VIA MEDICA

HOT TOPICS

Cardiology Journal
2007, Vol. 14, No. 1, pp. 1–5

ISSN 1507–4145

Increasing HDL: the torcetrapib story

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Clinical trials are an integral part of the process for developing new medical innovations and often provide unexpected information about the safety and effectiveness of new medical products before their approval. In December 2006, the Food and Drug Administration (FDA) was informed by Pfizer about suspending a large phase III trial evaluating the investigational cardiovascular therapy torcetrapib/atorvastatin due to an increased rate of mortality in patients receiving the combination therapy [1]. The drug which has been in development since the early 1990s was considered by Pfizer as one of the most important new developments for coronary heart disease (CHD) in decades. The decision of the Data Safety Monitoring Board was made after data analysis from the ILLUMINATE study, a randomized, double-blind evaluation of the effect of torcetrapib/atorvastatin vs atorvastatin alone on the occurrence of major cardiovascular events in 15 000 subjects with CHD or risk equivalents. It was recommended that trial should be halted due to an "imbalance of mortality and cardiovascular events". There were 82 deaths reported in the group that received torcetrapib/atorvastatin therapy and 51 deaths among those administered atorvastatin [2]. This substantial increase of mortality in patients receiving combination therapy was the reason for not only stopping the trial but also for suspending further research and production of torcetrapib, bringing the company's nearly 1 billion dollars investment in the drug into a total loss. The results of the ILLUSTRATE study evaluating whether the combination of torcetrapib and atorvastatin provides greater benefit, in terms of reduction in progression of coronary disease as determined by coronary intravascular ultrasound assessment of the atheroma volume, compared to atorvastatin alone in patients with CHD will be presented at the Scientific Meeting of the American College of Cardiology 2007 in New Orleans [2].

Several epidemiological studies have identified both low-density lipoproteins (LDL) and high-density lipoproteins (HDL) as independent factors that modulate the risk of coronary heart disease. Statins (HMG-CoA reductase inhibitors) which reduce LDL levels and lower triglyceride levels are the most commonly prescribed agents for the therapy of hypercholesterolemia, and are considered the most effective therapy in the prevention of atherosclerosis [3]. However, it has been shown that less than 50% of treated patients respond favorably, while the others continue to develop cardiovascular disease and in most of the non-responsive patients, low plasma HDL is encountered. Treatment limited to LDL fails to capture a significant portion of patients at risk for CHD, and patients effectively treated for elevated LDL still experience a significant number of coronary events. Thus increasing attention is being paid to other lipoprotein fractions, such as HDL and triglycerides, as additional potential targets of therapy. Increased serum triglycerides combined with low HDL, a condition often associated with smaller, dense LDL particles, is frequently referred to as atherogenic dyslipidemia or the „lipid triad" and is most often seen in the context of the metabolic syndrome [3–6].

Epidemiological studies have demonstrated that decreased HDL constitutes a powerful independent risk factor for CHD and more importantly, elevating HDL has been shown to decrease this risk [7, 8]. Rising HDL levels is an important target for treatment of dyslipidemia, especially in preexisting

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atherosclerosis, largely due to its function in reverse cholesterol transport. In addition, other important roles include fibrinolysis, antioxidant functions, and the reduction of platelet aggregability. Elevating HDL can be achieved by lifestyle changes as well as by the use of statins, fibrates or nicotinic acid, albeit to a limited extent [9, 10]. Statins increase plasma HDL concentrations by 10% to 15%, while fibrates and niacin raise HDL by up to 25% to 30% [3, 10].

Several new therapies for substantially increasing HDL cholesterol levels are under investigation. Recently published reviews by Kastelein [8] and Forrester and Shah [11] describe different potential methods of increasing HDL and/or enhancing reverse cholesterol transport, including inhibitors of the cholesterol ester-transfer protein (CETP), apolipoprotein A-I Milano, DF4 (synthetic peptide mimetic of apolipoprotein A-I), the dual peroxisome-proliferator-activated receptor agonists, and rimonabant (an endocannabinoid receptor inhibitor). Combining these new agents with existing LDL cholesterol lowering agents may improve the cardiovascular risk reductions currently attainable.

Extensive research conducted to develop novel drugs to substantially increase HDL levels resulted in the development and clinical testing of CETP inhibitors, a crucial protein in the transport of cholesterol from the periphery to the liver for secretion into bile, known as reverse cholesterol transport [9, 11]. Two pharmacological small-molecule inhibitors of CETP, JTT-705 (Roche) and torcetrapib (Pfizer) have been shown to effectively raise HDL cholesterol in humans when either used as a monotherapy or combined with statins that lower LDL cholesterol.

