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Review Article

Inhibitors of cholesteryl ester transfer protein – a step forward in the treatment of coronary artery disease?

Sheila A. Doggrell
School of Biomedical Sciences, University of Queensland, QLD 4072, Australia. e-mail: s_doggrell@yahoo.com

CONTENTS

Abstract

Although the LDL cholesterol-lowering statins have reduced the mortality and morbidity associated with coronary artery disease (CAD), considerable mortality and morbidity remains. Increasing HDL cholesterol levels is associated with reduced CAD mortality and morbidity. In healthy subjects with mild dyslipidemia, treatment with JTT-705 decreased cholesteryl ester transfer protein (CETP) activity, increased HDL cholesterol and decreased LDL cholesterol. Similarly, another CETP inhibitor, torcetrapib, has recently been shown to increase HDL cholesterol by 46%, decrease LDL cholesterol by 8% and have no effect on triglycerides in subjects with HDL cholesterol levels below 1.0 mmol/l. Increasing HDL cholesterol with inhibitors of CETP represents a new approach to dyslipidemia that requires further investigation, especially in patients with CAD.

Introduction

Although the LDL cholesterol-lowering statins reduce the mortality and morbidity associated with coronary artery disease (CAD) (reviewed in 1), considerable mortality and morbidity remain. Low HDL cholesterol levels (< 0.91 mmol/l) are an independent risk factor for premature coronary disease (2). Epidemiological studies suggest that an increase in HDL cholesterol of 0.03 mmol/l is associated with a 2-4% reduction in the risk of cardiovascular disease (3). Although statins do increase HDL cholesterol levels, they only do so modestly (5-10%) (1).

The importance of increasing HDL cholesterol levels has also been demonstrated in studies in which the levels were increased with fibrates (gemfibrozil, fenofibrate). In the landmark Veterans Affairs High-Density Lipoprotein Intervention Trial (VA-HIT), subjects with CAD had low LDL cholesterol, and this was therefore not a risk factor. However, the subjects did have low HDL cholesterol as a risk factor, and gemfibrozil was used to increase HDL cholesterol levels. The 2,500 men enrolled were treated with either gemfibrozil or placebo for 1 year. Gemfibrozil increased HDL cholesterol by 6%, without altering LDL cholesterol, and also reduced triglycerides by 31%. Associated with this decrease in HDL cholesterol was a reduction (22%) in the primary endpoint of non-fatal myocardial infarction or death from CAD in 5 years (4). Subsequent analysis showed that treatment with gemfibrozil also reduced the incidence of stroke in this group (5).

In patients with type 2 diabetes, LDL cholesterol levels of 3.4 mmol/l and HDL cholesterol levels of 1.03 mmol/l, fenofibrate increased HDL cholesterol by approximately 8%, and decreased LDL cholesterol by approximately 6% and triglycerides by about 30%. These changes in lipids were associated with a reduction in the angiographic progression of CAD (6).

As these benefits of fibrates resulted from rather modest increases in HDL cholesterol, attempts are being made to develop drugs that have a more pronounced effect on HDL cholesterol. One approach is the inhibition of cholesteryl ester transfer protein (CETP).

Cholesteryl ester transfer protein (CETP)

CETP is a glycoprotein secreted from the liver that circulates in the plasma, bound mainly to HDL cholesterol (reviewed in 7). It promotes the transfer of cholesteryl esters from antiatherogenic HDL cholesterol to proatherogenic apolipoprotein B-containing lipoproteins (VLDL, VLDL remnants, IDL and LDL cholesterol). When the

level of VLDL cholesterol is increased (as it is in type 2 diabetes), HDL cholesteryl esters are preferentially transferred by CETP to larger VLDL particles, which become cholesterol-rich and potentially more atherogenic (7). This suggests that inhibition of CETP to increase HDL cholesterol levels may be a useful therapeutic approach.

CETP deficiency is a frequent cause of elevated HDL cholesterol in Japan (8). Humans with heterozygous CETP deficiency and HDL cholesterol > 1.55 mmol/l have a reduced risk of CAD (7). This supports the therapeutic approach of inhibiting CETP to raise HDL cholesterol levels. There are also several CETP polymorphisms with small changes in plasma CETP and HDL levels, but there is no clear-cut link between these and atherosclerosis, probably because the changes are small (7).

