to human plasma at 1.5 to 2.0 mCi/100 mL. The plasma was incubated 18 hours at 37°C to allow endogenous CETP activity to distribute labeled-CO into all lipoprotein classes. Lipoprotein subclasses were obtained by sequential ultracentrifugation, collecting LDL and HDL at the 1.019 to 1.063 g/mL and 1.10 to 1.21 g/mL density cuts, respectively, followed by extensive dialysis.

Assay of CETP Activity

For determination of plasma CETP activity, transfer of H-CO from HDL to the nonHDL plasma fraction and from 14C-CO-labeled LDL to HDL were determined simultaneously. For in vitro assay, tracer levels of H-HDL and 14C-LDL were added to plasma and the samples incubated for 1.5, 2.25, and 3 hours in quadruplicate; after which, the nonHDL fraction was precipitated by adding an equal volume of 20% (wt/vol) PEG8000, and radioactivity in the HDL containing supernatant was determined by scintillation counting. The fraction of cholesteryl ester (CE) transferred was calculated from the loss of H- and 14C-radioactivity from the HDL and nonHDL fractions, respectively, relative to the nonHDL fraction. The transfer rate (nmol/h) that, on integration, gave the nmol of CE transferred per time period. The percent inhibition, relative to control, was calculated using data for the linear portion of the transfer curve. The near equivalence of results (see Results) demonstrated that for the purposes of the clinical trial, the former method would be sufficient.

For the ex vivo clinical plasma samples, a single-baseline fasted plasma sample was retained as the control for the subsequent samples. In planning this trial, it was foreseen that after breakfast and during the day, postprandial effects would increase the pool of TG-rich lipoproteins; torcetrapib, especially with increasing dose, would increase the HDL fraction. Therefore, a typical unidirectional CE-transfer assay, using either labeled LDL or HDL as donor, would show increases or decreases in apparent activity, relative to the fasted baseline plasma, caused by mass action effects, and thus obscure the direct effects of torcetrapib binding to CETP. However, preclinical in vitro studies using fasted plasma supplemented with very low-density lipoprotein (VLDL), LDL, or HDL (data not shown) demonstrated that such substrate-dependent changes in apparent inhibition with torcetrapib could in large part be minimized by performing a dual-label transfer assay. By determining H-HDL-C-nonHDL and 14C-LDL >HDL transfer simultaneously and calculating the apparent percent inhibition relative to the unsupplemented control for each assay, the average of the 2 values was, in most cases, in good agreement with the actual percent inhibition value determined relative to the substrate-matched controls. Therefore, CETP activity for clinical plasma samples was determined by the dual-label assay, performed in triplicate at zero time and after 3 hours of incubation. Analysis of the dose response was performed using the WinNonLin nonlinear estimation program (Pharsight, v3.2).

CETP Mass and Western Blot Detection

Plasma CETP concentrations were measured quantitatively by immunoradiometric assay and are expressed as µg CETP protein per mL plasma. To convert µg/mL to nM, divide by 0.0531. The change in apparent size of the CETP-containing species in plasma was determined by native PAGE/Western blot analyses using 125I-labeled anti-CETP monoclonal antibody for detection. Determination of Plasma Levels of Torcetrapib

Plasma samples were shipped on dry ice to Northwest Bioanalytical in Salt Lake City, Utah for analysis. Drug concentrations were determined using a gas chromatographic/mass spectrometry detection method developed internally at Pfizer Global Research and Development. The plasma samples were subjected to a protein precipitation followed by liquid/liquid extraction and chemical derivatization. The organic layer was evaporated and the residue reconstituted and analyzed by gas chromatographic/mass spectrometry detection. The dynamic range of the assay was 0.500 to 100 ng/mL.

Plasma Lipids and Apolipoproteins

Analysis was performed by Medical Research Laboratories in Highland Heights, Kentucky. TG-C, HDL-C, and plasma TG were assayed enzymatically using a Hitachi 747 analyzer. For HDL-C, the HDL fraction was obtained by heparin/manganese precipitation of the nonHDL lipoprotein fraction. LDL-C was estimated by the
method of Friedewald.\textsuperscript{17} Apolipoproteins A-I, E, and B were determined by immunoturbidimetric methods using a Behring nephelometer.