The CETP is a plasma glycoprotein manufactured in the liver. It circulates in the blood, bound predominantly to HDL. Two principal actions of CETP have been identified. The primary action of CETP is to mediate the transfer of cholesterol esters from HDL to very low-density lipoproteins (VLDL) and LDL in exchange for triglycerides. CETP also promotes the transformation of HDL 2 to HDL 3, an action that could promote reverse cholesterol transport. CETP inhibition, on the other hand, results in an increase in HDL by markedly delaying catabolism of apolipoproteins apoA-I and A-II. This action can also increase reverse cholesterol transport. This overlap of the potential effects of CETP and CETP inhibition has served to confound an understanding of potential therapeutic mechanisms in atherosclerosis [11–13].

The CETP gene mutation discovered in the Japanese population (with a prevalence of about 11%) was accompanied by a substantial increase in HDL and affected individuals were resistant to atherosclerosis [12–15]. During the ensuing years, at least 13 different mutations in the coding region of the CETP gene have been identified. Earlier studies in the Japanese population have demonstrated that a CETP deficiency was associated with longevity [12]. In a recent study on the lipoprotein phenotype and longevity, the subjects with exceptional longevity (mean 98 years) were Ashkenazi Jews, as well as their offspring [16]. There was a significant increase in both HDL and LDL particle size in probands and their offspring as compared to age matched control groups. With regard to human CETP mutations and the associated reduction in CETP levels, recent analysis of prospective data is consistent with the results of a previous study of Japanese subjects in concluding that CETP deficiency is protective when associated with HDL levels $\geq$ 60 mg/dl [14, 17]. A recent study with a seven-year follow-up of 2340 men aged 71–93 in the Honolulu Heart Program, demonstrated that the age-adjusted CHD incidence rates were significantly lower in men with high versus low HDL levels [18]. After adjustment for age, hypertension, smoking, and total cholesterol, the relative risk of CHD for those with HDL levels $\geq$ 60 mg/dl, compared to those with HDL levels $<$ 40 mg/dl, was 0.6. Men with a CETP mutation had the lowest (although not statistically significant) rates of CHD. These data indicate that HDL remains an important risk factor for CHD in the elderly.

The first results from clinical trials on torcetrapib were very promising and demonstrated its ability to raise HDL levels very effectively. In healthy young subjects with the highest torcetrapib dose (120 mg/twice daily), CETP activity decreased by 80%, while the CETP mass increased, apparently because the mechanism of action of torcetrapib represents the shift of free CETP to the HDL-bound form [19]. With the above treatment, plasma LDL decreased by 42%, HDL increased by 91%, as did apoA-I and apoE, by 27% and 66%, respectively, while apoB was reduced by 26%. Cholesterol ester content decreased and triglyceride content increased in the non-HDL plasma fraction, with contrasting changes occurring in HDL. These effects of CETP inhibition resembled those observed in partial CETP deficiency.

In subjects with low HDL cholesterol levels, CETP inhibition with torcetrapib markedly increased HDL cholesterol levels and also decreased

LDL cholesterol levels, both when administered as monotherapy and when administered in combination with atorvastatin [20]. Torcetrapib (120 mg/daily) has been shown to increase HDL cholesterol levels by 46% when given alone and in combination with atorvastatin (61%) as well as to decrease LDL cholesterol levels by more than that achieved by atorvastatin alone. Treatment with torcetrapib (120 mg/twice daily) increased HDL levels by 106%. Torcetrapib also reduced LDL cholesterol levels by 17% in the atorvastatin cohort.

A recent multi-center, randomized, double-blind, placebo-controlled, parallel-group, dose-ranging study on 493 subjects, evaluating torcetrapib and atorvastatine for 12 weeks in patients with elevated LDL without overt CHD also demonstrated rapid and dose-dependent increases in HDL and decreases in LDL cholesterol [21]. In all published reports no serious adverse events due to torcetrapib treatment were reported. However, it has been demonstrated that of the patients receiving torcetrapib, 1.6% experienced elevations in blood pressure defined as 1) systolic blood pressure (SBP) ≥ 15 mm Hg or diastolic blood pressure (DBP) ≥ 10 mm Hg from baseline at 3 consecutive visits or 2) SBP ≥ 180 mm Hg with a ≥ 20 mm Hg change from baseline or DBP ≥ 105 mm Hg with a ≥ 15 mm Hg change from baseline at a single visit [22]. The mechanism behind this response is unknown.