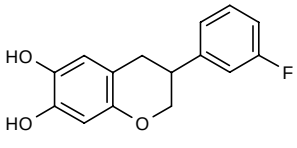
Antisense and antibodies against CETP

Mice and rats do not possess CETP and have metabolic pathways that make them resistant to diet-induced atherosclerosis. Thus, these rodents are not good models for human atherosclerosis. On the other hand, cholesterol-fed rabbits do develop atherosclerosis and can be used as a model of human atherosclerosis. In this model, antisense oligodeoxynucleotides against CETP decreased total cholesterol while increasing HDL cholesterol, and these changes were associated with decreased aortic cholesterol content and the percentage of lesions (9). Similarly, in cholesterol-fed rabbits, an antibody to CETP reduced plasma CETP activity, increased HDL cholesterol and decreased LDL cholesterol and the atherosclerotic lesions (10).

In a phase I clinical trial conducted with a CETP vaccine (CETi-I), healthy adults developed anti-CETP antibodies. The vaccine was well tolerated and there were no laboratory abnormalities (11). Small-molecule inhibitors of CEPT have now been developed (discussed below) and these may be preferred to antibodies for clinical use.

CGS-25159 and SC-71952

CGS-25159 (**1**) inhibited CETP with an IC_{50} value of approximately 10 μM. After oral administration to normolipidemic hamsters, CGS-25159 (10 mg/kg/day for 4 days) reduced CETP activity by 35-60%. Treatment with CGS-25159 at 30 mg/kg for 7 days increased HDL cholesterol by 19%. In 0.2% cholesterol-fed hamsters,



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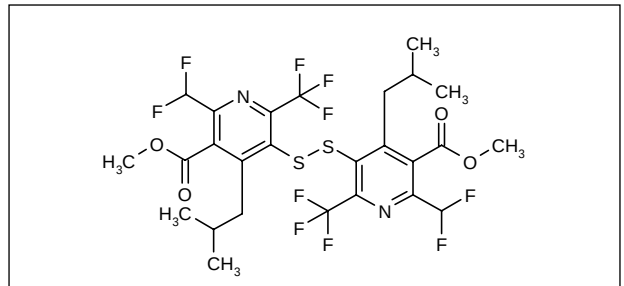

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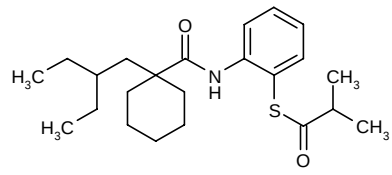

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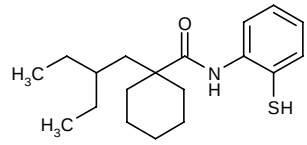


(**4**)

CGS-25159 (30 mg/kg for 14 days) increased HDL cholesterol by about 29%, while decreasing total cholesterol and triglycerides (12). Despite these interesting results showing that an inhibitor of CETP increases HDL cholesterol *in vivo*, there have been no further reports of development of CGS-25159 by Novartis.

SC-71952 (**2**), a substituted analogue of nicotinic acid methyl ester, was identified at Pharmacia (now Pfizer) as an inhibitor of CETP with an IC_{50} value of about 1 μM in a random screen of a chemical library (13). The effects of SC-71952 on HDL cholesterol or models of atheroma have not been published to date.

JTT-705

Using a lead disulfide compound, systematic chemistry was used by Japan Tobacco to obtain the small-molecule CETP inhibitor JTT-705 (**3**) (14). *In vitro*, JTT-705 inhibited plasma CETP activities of humans, rabbits, hamsters, cynomolgus monkeys and marmosets with IC_{50} values in the range of 1-12 μM. The thiol and orally active form JTP-25203 (**4**) also inhibited CETP activities with IC_{50} values in the range of 0.4-2.8 μM (15).

In rabbits, an oral dose of the thioester JTT-705 (30 mg/kg) inhibited CETP activity by 96%. In regularly fed rabbits, JTT-705 increased HDL cholesterol levels. In cholesterol (0.2%)-fed rabbits, JTT-705 (0.75% in the diet for 6 months) inhibited CETP activity, increased HDL cholesterol levels by 90% while decreasing non-HDL

cholesterol by about 45%, and inhibited the progression of atherosclerosis in the aorta. Thus, the lesion area in the aortic arch was 30% in the control group, but only 9% in rabbits treated with JTT-705 (16). When another group studied the effects of JTT-705 (100 or 300 mg/kg for 3 months) in rabbits with severe hypercholesterolemia fed 0.25% cholesterol, they confirmed that JTT-705 decreased CETP levels and increased HDL cholesterol, but were unable to show an effect on atheroma at this time point (atheromatous area: control 58%, JTT-705 60%). In this study, JTT-705 was also shown to increase triglycerides and non-HDL cholesterol levels (17). This suggests that JTT-705 may not be effective in severe hypercholesterolemia, as seen in familial hypercholesterolemia, or over a short time course.

