

REFLECTION

Unending saga of fighting cholesterol: Evacetrapib is another fallen warrior

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ABSTRACT

Despite an enormous success in reducing morbidity and mortality in cardiovascular disease (CVD), statins and modern antihypertensive medications are not universally effective. Research has focused on potential molecular targets in dyslipidemia. Decades-long, expensive trial with CETP (cholesterylester transfer protein) inhibitor evacetrapib, came in April 2016 to crash landing. Despite dramatic improvement in “good” HDL-cholesterol and decline in “bad” LDL-C, the effect of evacetrapib in CVD patients was comparable to placebo. Notwithstanding failure in this molecular target field, results with another agent the PCSK9 inhibitor, may identify the molecular site that would normalize dyslipidemia, without harming physiologically essential lipids (Fig. 2, Ref. 19). Text in PDF www.elis.sk.

KEY WORDS: CETP, cholesterylester transfer protein inhibitor, evacetrapib, dyslipidemia, lipoproteins, cardiovascular disease.

Motto: How can a drug that lowers lipids presumably associated with health benefit, not show any favorable clinical outcome?

S.J. Nicholls

The scientific session of the American College of Cardiology in Chicago on April 3, 2016, dealt a fatal blow (1) to potentially hopeful, decades-long effort to introduce a CETP inhibitor. Evacetrapib (EVC) (Fig. 1) was endowed with expectations to become another, more effective cholesterol modifying agent. Dr Nicholls, a researcher from the Cleveland Clinic reported disappointing results with EVC (2) in a Phase III trial that included 12,092 patients of an average age of 65 with high risk for cardiovascular disease (CVD). Patients were randomly divided into two equivalent cohorts, taking EVC or placebo for at least 1.5 years.

Laboratory numbers with EVC were astonishingly good. LDL cholesterol (LDL-C) levels decreased 37 per cent to an average of 55 mg/DL from 84. Patients HDL-C levels rose 137 per cent to an extraordinary high of 104 mg/DL from 46. However, there was no significant benefit when compared to placebo in the clinical outcome: rate of myocardial infarction, stroke or mortality from CVD. The sponsor of EVC research, the pharmaceutical company Eli Lilly stopped the study in October 2015, citing futility, after publication of unfavorable interim results (3).

Rejection of EVC was a shocking disappointment for lipid researchers and for the pharmaceutical investor Eli Lilly. Regarding laboratory values, EVC did everything that was considered

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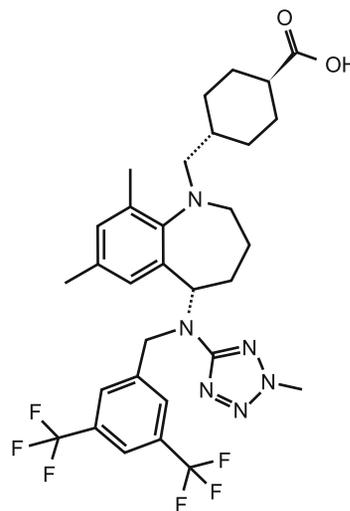


Fig. 1. Structure of evacetrapib.

favorable: dramatic decline of the “bad guy” LDL-C and equally impressive rise in presumably beneficial HDL-C. The effect on CVD complications was nearly identical with placebo. This non-inferiority end point brought an end to many years of very expensive research.

What is the substance of this unexpected controversy? Medical science for more than forty years (4, 5, 6) has been aware that high levels of plasma LDL-C and low HDL-C represent risk for atherogenesis and CVD. LDL-C plays a causative role in the development and progression of atherosclerosis.

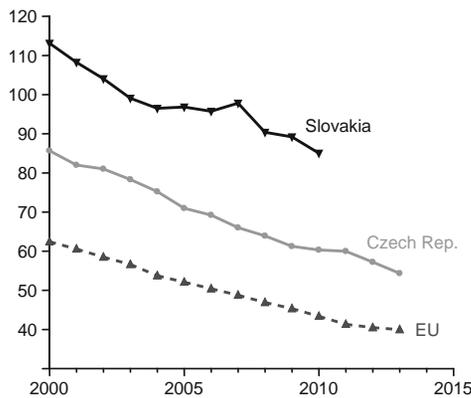


Fig. 2. Decrease of premature cardiovascular mortality (8). SDR – standardized premature mortality at age 0 – 64 years.

Preventive and therapeutic interventions resulted in a dramatic decline of CVD (7, 8) (Fig. 2) mostly due to beneficial effect of statins (9) and more effective blood pressure control. Yet, some patients with dyslipidemia do not adequately respond to statins. This at risk population has generated continuing efforts to identify agents that may manage dyslipidemia and atherogenesis more effectively.

EVC became a hopeful candidate (10, 11, 12, 13, 14) for new generation of lipid modifying agents. It belongs to a class of CETP, cholesteryl ester transfer protein inhibitors. EVC inhibits cholesteryl ester transfer protein (CETP), blocking the transfer of cholesteryl ester from HDL to LDL, thereby raising HDL and lowering LDL.

Inhibition of the CETP was expected to beneficially influence the balance between LDL-C and HDL-C but clinical outcome did not support improvement in laboratory numbers. There had been other CETP inhibitors that were tried to optimize the metabolic lipid profile. Torcetrapib and dalcetrapib improved the numbers (10) but they resulted in a rise in blood pressure and in an increased mortality. They were judged unsuccessful and further trials were discontinued (16).

Intensive past attempts to optimize the metabolic lipid profile include regulation of cholesterol absorption (resins, bile acid sequestrants, ezetimibe), derivatives of nicotinic acid and fibrates. Lowering the LDL-C with statins, inhibitors of HMG-CoA reductase is still the most important pharmacotherapy. Still, there is a segment of individuals at risk for CVD who do not adequately respond to statin (9).

Failure of CETP inhibitors brought unexpected uncertainty for the decades-long dogma of potential role of the LDL-C and HDL-C. It appears that the prevention and management of CVD is more intricate than a simple attempt to reduce plasma cholesterol to physiologically unnatural level (17, 18). HDL-C seems to be less causally related to CVD risk than the LDL-C. Trials to reduce CVD by mainly raising HDL-C have been less convincing.

Novel agents that appear promising (18) include a monoclonal antibody to PCSK9 which binds at the surface of hepatocytes to the receptor of LDL-C. The result is that using the inhibitor, more

receptors at the cell surface are available to remove LDL-C from the circulation. Alirocumab and evolocumab were approved by the Food and Drug Administration in the US to block the PCSK9. Among the LDL-C lowering therapies, PCSK9 inhibitors appear the most promising class, but have relatively large cost compared to statins. There are attempts to develop a vaccine that targets the PCSK9 (19).

Conclusion

Evacetrapib, initially hoped to manage dyslipidemia by inhibiting the protein at liver cell surface that transfers cholesteryl ester from HDL to LDL, was declared ineffective after decade of research. These results indicate that the pathogenesis of dyslipidemia is far more complex than a simple balance between HDL cholesterol and LDL-C. Focus has shifted to identification of the pivotal metabolic process that would reveal the “magic bullet” which normalizes metabolism without harming physiologically vital lipid constituents.

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