Analysis was performed by Pfizer in Groton, Connecticut. Baseline samples and samples 7 and 14 days after the first dose were assayed for total plasma cholesterol, TG, and PL by enzymatic methods. Samples from the 60- and 120-mg daily and 120-mg twice-daily groups were fractionated by FPLC, using Superose 6 and Superdex 200 columns connected in tandem, into the major lipoprotein classes, VLDL, LDL, and HDL. Fractions for all samples were assayed for total cholesterol. For the 120-mg twice-daily samples, fractions for drug-treated subjects were also assayed for PL, free cholesterol (FC), and TG. CE was derived by subtracting FC from total cholesterol. Calculation of plasma lipoprotein content by FPLC was corrected for individual lipid recovery. Recoveries for total cholesterol were 97\%±5\% (n=72 runs). For PL, FC and TG recoveries were 98\%±4\%, 90\%±9\%, and 86\%±11\% (n=18 runs each).

Results

CETP Activity and Mass

Torcetrapib (CP-529,414) (Figure 1) evolved from a series of inhibitors identified by high throughput screening for inhibition of CE transfer activity in an assay using native human plasma CETP. A typical inhibition curve for whole human plasma, having a CETP concentration of 37 nM, is shown in Figure 2A. The IC50 for torcetrapib determined from the linear portion of the curves (25 to 80 nM) was 52 and 65 nM for the \textsuperscript{3}H-HDL and \textsuperscript{14}C-LDL CE transfer assays, respectively, using the specific activity-adjusted calculation, and 47 and 61 nM using a single exponential decay function (see Methods). This agreement in methods demonstrated that the latter method\textsuperscript{15} was sufficient for calculating relative inhib...
The results obtained by Medical Research Laboratories for HDL-C were 12\pm 0.37, with no significant difference between treated subjects (1.75\pm 0.34; n = 30) and placebo (1.97\pm 0.42; n = 10). With treatment, a dose- and time-dependent increase in CETP mass was observed. The increase in plasma CETP was significant by 24 hours after the first dose versus baseline for both the 120-mg daily (2.34\pm 0.30 versus 1.67\pm 0.23 \mu g/mL; P<0.002) and 120-mg twice-daily (2.27\pm 0.17 versus 1.64\pm 0.11 \mu g/mL; P<0.001) groups. CETP mass continued to increase during the course of the 2-week study, becoming significant (P<0.001) for all treatment groups by 14 days. For placebos, a trend toward increasing CETP was not significant at any time point. Figure 3B and C demonstrate the effects of a single 30-mg dose of torcetrapib versus placebo on the plasma distribution of CETP. By 2 hours after the dose, the apparent molecular weight of the CETP had shifted to a larger form. By 36 hours, it had in large part returned to its former state. Little change was observed for placebo (Figure 3B). This drug-induced change in plasma CETP appears because of the mechanism of action of the inhibitor and represents the shift from free CETP to an HDL-bound form.

**Plasma Lipids and Lipoproteins**

The results obtained by Medical Research Laboratories for TPC and TG, HDL-C, LDL-C, and apoA-I, B, and E for placebo and torcetrapib groups at baseline and 24 hours after the last dose are presented in Table 1. Expressed as the mean of individual percent change from baseline, HDL-C increases were significant at all doses, relative to placebo. Treatment with 10, 30, 60, and 120 mg daily and 120 mg twice daily resulted in 16\%, 28\%, 62\%, 73\%, and 91\% increases in HDL-C, respectively, with no significant changes in TPC. This lack of effect on TPC despite the large increase in HDL-C was caused by a reciprocal decrease in nonHDL-C, with LDL-C decreased 21\% with 120-mg daily and 42\% with 120-mg twice-daily dosing. Consequential to these changes were the significant lowering in the LDL-C/HDL-C ratios for doses of 30 mg and greater. With the 30-mg dose, LDL-C/ HDL-C decreased from 2.39 at baseline to 1.59 at 14 days, and with 120 mg twice daily from 1.91 to 0.59. Consistent
with these changes in lipoprotein were the altered levels of apolipoproteins. At the highest dose, apoA-I and apoE increased, respectively, by 27% and 66%, whereas apoB decreased by 26%.