A more detailed study of the effects of JTT-705 in normolipidemic rabbits showed that at a dose of 100 mg/kg/day there was an increase in plasma HDL cholesterol on the first day. However, a reduction in HDL triglycerides was only observed after the third day. In normolipidemic hamsters, JTT-705 (50-100 mg/kg/day for 7 days) also increased plasma HDL cholesterol and decreased HDL triglycerides, but was without effect on non-HDL cholesterol and triglycerides. In the normolipidemic marmoset, JTT-705 similarly reduced CETP activity on days 1 and 28. JTT-705 at 90 mg/kg/day maximally increased HDL cholesterol in the marmoset by 81%, decreased HDL triglycerides by 42%, without affecting non-HDL cholesterol and triglyceride levels (15).

Apolipoprotein A-I (apo A-I) is a major component of HDL cholesterol. Apo E-rich HDL cholesterol can bind to LDL receptors and scavenger receptors, and may play an important role in cholesterol efflux, and this is supported by the fact that apo E deficiency is associated with atherosclerosis. More detailed studies of the lipids involved showed that JTT-705 (0.75% in rabbit chow) increased the plasma levels of HDL cholesterol, HDL2 cholesterol, HDL phospholipids and apo A-I, while decreasing HDL triglycerides. JTT-705 also increased apo A-I mRNA levels in the liver, and this suggests that JTT-705 may increase the synthesis of apo A-I (18). When the HDL cholesterol was subfractionated, it was shown that the apo E-rich component was increased by JTT-705 (19).

The enzymes paraxonase and PAF acetylhydrolase are associated with HDL cholesterol, and protect LDL cholesterol from oxidation associated with the development of fatty streaks. In rabbits, JTT-705 increased the activity of both of these enzymes, which is potentially antiatherogenic (19).

Three phase I studies with JTT-705 have been performed. In a single-dose study (100-1800 mg/day), JTT-705 was well tolerated in healthy white men. A 2-period crossover bioavailability study showed that JTT-705 induced greater CETP inhibition postprandially compared with the fasted state. In a 14-day multiple-dose study, JTT-705 (600 or 900 mg/day) increased plasma HDL cholesterol while decreasing LDL cholesterol (20).

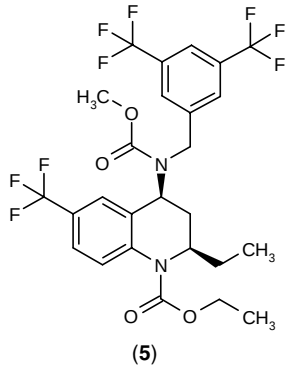
These studies were followed by an extended phase II trial assessing the safety and efficacy of JTT-705 (300, 600 or 900 mg/day) over 4 weeks in subjects with mild dyslipidemia (20). The phase II trial recruited 298 healthy individuals (64 women) with HDL cholesterol of 1.6 mmol/l or less and triglyceride levels of 4.5 mmol/l or less, but no set limits on LDL cholesterol levels. Subjects with unstable angina, previous myocardial infarction or type 2 diabetes were excluded. In these otherwise healthy subjects with mild dyslipidemia (HDL cholesterol = 1.2 mmol/l, LDL cholesterol = 3.9 mmol/l), treatment with 300-900 mg/day of JTT-705 for 4 weeks decreased CETP activity, increased HDL cholesterol and decreased LDL cholesterol. The effect at the 600 mg/kg dose was clearly greater than at the 300 mg/kg dose, whereas the effect at the 900 mg/kg dose was only slightly greater than that at 600 mg/kg/day. The highest dose decreased the CETP activity by 37%, increased HDL cholesterol by 34% and decreased LDL cholesterol by 7%. JTT-705 also increased HDL2 and HDL3 cholesterol and apo A-I and A-II levels, but did not alter the levels of triglycerides. With washout, the effects of JTT-705 were readily reversible. JTT-705 was well tolerated. There was a higher incidence of gastrointestinal complaints with JTT-705, but this did not result in any withdrawals

Japan Tobacco and Roche recently entered a licensing agreement relating to the development and commercialization of JTT-705, with Roche obtaining rights outside Japan and Korea (21, 22).