Data from the Lipid Research Clinics and the Framingham Heart Study suggest that the total-to-HDL cholesterol ratio may be more predictive of CHD than total cholesterol or LDL cholesterol [6, 23]. The current trend in dyslipidemia treatment is the greater use of combination lipid altering drug therapy. This tendency is largely due to the facts that: 1) atherosclerosis is a multifactorial process and its treatment does not appear to be possible with a single lipid altering drug that predominantly treats only one lipid parameter; 2) more patients are being considered as candidates for more aggressive lipid treatment goals, which cannot be achieved with one lipid altering drug; 3) the use of two or more lipid altering drugs in lower doses may result in less potential for side effects and toxicity, while at the same time have a greater potential for more global improvement in lipid parameters by the use of differing lipid-altering agents that treat different lipid targets [5].

Does the combined use of statins and CETP inhibitors have the potential for markedly improving the effectiveness in reducing the risk of cardiac events in patients with cardiovascular disease? The promising data on torcetrapib and atorvastatin demonstrated the great expectations of this novel combination therapy. However, the limited number of clinical trials, investigating the pharmaceutical CETP inhibition has shown an urgent need for large randomized trials to judge the safety and efficacy and to assess the long-term effects of CETP inhibition on atherosclerosis. Considering the results of today's clinical practice of managing dyslipidemia, another issue that warrants investigation is the safety and efficacy of combination therapy of CETP inhibition together with evidence-based LDL cholesterol reduction. The extensive data on the short-term and long-term effects of CETP inhibition in humans will have to determine whether CETP inhibition decreases the risk of atherosclerotic disease in dyslipidemic patients.

In addition, recent data indicate that CETP inhibition may be beneficial to hypertriglyceridemic individuals [4]; however, these results also need to be confirmed by clinical endpoint trials. Despite animal, epidemiological, and genetic data, we cannot predict the antiatherogenic effect of CETP inhibition or identify populations in which the intervention might be more or less effective. Although CETP inhibitors have only been tested in a limited number of patients and data from big multicenter studies are not available yet, the current results indicate that CETP inhibition has the potential to be of great importance in the future treatment of dyslipidemia.

The effect of CETP and its inhibition may be modified by the genetic and metabolic milieu [11]. Based on human genetic data it has been speculated that CETP deficiency may be antiatherogenic when it is associated with a significant increase in HDL (> 60 mg/dL) but that it is not protective in the presence of substantial hypertriglyceridemia and major increases in LDL cholesterol. Studies in hyperlipidemic rabbits are consistent with this idea and suggest that despite a major increase in serum HDL, the HDL itself is insufficient to be antiatherogenic. An additional reasonable speculation is that the effect of the metabolic milieu on CETP inhibition may involve alterations in HDL function, catabolism, or particle distribution [11, 24].

Although there are several similar drugs to torcetrapib in the pipeline, scientists are trying to find out whether the problems with torcetrapib come from lowering HDL cholesterol, lowering a particular type of HDL cholesterol, or from some unique characteristic of the torcetrapib molecule itself. Researchers will likely investigate the conditions related to hypertension, since the drug is known to elevate blood pressure (3–4 mm Hg).

Some experts believe the increase in blood pressure could be managed, while others noted that such an increase would translate, population wise, into a 20% higher stroke mortality and a 12% higher mortality from CHD [2].

Studies on torcetrapib were undergoing criticism already during development. When the first human studies were launched, beside the strictly scientific and clinical implications of torcetrapib trials, there were also concerns about how Pfizer was studying and marketing the future drug which was hoped to be approved by the FDA in 2007. The company was planning to sell torcetrapib only in combination with its own atorvastatin and Pfizer's clinical trials studied torcetrapib only in combination with this best-selling drug in the world (sales of atorvastatin account for about half of Pfizer's annual profits), on which the company's patent is due to expire in 2010. This controversial decision drew big criticism from the medical community [25] and finally the company has changed its strategy. So far there are almost no efficacy trial data based on the combination therapy with the other statins.

The concept of HDL elevation is still intriguing and open for investigation. Several pharmaceutical companies have similar compounds in the pipeline but after the recent experience with the torcetrapib/atorvastatin combination, trials with HDL elevating compounds will be under new scrutiny. Most likely our understanding of HDL metabolism and pathways is still incomplete and simple inhibition of CETP may not be a solution. There is also a need for pharmacogenomic investigations of the results of the ILLUMINATE trial which could possibly unveil which genetic polymorphism predispose to harmful versus beneficial effect of the CETP inhibitors.

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