The plasma cholesterol profiles generated by FPLC fractionation for subjects in the placebo, 60-mg, 120-mg daily, and 120-mg twice-daily groups are shown in Figure 4. Mean change in HDL-C after 14 days of treatment relative to baseline were $-4\pm%14\%$, $+71\%\pm35\%$, $+80\%\pm19\%$, and $+93\%\pm45\%$, $(-2\%\pm32\%, +36\%\pm45\text{ mg/dL})$, respectively. A shift in HDL to larger size was also evident with treatment. The changes in LDL-C determined by Friedewald calculation and shown in Table 1 were confirmed by the FPLC separation. At 60 mg, 120 mg daily, and 120 mg twice daily, LDL-C was decreased $8\%\pm16\%$, $21\%\pm28\%$, and $42\%\pm7\%$, respectively, $(-8\%\pm24\%\pm45\text{ mg/dL})$, whereas placebo LDL-C increased slightly by $12\%\pm9\%$. The plasma PL profile for the 120-mg twice-daily group (not shown) demonstrated a 54% increase in HDL-PL ($+50\%\text{ mg/dL}, P<0.001$ relative to baseline), and a reduction in LDL-PL of $33\% (-23\%\text{ mg/dL}, P<0.02)$. In the same group, VLDL-PL decreased by 14% ($7\%\text{ mg/dL}$), and plasma PL increased by 10% ($19\%\text{ mg/dL}$, from $182\pm33$ to $201\pm26$), with neither change reaching significance.

Analysis of FPLC fractions for TG and FC, in addition to total cholesterol and PL, allowed the lipid composition for plasma and lipoprotein to be calculated for the 120-mg twice-daily group (Table 2). Results are expressed as mol percent of total lipid and compares 7 and 14 days of treatment to baseline. For total plasma, the only significant change was an increase in PL content. TG increased and CE decreased in LDL. Although the expected reciprocal decrease in HDL TG was significant, the trend toward increased CE was not. A significant 5% increase in HDL FC did occur, as did a slight decrease in PL. Using the information in Table 2 for FC and CE, it can be calculated...
that of the total 46.5 mg/dL increase in HDL-C observed for this group after 2 weeks treatment (Table 1), 15.0 mg/dL is due to FC and 31.5 mg/dL is due to CE.

Discussion

In this study, the CETP inhibitor torcetrapib was tested in healthy young subjects over a 2-week period. Escalating dose led to an increase in the degree and duration of CETP inhibition, with up to 100% inhibition determined for individuals by 4 to 8 hours after the initial dose. Lipoprotein lipid and apoprotein levels responded to CETP inhibition and HDL-C increased significantly with treatment at all doses tested. In contrast, nonHDL-C decreased, resulting in no significant change in TPC. Accompanying these lipoprotein changes were corresponding changes in apoproteins. Apolipoproteins A-I and E increased, and apoB decreased with treatment. Although apoA-II was not measured in this study, in a subsequent trial torcetrapib treatment also increased apoA-II, although not as much as apoA-I. Not surprisingly, these effects are consistent with those seen in human CETP deficiency. Complete CETP deficiency has been associated with 3- to 4-fold elevations in HDL-C, up to 40% reductions in LDL-C, and 40% to 90% increases in TPC relative to unaffected family members or controls. Furthermore, apoA-I and apoE levels were found to be increased 70% to 150% and 2- to 6-fold, respectively; apoB was reduced 30% to 40%. Partial CETP deficiency, with 40% to 70% of normal CETP activity or mass, results in more modest effects: HDL-C increases 25% to 70%, apoA-I and E increase 20% to 40%, and TPC, LDL-C, and apoB show little or no change. By creating a range of partial deficiencies in CETP activity using torcetrapib, we have reproduced the expected phenotypes. The 120-mg twice-daily dose maintained inhibition at ≥80% and by 2 weeks raised HDL-C, apoA-I, and ApoE by 91%, 27%, and 66%, respectively, and lowered LDL-C and apoB by 42% and 26%. However, in contrast to complete CETP deficiency, TPC levels were unchanged.

Figure 4. Plasma cholesterol distribution. Plasma was fractionated by FPLC and the cholesterol content in each fraction determined enzymatically at baseline () and after 7 days (green - - ) and 14 days (red - - - ) of treatment for placebo, A; 60 mg daily, B; 120 mg daily, C; and 120 mg twice daily, D. For all groups n = 6.