Torcetrapib

Pfizer is developing torcetrapib (CP-529414; **5**) as a new CETP inhibitor. Torcetrapib evolved from a series of inhibitors identified by high-throughput screening for inhibition of cholesteryl ester activity in an assay using native human plasma CETP. The IC_{50} values for torcetrapib were 52 and 65 nM, respectively, in HDL cholesterol and LDL cholesterol cholesteryl ester transfer assays (23).

The results from two clinical studies with torcetrapib were published almost simultaneously in 2004. In one study, 40 healthy subjects were randomized to placebo or



(**5**)

torcetrapib at 10, 30, 60 and 120 mg once daily or 120 mg twice daily for 14 days. Baseline levels of HDL cholesterol and LDL cholesterol were 1.32 and 2.79 mmol/l, respectively. Doses of torcetrapib of 30 mg/day and higher gave 80% or more inhibition of CETP activity, and E_{max} modeling indicated an EC_{50} of 43 nM, which is similar to the *in vitro* value. HDL cholesterol was increased by 16%, 28%, 62%, 73% and 91%, respectively, at doses of 10, 30, 60 and 120 mg once daily and 120 mg twice daily. There was a decrease in non-HDL cholesterol, with LDL cholesterol decreasing 21% and 42%, respectively, with torcetrapib 120 mg once and twice daily. Torcetrapib also decreased apo A-I levels (by 26% at 120 mg b.i.d.), while increasing apo E (by 66% at 120 mg b.i.d.). There were no significant chances in triglyceride levels (23).

In the other study, subjects enrolled had to have HDL cholesterol levels below 1.0 mmol/l, triglyceride levels below 4.5 mmol/l and LDL cholesterol below 4.1 mmol/l, with or without atorvastatin treatment. At randomization, the 10 subjects who went on to receive torcetrapib alone had LDL cholesterol of 3.47 mmol/l, HDL cholesterol of 0.85 mmol/l and triglycerides of 1.83 mmol/l. The other 9 subjects had initial LDL cholesterol levels of 4.1 mmol/l or greater and were treated with atorvastatin 20 mg, which lowered LDL cholesterol levels to 2.33 mmol/l. This group had similar HDL cholesterol and triglyceride levels to the subjects not treated with atorvastatin. All subjects then received torcetrapib (120 mg/day) for 4 weeks, and the subjects not taking atorvastatin went on to receive torcetrapib (120 mg b.i.d.) for the following 4 weeks. Torcetrapib 120 mg once daily lowered CETP activity by 38%, and inhibition was increased to 65% at a dose of 120 mg twice daily. In the subjects taking atorvastatin, torcetrapib 120 mg once daily lowered CETP activity by 28%. Torcetrapib 120 mg once and twice daily increased HDL cholesterol to 1.2 (46%) and 1.8 mmol/l (106%), respectively. In the subjects treated with atorvastatin, torcetrapib once daily also increased HDL cholesterol to 1.2 mmol/l. Torcetrapib increased plasma levels of HDL apo A-I and A-II, and of the HDL cholesterol subclasses HDL2 and HDL3. The apolipoprotein values were increased by 10-16% by once-daily torcetrapib with and without atorvastatin treatment. Torcetrapib 120 mg twice daily increased the plasma levels of HDL apo A-I and A-II by 36% and 21%, respectively. Torcetrapib had no effect on total cholesterol or phospholipids. LDL cholesterol was decreased by 8%, 17% and 17%, respectively, by torcetrapib once daily, twice daily and in combination with atorvastatin. Once-daily torcetrapib had no effect on triglycerides, but twice-daily dosing and combination with atorvastatin reduced triglycerides by 26% and 18%, respectively. The cholesterol levels within large HDL cholesterol particles (8.8-13.0 nm) were increased from approximately 0.26 mmol/l to about 0.70 mmol/l by once-daily torcetrapib with and without atorvastatin, and to 1.16 mmol/l by twice-daily torcetrapib. Together with the increased HDL cholesterol levels, large HDL cholesterol particles increased from about 8.5 nm to 9.1 and 9.7 nm, respectively, on these regimens. Torcetrapib did not alter cholesterol levels in small HDL cholesterol particles (7.3-7.7 nm). Torcetrapib alone increased the cholesterol levels in large LDL cholesterol particles, while reducing the cholesterol levels in small LDL particles. In subjects treated with atorvastatin, torcetrapib had smaller, nonsignificant effects on LDL particle cholesterol levels. Although there were no serious adverse events and no withdrawals due to adverse effects, headache was common with torcetrapib (24).