**TABLE 2. Plasma and Lipoprotein Lipid Composition for the 120-mg Twice Daily Group**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>7 Days</th>
<th>14 Days</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>FC</td>
<td>CE</td>
<td>PL</td>
</tr>
<tr>
<td>Plasma FC</td>
<td>16.5 ± 1.5</td>
<td>16.8 ± 0.8</td>
<td>16.8 ± 0.6</td>
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<tr>
<td></td>
<td>39.1 ± 4.5</td>
<td>37.7 ± 4.9</td>
<td>37.6 ± 2.2</td>
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<tr>
<td></td>
<td>30.7 ± 2.7</td>
<td>33.4 ± 1.8</td>
<td>34.6 ± 1.1</td>
</tr>
<tr>
<td></td>
<td>13.7 ± 7.4</td>
<td>12.1 ± 5.9</td>
<td>11.0 ± 2.0</td>
</tr>
<tr>
<td>LDL FC</td>
<td>21.6 ± 3.0</td>
<td>24.0 ± 5.8</td>
<td>22.0 ± 0.8</td>
</tr>
<tr>
<td></td>
<td>44.2 ± 2.4</td>
<td>36.4 ± 7.1</td>
<td>37.5 ± 1.8</td>
</tr>
<tr>
<td></td>
<td>22.8 ± 0.6</td>
<td>23.0 ± 0.8</td>
<td>23.9 ± 1.0</td>
</tr>
<tr>
<td></td>
<td>11.5 ± 3.2</td>
<td>16.6 ± 5.0</td>
<td>16.6 ± 2.4</td>
</tr>
<tr>
<td>HDL FC</td>
<td>8.6 ± 1.1</td>
<td>13.6 ± 1.3</td>
<td>13.6 ± 0.9</td>
</tr>
<tr>
<td></td>
<td>39.8 ± 2.8</td>
<td>42.6 ± 2.7</td>
<td>42.0 ± 1.2</td>
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<tr>
<td></td>
<td>45.3 ± 1.4</td>
<td>41.5 ± 2.3</td>
<td>42.6 ± 2.1</td>
</tr>
<tr>
<td></td>
<td>6.3 ± 2.7</td>
<td>2.3 ± 0.5</td>
<td>1.9 ± 0.3</td>
</tr>
</tbody>
</table>

Plasma and FPLC fractions were analyzed for free and esterified cholesterol, phospholipid, and triglyceride as described in Methods. Fractions were assigned to the major lipoprotein classes based on the total cholesterol profiles, and the nmol/fraction for each lipid were summed. For each lipid class, its contribution to the total lipid content of plasma, LDL, and HDL, expressed as mole %, was calculated for each subject. Values shown are the mean mol % ± SD for the 6 subjects in this group. Significance difference after 7 and 14 days relative to baseline was determined using a Student t test.

**P**<0.05.

**P**<0.01.

**P**<0.001.
Treatment with torcetrapib produced increases in plasma CETP concentrations up to 3.5-fold. This effect is likely caused by the mechanism of inhibition of torcetrapib, which appears to act by enhancing the association of CETP for its lipoprotein substrates and thereby creating a nonproductive complex (Clark et al, manuscript in preparation). As a result, the half-life of plasma CETP, believed to be a fraction of a day, may assume that of HDL, which is 4 to 6 days. Because this increase in CETP mass occurs within the first day, and in the absence of changes known to stimulate CETP expression such as increases in total plasma cholesterol, it seems unlikely to result from inhibitor effects on gene expression. However, this remains to be determined. Subsequent 8-week studies have shown that the rise in CETP mass plateaus at a 3- to 4-fold increase from baseline (data not shown). Inhibitor-induced complex formation between CETP and HDL is not expected to directly affect HDL function because average CETP levels are low (20 to 60 nM) relative to HDL particle concentration (10 to 30 μmol/L).

To gain greater insight into the nature of the changes induced by CETP inhibition, the distribution of plasma FC, CE, PL, and TG was determined for plasma from the 120-mg twice-daily-treated subjects. An enrichment in PL with treatment from 30.7 to 34.6 mol percent (P < 0.01) was the only significant change in plasma lipid. This can be explained by the increase in HDL and decrease in LDL, relatively PL-rich and poor lipoproteins, respectively. The TG content of HDL decreased, but the change in CE did not reach significance. For LDL, TG increased and CE decreased. These changes in neutral lipid, such as the large increase in CE/PL ratio for HDL, have been reported previously for subjects with CETP deficiency.