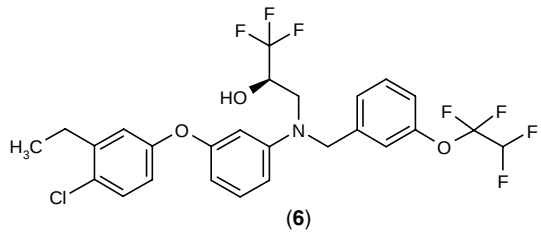
A characteristic of patients with CAD is that they have lower levels of large HDL cholesterol particles and higher levels of small LDL cholesterol particles than subjects without CAD. In the above study, the authors point out that torcetrapib increased large HDL cholesterol particles and decreased small LDL cholesterol particles to levels similar to those in normolipidemic subjects (24).

Large-scale phase III trials evaluating the efficacy and safety of torcetrapib in combination with atorvastatin are now in progress. A multicenter, randomized trial is comparing the torcetrapib/atorvastatin combination with atorvastatin alone in preventing the progression of coronary atherosclerosis (measured by intravascular ultrasound) in patients with nonobstructive CAD (20-50% stenosis). Overall, the global phase III program will involve 12,000 patients in dyslipidemia studies and another 13,000 patients in cardiovascular morbidity and mortality studies (25).

Other CETP inhibitors

In addition to torcetrapib, Pfizer has a series of CETP inhibitors that began development at Pharmacia, including compound **6**. This compound inhibits CETP activity in human plasma with an IC_{50} of 59 nM, and increases HDL cholesterol levels in hamsters to a small extent following oral dosing (26).

Japan Tobacco has discovered a compound (**7**) that is structurally related to JTT-705 but is 4-fold more potent in inhibiting CETP (IC_{50} = 2 μM) than JTT-705 (27).



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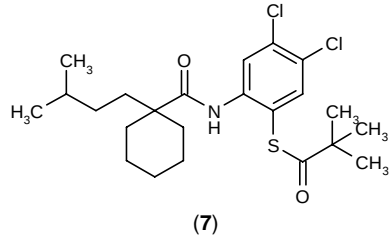

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Conclusions

Prior to its study in humans, the ability of JTT-705 to slow the progression of atherosclerosis in cholesterol-fed rabbits was reported in a peer-reviewed journal. An effect of JTT-705 on atherosclerosis was not observed, however, in a more severe model of hypercholesterolemia. No reports of the effects of torcetrapib in animal models of atheroma have appeared in the peer-reviewed literature.

Clinical trials with JTT-705 and torcetrapib have involved small groups of middle-aged, relatively healthy individuals. These trials suggested that JTT-705 might be associated with gastrointestinal disturbances and that torcetrapib might cause headache, indicating that further safety and tolerability trials should be undertaken with these agents in larger patient groups. The most interesting trials with the CETP inhibitors will be those in older patients with CAD to determine whether these drugs can inhibit the progression of the disease and reduce mortality and morbidity.

At present, the fibrates are used to increase HDL cholesterol levels and their benefits have been demonstrated in a large clinical trial. However, greater increases in HDL cholesterol have been reported with the CETP inhibitors than with the fibrates. On the other hand, triglycerides are independent risk factors for CAD, especially in the presence of diabetes (reviewed in 28). While the fibrates cause a major reduction in triglyceride levels, JTT-075 and the lower dose of torcetrapib alone had no effect on triglyceride levels, and in one study JTT-075 was shown to increase triglyceride levels. The CETP inhibitors therefore may have both advantages and disadvantages over the fibrates, depending on the type of dyslipidemia, and this will need to be tested both experimentally and clinically. For instance, in the presence of high levels of triglycerides and marginally low HDL cholesterol, the fibrates may have advantages over the CETP inhibitors.

Raising HDL cholesterol with inhibitors of CETP is a new approach to treating dyslipidemia that requires further investigation, especially in patients with CAD.

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