Of interest was the significant increase in HDL FC content with treatment from 8.6 ± 1.1 mol % at baseline to 13.6% ± 0.9% after 14 days at the highest dose. Because FC increased to a greater degree than CE, the FC/CE ratio increased from 0.216 ± 0.022 to 0.323 ± 0.013 (P < 0.001). The net result of the multiple lipid changes was a slight increase in the ratio of polar/neutral lipid, (FC + PL)/(CE + TG), from 1.17 ± 0.06 to 1.28 ± 0.07 (P < 0.01). In some, but not all studies, complete CETP deficiency has been associated with HDL with decreased FC/CE ratios caused by an enrichment in CE, as well as slightly decreased ratios of polar/neutral lipids. Such HDL has been reported to be less efficient in promoting cholesterol efflux from cells and in LCAT activity. This has led to the speculation that such HDL might be dysfunctional with regard to reverse cholesterol transport (RCT) and that increased levels of HDL resulting from CETP deficiency may not be protective against atherosclerosis. In this study, torcetrapib provided high, but not complete, inhibition of CETP, leading to elevated HDL having increased FC/CE content. The increase in CE and decrease in PL are more like those seen with partial deficiency than the large effects that have sometimes been observed with total absence of CETP.

CETP inhibition with torcetrapib raised HDL cholesterol and PL up to 91% and 54%, respectively. Plasma PL as well as apoE levels were also increased. Presumably, much of this increase in apoE was associated with HDL. Chiba et al. separated apoE-poor and apoE-rich HDL from the plasma of homozygous (no CETP activity) and heterozygous (43% of normal activity) subjects. Whereas the apoE-rich subtraction accounted for only 13% of HDL-C for normal controls, in the heterozygotes and homozygotes it comprised 19% and 45%, respectively. For heterozygotes and homozygotes, the apoE-rich HDL had substantially elevated FC/CE. Therefore, the increased FC content for HDL seen with torcetrapib may be related to increased levels of apoE containing HDL.

Of relevance to the possible effects of these changes on RCT is the report that sera from transgenic mice expressing CETP removed less cholesterol from cells than sera from background mice, even though HDL from the former were more efficient on a per particle basis than that of nonCETP mice. In this case, the ∼70% greater HDL-C level for the nontransgenic sera seemed to more than make up for the lower efficiency. Also, in a study relating cholesterol efflux to various parameters in human serum, HDL PL concentration was found to be the best predictor of total efflux capacity. Additionally, in vivo studies with rabbits have suggested that large apoE-containing HDL were efficient in accepting cholesterol preloaded into the periphery and that a significant portion of this cholesterol was delivered to the liver.

The report that subjects in the Honolulu Heart Study with partial CETP deficiency had an apparent increase in CHD had suggested that lowered CETP levels might not be atheroprotective. More recent analysis of prospective data from this study revealed no statistically significant relationship between heterozygous deficiency and CHD or stroke, although a trend toward a lower incidence of adverse cardiovascular events was indicated. The results of the Honolulu Heart Study are consistent with those of a large population study of Japanese men and women in suggesting that an HDL-C level of ≥60 mg/dL is protective regardless of whether it is associated with CETP deficiency. Many factors that determine the contribution of HDL to RCT remain undefined, such as the physiological roles of HDL subpopulations and the magnitude of cholesterol transport as free versus esterified cholesterol. Therefore, it remains unclear how RCT after CETP inhibition will compare to the uninhibited state. However, the beneficial effects of elevated HDL are not expected to depend solely on promotion of RCT but on its antiinflammatory and related roles as well. Supporting the concept that CETP inhibition would be beneficial are the studies demonstrating that inhibition of CETP in rabbits by injection of antisense oligodeoxynucleotides, by vaccination to generate autoantibodies, and by administration of the synthetic CETP inhibitor JTT-705 reduced atherosclerotic lesions. In the case of rabbits made severely hypercholesterolemic, however, JTT-705 failed to reduce atherosclerotic lesion formation, suggesting that additional lowering of nonHDL lipoprotein was required. Further trials of increasing size and duration will need to be conducted to demonstrate whether such a therapy can prevent or retard CHD in humans. In this study, torcetrapib was shown to be a well-tolerated and potent inhibitor of CETP and therefore appropriate for such trials.

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References


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